THE EFFECT OF PRIMARY SJÖGREN'S SYNDROME ON THE SENSES OF SMELL, TASTE AND SEXUALITY IN FEMALE PATIENTS IN THE UK: IMPACT ON QUALITY OF LIFE

Thesis submitted in partial fulfilment of the requirements of the degree of Doctor of Philosophy (PhD) to the University of London

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To
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Abstract

It is well established that mucosal dryness is the most common symptom in primary Sjögren's Syndrome (pSS) patients, affecting the nasal, oral and genital mucosa. A systematic review was conducted and a study with the following aims was established: 1) To assess the functions of the smell, taste and sexuality in patients with pSS. 2) To determine whether the mucosal dryness has an impact on the functions of the smell, taste and sexuality in pSS patients. 3) To investigate the impact of the impairment of the functions of smell, taste and sexuality on the quality of life (QoL) and mental health well-being in women with pSS.

Methodology: Sixty-five pSS patients and 62 sex-matched healthy volunteers were recruited for this study. The smell function was assessed by the University of Pennsylvania Smell Identification Test (UPSIT). The taste function was comprehensively evaluated by assessing the gustatory function using the Taste Strips Test (TST), and the neurosensory threshold by an electrogustometer (EGM). The sexual function was assessed by the Female Sexual Function Index (FSFI). The oral dryness was assessed by means of stimulated and unstimulated salivary flow rate (SFR), clinical assessment of oral dryness scale (CODS) and Xerostomia Inventory (XI). The World Health Organisation Quality of Life-BRÉF (WHOQoL-BRÉF) and Oral Health Impact Profile-14 (OHIP-14) were used for the general and oral health related QoL respectively. The Hospital Anxiety and Depression Scale (HADS) was used to assess the mental health status.

Results: Data analysis showed that the smell dysfunction was twice as prevalent in the patients group (41.5%, n=27/65) compared with healthy volunteers (24.1%, n=15/62). This difference was even more pronounced when assessing the gustatory function impairment, which was six times more prevalent in pSS patients (54%, n=34/63) than in healthy participants (8.3%, n=5/60). The neurosensory threshold of taste was three times higher in the patients' group (31.7%, n=20/64) compared with the healthy volunteers (9.8%, n=6/61), and was associated with gustatory deterioration in pSS group (β=-0.4, 95% CI=-0.2 – 0), indicating possible neurological impairment in this group. As expected, the salivary flow rate and the clinical oral dryness score were significantly lower in the patient group compared

with healthy volunteers. No evidence was found to support that the oral dryness was associated with deterioration of smell, taste or sexual functions in pSS patients. The number of sexually active pSS patients (n=28) was half of that in the healthy volunteers group (n=42), and the FSFI showed that the sexual function was significantly impaired in pSS patients (p=<0.05). The self-administered questionnaires showed that the life quality was significantly compromised in patients, who were more anxious (58.5%, n=38/65) and four times more depressed (32.3%, n=21/65) compared with healthy volunteers (Anxiety=21%, n=13/61; depression=8.2%, n=5/61). However, neither smell nor taste dysfunction were contributory factors to the reduced QoL, but the sexual dysfunction was the main factor contributed to the compromised general QoL in pSS patients.

Conclusion: The smell, taste and sexual impairment are manifestations seen in pSS, but only the sexual dysfunction appear to have a diminishing effect on the QoL and mental health well-being of patients. The taste deterioration in pSS does not seem to be associated with mucosal dryness but maybe precipitated by a Sjögren's syndrome-associated neuropathy.

List of awards and presentations

- Grant from the BSODR to present part of the results of this study at the IADR/PER Meeting, July 2018, London, UK.

- Best poster presentation at the annual meeting of the British Sjögren's Syndrome Association (BSSA), October 2016, Swindon, UK.

- Oral and poster presentation at the European Association of Oral Medicine (EAOM) Congress, September 2016, Turin/ Italy.

- Poster presentation at William Harvey Day, October 2016, QMUL, London UK.

- Poster presentation at the IADR General Session, Antimicrobial Strategies for Caries Control, San Francisco, March 2017, California, USA.

- Oral presentation at the British Society for Oral and Dental Research (BSODR), September 2017, Plymouth, UK.

- Oral presentation at the IADR/PER Meeting, Head and Neck Conditions, in July 2018, London, UK.

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Abbreviations

Acronym	Definition
AECG	American European Consensus Group
ANA	Antinuclear antibody
Anti-La/SSB	Anti-Sjögren's-syndrome-related antigen B
Anti-Ro/SSA	Anti-Sjögren's-syndrome-related antigen A
ACR	American College of Rheumatology
CN V	Fifth cranial nerve (Trigeminal)
CNS	Central nervous system
CODS	Clinical Oral Dryness Score
CRF	Case Report Form
CTN	Chorda tympani nerve
DHEA-S	Dehydroepiandrosterone Sulphate
EGM	Electrogustometer
ESDAI	EULAR Sjögren's Syndrome Disease Activity Index
ESPRI	EULAR Sjögren's Syndrome Patient Reported Index
ESR	Erythrocyte Sedimentation Rate
EULAR	European League Against Rheumatism
FSFI	Female Sexual Function Index
HADS	Hospital Anxiety and Depression Index
Hb	Haemoglobin
HRQoL	Health related quality of life
KCS	Keratoconjunctivitis sicca
MAF	Multidimensional Assessment of Fatigue
MS	Multiple Sclerosis
NM	Neurological manifestation
OHRQoL	Oral health related quality of life
OHIP	Oral Health Impact Profile
PD	Parkinson's disease
PN	Peripheral neuropathy
PNS	Peripheral nervous system
PROFAD	Profile of Fatigue and Discomfort
pSS	Primary Sjögren's Syndrome
QoL	Quality of life
RA	Rheumatoid Arthritis
SD	Sexual dysfunction
SF-36	Short form-36
SICCA	Sjögren's International Collaborative Clinical Alliance
SLE	Systemic Lupus Erythematosus
SS	Sjögren's Syndrome
SSFR	Stimulated Salivary Flow Rate
sSS	Secondary Sjögren's Syndrome
SXI	Summated Xerostomia Inventory
TBI	Traumatic brain injury

TST	Taste Threshold Test
UPSIT	University of Pennsylvania Smell Identification Test
USSFR	Unstimulated Salivary Flow Rate
VAS	Visual Analogue Scale
WHO	World Health Organisation
WHOQoL-BRÈF	World Health Organisation Quality of life-BRÈF
XI	Xerostomia Inventory
µA	microampere

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CHAPTER 1: INTRODUCTION

Introduction

Sjögren's Syndrome (SS) is an inflammatory autoimmune rheumatic disorder that affects exocrine glands, especially salivary and lacrimal glands, causing reduction of the glandular secretions (Fox, 2005). The glandular dysfunction can result into dryness of the related mucosal surfaces, typically ocular and oral mucosa, but nasal and genital mucosa can also be affected (Rasmussen et al., 1986, Jacobsson et al., 1992, Marchesoni et al., 1995). It is well established that mucosal dryness is the main characteristic feature of the syndrome (Henkin et al., 1972, Isik et al., 2016), which can be severe enough to affect the functions of the related organs, namely the smell, taste and sexuality. However, the extent to which the mucosal dryness alters these functions is not well known.

Deterioration of the smell and taste is a frequently reported symptom by pSS patients. Henkin et al. (1972) and Kamel et al. (2009) found that smell and taste are impaired and compromising each other in pSS patients, and influenced by the dryness of the mucosal surfaces. Negoro et al. (2004) showed that taste dysfunction was less frequently found in SS patients than previously reported, and that it was affected by the oral dryness, in a way that impedes substances from reaching the taste buds. Weifenbach et al. (1995) and Gomez et al. (2004) reported different results of the lack of association between taste deficit and mucosal dryness in SS patients. Therefore, the evidence in the literature regarding the smell and taste dysfunction in SS patients is conflicting.

Women with SS often suffer from vaginal dryness and dyspareunia, and the possible explanation for these symptoms is the local inflammation of vaginal mucosa (Skopouli et al., 1994, Marchesoni et al., 1995, Mulherin et al., 1997, Cirpan et al., 2007). Mulherin et al. (1997) presented evidence of the association between oral symptoms and vaginal dryness in SS patients. Other studies suggested that dryness and dyspareunia could adversely influence the sexual well-being of SS women (van Nimwegen et al., 2015, Priori et al., 2015). Sexual well-being is an important aspect of the life quality, and addressing this is an essential component of delivering holistic patient-centred care.

There have been several studies showing that the quality of life is compromised in SS patients (Kamel et al., 2009, van Nimweden et al., 2014), however, there is none that looked at the collective effect of the smell, taste and sexual impairment on patients' well-being.

In this study, we hypothesised that the functions of the smell, taste and sexuality are impaired due to dryness of the mucosal linings in pSS patients (Primary hypothesis), and that this impairment compromises the QoL and the mental health status of these patients (Secondary hypothesis).

This is the first study that presents the collective effect of the senses dysfunction, and provides clinical evidence for the need to establish management pathways to address these problems.

CHAPTER 2: LITERATURE REVIEW

2.1 History of Sjögren's Syndrome

A Swedish ophthalmologist, Henrik Sjögren, was the first to give a comprehensive description of the syndrome that later took his name (Manthorpe et al., 1981, Jonsson and Brun, 2010). In his doctoral thesis in 1933, Sjögren detailed his findings, clinical and histological, in a study of 19 women suffering from xerostomia and keratoconjunctivitis sicca, 13 of whom had arthritis (Sjögren, 1933, Jonsson and Brun, 2010). Sjögren's findings shed light on the relationship between oral and eyes dryness, with rheumatic disorders.

Before it was well defined by Sjögren, the syndrome was imprecisely described by Johann Mikulicz in 1892 (Mikulicz, 1937). Mikulicz presented evidence of bilateral painless swelling in the parotid, minor salivary and lacrimal glands of a Prussian man, associated with profuse round cells infiltration, but no symptoms of xerostomia or kerato-conjunctivitis sicca. Mikulicz was not sure of the disease's nature, which led him to describe the case as a "mystery", and to diagnose the condition as a category of lymphoma. In 1925, the term "Gougerot Syndrome'', named after a French dermatologist, was used in France. Gougerot described three cases with severe oral, lacrimal and vaginal dryness, (Gougerot, 1946). This was the first understanding of the sicca nature of the syndrome prior to Sjögren's description.

In 1949, Holm reported a link between salivary and lacrimal glands malfunction with rheumatologic conditions, which facilitated the diagnosis of the syndrome (Holm, 1949). Since the 1960s, the understanding of the nature and aetiology of the syndrome and the correlated clinical and serological measures has been improved. For instance, a link was made between lymphoma and Sjögren's Syndrome by Talal and Bunim (1964), which helped explain Mikulicz findings of relating the syndrome to lymphoma. Thereafter, the first differentiation into primary and secondary was presented by Bloch et al. (1965). The first histologic assessment of the lymphocyte infiltration that occur in the labial glands was suggested by Chisholm and Mason (1968), and the presence of autoantibodies (Ro/SSA) found in blood serum was first described in 1969 by Clark et al. (1969), which has now become a clinical objective measure for the diagnosis of the syndrome.

2.2 Classification and diagnostic criteria

Sjögren's syndrome (SS) is categorised into two types, primary (pSS) and secondary (sSS) (Kassan and Moutsopoulos, 2004, Mitsias et al., 2006, Jonsson and Brun, 2010). The latter occurs in conjunction with other autoimmune diseases, such as Rheumatoid Arthritis (RA) or Systemic Lupus Erythematosus (SLE), whilst pSS presents on its own (Jonsson and Brun, 2010). The first illustration for this classification was suggested by Bloch et al. (1965).

Since then, the need to establish unique criteria to serve as a clinical diagnostic standardization for SS patients was raised. This was deemed necessary, to provide comparable data, which is an essential requirement for research purposes. This concern led to the presentation of the Preliminary European Classification criteria by a multicentre project between 1988 and 1996 (Vitali et al., 2002). Ever since it was released, the European criteria has largely been employed in observational and interventional studies, as well as in clinical practice. These criteria set were based on six items; any four out of the six items meet the diagnosis of pSS. These items included (a) ocular symptoms (subjective), (b) oral symptoms (subjective), (c) ocular signs (objective, defined by positive Schirmer-1 test and/or Rose Bengal score), (d) salivary glands involvement assessed by parotid sialography, scintigraphy and unstimulated salivary flow rate, (e) focus score assessed by salivary gland biopsy, (f) the presence of autoantibodies represented by antinuclear antibodies (ANA), rheumatoid factor and/or anti-Ro and anti-La/SSB.

However, a number of criticisms was raised after releasing these criteria set. The main one being the possibility of fulfilling the criteria in the absence of either positive salivary glands biopsy or positive autoantibodies. This means that patients with sicca symptoms (dry eyes and mouth syndrome without evidence of autoimmune disease present) who are not showing autoimmune antibody might also be classified as pSS with these criteria. Hence, between 1998 and 2002, the European criteria were revised by experts from America and Europe after conducting another study on a different study group to improve accuracy, whilst maintaining the previous scheme of the original criteria. The revised criteria is known as the American-European Consensus Group criteria (AECG) (Appendix 1) (Vitali et al., 2002). Its strength lies in the obligatory inclusion of one of the

two objective measures; positive histology and/or presence of autoantibodies. This resulted in an accurate diagnosis clinically and a better-defined pSS group of patients. This made the research results of investigations using these criteria more reliable and consistent. In fact, since its publication, the AECG criteria have been used in more than 1300 studies around the world (Vitali et al., 2013), which supports its credibility and global acceptability.

Subsequent to the publication of the AECG criteria, the Sjögren's International Collaborative Clinical Alliance (SICCA), was established in the USA to oversee an international SS depository of clinical data to serve as supporting information for future SS studies (Daniels et al., 2009, Whitcher et al., 2010, Daniels et al., 2011, Malladi et al., 2012, Shiboski et al., 2012). The project was multicentre, conducted as a collaboration between the USA and several other sites across the world including the UK. A large number of patients (n=2090) were recruited for this observational study. The investigators used the AECG criteria to recruit their study group to come up with a new set of diagnostic criteria, which dictated that for the diagnosis of pSS patients must have at least two of the following three items: (a) positive anti-Ro and/or anti-La antibodies, or positive rheumatoid factor and antinuclear antibody; (b) positive keratoconjunctivitis sicca, with an ocular staining score of more than three; (c) positive results of labial glands biopsy defined by a lymphocytic focus score of more than one focus/4mm2 (Shiboski et al., 2012). In addition to the built in bias of study group selection in this study, the resulted diagnostic criteria was not supported by evidence, but rather depended on observation in a large number of patients. Although the authors of the SICCA study presented their results as superior to the previously published criteria, others have shown that a misclassification can occur especially when patients meet only one of the SICCA criteria, and presenting with oral and ocular complaints of dryness, which both have not been included in these criteria (Vitali et al., 2013). Interestingly, the SICCA team ignored including two important symptoms of SS, these were the mouth dryness and/or the increase in the DMF score. Although the SICCA team acknowledged the importance of these two symptoms and that they were considered for years as manifestations of the hallmark of SS diagnosis.

Additionally, unlike the AECG criteria, the SICCA criteria does not discriminate between the subdivisions of SS (primary and secondary SS). A number of studies have shown that there is a distinction between the two subdivisions in terms of the degree of associated arthritis, presence of certain autoantibodies, severity of oral manifestations, levels of certain proinflammatory cytokines, B lymphocyte titre and even in the proteomic constituents of saliva (Tsampoulas et al., 1986, Gal et al., 2000, Shiari et al., 2006, Hernandez-Molina et al., 2010, Baldini et al., 2011, Furuzawa-Carballeda et al., 2014, Hwang et al., 2014). Therefore, differentiation between the two subtypes of the syndrome is important. The question remains whether there was a need to come up with a new criteria altogether taking into account that the AECG criteria has been used successfully for a number of years including in the SICCA study.

Rasmussen et al. (2014) have conducted a comparison between the, the AECG and SICCA criteria, on 837 participants in Minnesota, USA. The comparison showed that there was no significant difference (p=0.19) in classifying SS patients using both systems. Similarly, a literature review by Bowman and Rao (2014) concluded that the SICCA criteria cannot be considered as a novel scheme.

A newly published set of criteria that combined features of the SICCA and AECG criteria, were recently validated and called the American College of Rheumatology (ACR)-European League Against Rheumatism (EULAR) (Tsuboi et al., 2017). The methodology of these criteria was based on data and clinical judgement of experts, and a final definition of pSS was based on five objective items. These were the presence of focus score of ≥1 (based on number of foci/4 mm^2), positive anti-SS-A/Ro, ocular staining of ≥5 (or Van Bijsterveld Score of ≥4), Schirmer's test of ≤5 mm/5 min on at least one eye and unstimulated salivary flow rate of ≤0.1 mL/min. The performance of these criteria showed higher sensitivity but lower specificity than the most widely accepted diagnostic criteria of the revised Japanese criteria (Fujibayashi et al., 2004), AECG and ACR criteria. A high specificity, which the new criteria lacks, is an important aspect of diagnostic criteria, because it prevents subjects without pSS to fulfil the diagnosis and to enter clinical studies or trials. Consequently, there is a strong argument in favour of using the AECG criteria in diagnosing pSS patients.

2.3 Epidemiology

2.3.1 Incidence

Studies of the incidence of primary Sjögren's Syndrome (pSS) from around the world are summarised in table 2-1. The reported incidence of SS was found to be ranging from 3.9 in the period 1976-1992, to 11.8 in the period 2005-2009.

A study from Olmstead County, Minnesota, USA, reviewed the data retrospectively between the years 1976 and 1992 with a total reached population of 108,145 in 1992, found that the annual incidence of pSS was 3.9 per 100,000 (95% CI=2.8-4.9). The study reported that when age was adjusted, the female to male ratio was 13:1 (Pillemer et al., 2001). It is worth noting that this study was based in one state in the USA and therefore not necessarily representative of the whole of the USA.

Interestingly, another study conducted in Slovenia by Plesivcnik Novljan et al. (2004), concluded annual incidence of pSS as 3.9 per 100,000 (95% CI=1.1-10.2), exactly the same as the above USA study, despite the difference in the study setting and population. The researchers examined the clinical records prospectively from 2000 to 2002, with a total population of 599,895 and a female to male ratio of 11:1. The study sample was representative of the whole country's population.

A further prospective study, conducted in the northwest of Greece with a total population of 488,435 for the period from 1982 to 2003. The study reported an incidence of 5.3 per 100,000 annually (95% CI=4.6-6.3), with a female to male ratio of 20:1 (Alamanos et al., 2006). The study was conducted in one particular region of Greece that was not representative of the whole country.

Three more studies were conducted in Taiwan (Weng et al., 2011, Yu et al., 2013b, Yu et al., 2013a), and their pooled incidence rate that was reported in a systematic review by Qin et al. (2014), was equal to 6.57 per 100,000 person yearly. It appears that Asians have higher incidence rate than other populations. This could be attributed to the impact of environmental factors that might trigger inflammatory response in susceptible individuals. The sample size and different study designs might also contribute to the

discrepancy in the incidence rate worldwide. In the UK, the frequently quoted incidence rate of SS is 0.6% of adults (BSSA).

All studies agreed that females are by far the most affected gender by SS. The F:M ratio ranges from 9:1 (Talal, 1992) to 13:1 (Ramirez Sepulveda et al., 2017). Despite the difference in the observed female to male ratios, the most quoted and accepted ratio is 9:1 (Bayetto and Logan, 2010, Manthorpe et al., 1981, Jonsson and Brun, 2010, Yee. and Paget., 2005, Jonsson et al., 2002).

Table 2-1 The incidence rate of pSS in both sexes.

Country	Author and date of publication	Study period	Study design	Criteria applied	pSS cases	Population or sample size	Female: male Ratio	Incidence rate (95% CI)/100,000
USA (Minnesota)	Pillemer et al, 2001	1976-1992	Population based (retrospective)	NS[1]	53	108,145	26:1	3.9 (95% CI 2.8 – 4.9)
Slovenia	Plesivcnik et al, 2004	2000-2002	Population based (retrospective)	European	71	248	11:1	3.9 (95% CI 1.1 – 10.2)
Greece	Alamanos et al, 2006	1982-2003	Population based (retrospective)	AECG[2]	422	500,000	20:1	5.3 (95% CI 4.6 – 6.1
China (Taiwan)	Weng et al, 2011	2005-2007	Population based (retrospective)	NS	3352	23 million	10:1	6 (95% CI 5.8 – 6.2)
China (Taiwan)	Yu et al, 2013	2000-2008	Population based longitudinal	ICD codes system[3]	855	1143	6:1	10.6 (95% CI 9.9 – 11.4)
China (Taiwan)	See et al, 2013	2005-2009	Population based	ICD codes system	583	4,953,660	6:1	11.8 (95% CI 10.8 – 12.7)

1: Not specified
2: American European Consensus Group Criteria
3: International Classification of Diseases

2.3.2 Prevalence

The prevalence of pSS varies between studies, depending on the diagnostic criteria applied and the study design conducted. It is known that the prevalence of any disease depends on its duration and incidence rate (Hennekens C and Buring J, 1987). Therefore, with incurable diseases the rate of incidence should be lower than that of the prevalence. This is confirmed in table 2-2 (Also see table 2-1), which enlists the available studies about the prevalence of pSS in different countries chronologically.

Table 2-2: The prevalence of primary Sjögren's Syndrome worldwide.

Country	Author, date of publication	Study Design	pSS cases	Total population	Criteria applied	Prevalence rate (95% CI)/ 100,000
UK	Whaley et al, 1972	Hospital based	4	122	NS	3300
USA Washington	Strickland et al, 1987	Retirement home based	2	103	NS	1900
Greece	Drosos et al, (1988)	Cross-sectional	3	62	European	4838
China	Zhang et al, 1995	Community Population Survey	16 7	2066	Copenhagen San Diego	770 330
Japan	Miyasaka et al., 1995	Population based	17000	~120,000,000	Japanese	1.9 males 25.6 females
Denmark	Bjerrum (1997)	Prospective population study	1 3	504	Copenhagen European	200 - 800 600 - 2.100
Greece	Dafni et al, 1997	Population Survey	5	837	European	600 (95% CI 190 - 1.390)
Slovenia	Tomsic et al. (1999)	Population Survey	2	332	European	600 (95% CI 70 – 2.160)
UK	Bowman et al, 2004	Population Survey	2	846	AECG[1]	100 - 400
Greece	Trontzas and Andrianakos (2005)	Population Survey	13	8740	AECG	150 (95% CI 90 - 210)
Mexico	Sanchez et al., 2005	Hospital based	40	300	AECG	2,700 (95% CI 900 – 4500)
Greece	Alamanos et al. (2006)	Population Based	422	488,435	AECG	92.8 (95% CI 83.7–101.9)
Turkey	Kabasakal et al, 2006	Cross-sectional population survey	6 13	831	AECG European	720 (95% CI 330 – 1.570) 1560 (95% CI 920 – 2.660)
Norway	Haugen et al, 2008	Population survey	155 69	2864	AECG European	220 (95% CI 150 - 320)[2] 1400 (95% CI 1.020 – 1.920)[3] 440 (95% CI 340 - 570)[2] 3390 (95% CI 2.770 – 4.140)[3]
Turkey	Birlik et al, 2009	Population Survey	6 10	2835	AECG European	210 (95% CI 30 - 290) 350 (95% CI 100 - 450)
Greece	Anagnostopoulos et al. (2010)	Cross-sectional population survey	4	1705	AECG	230 (95% CI 220 - 750)
Norway	Goransson e t al, 2011	Population Based	424	852,342	AECG	50 (95% CI 48 - 52)
Denmark	Eaton et al, 2011	Population Based	2615	5,472,032	ICD-10 [4]	48 (95% CI 45-49)
Italy	Sardu et al. (2012)	Population Based	10	2887	European	31 (95% CI 13-61)
China (Taiwan)	See et al. (2013)	Population Based	583	1,000,000	ICD-9[5]	58.3 (95% CI 53.6 - 63.0)
France	Maldini C et al, 2013	Cross-sectional	133	1,172,482	AECG	10.2 (95% CI 8.5 – 12.2)
China (Taiwan)	Yu et al, 2013	Population based longitudinal study	154	963,355	ICD-9	16 (95% CI 4.3–18.7)
Brazil	Valim et al. (2013)	Cross-sectional population survey	2	1205	AECG	170 (95% CI 20 – 598.3)

1: American European Consensus Group Criteria

2: ages 40-44 years;

3: 71-74 years;

4: International Classification of Diseases-10th version;

5: International Classification of Diseases-9th version

NS: Not specified

2.4 The relationship of the clinical variables and QoL

SS has been shown to negatively affect the general and oral health related quality of life of patients (Strombeck et al., 2003, Lopez-Jornet and Camacho-Alonso, 2008). The mental health well-being was found to be markedly affected in SS patients that can be characterised by a combination of anxiety and/or depression (Bongi et al., 2013, van Nimwegen et al., 2015). Mucosa-associated dryness is the main clinical feature of SS that can affect the function of the related organs and interfere with the quality of life. In order to facilitate understanding the relationship between the clinical variables and the health-related quality of life, Wilson and Cleary (1995) proposed a conceptual model of patients' outcome that was revised and simplified later on by Ferrans et al. (2005) (Figure 2-1). The revised Wilson and Cleary model encompasses the following:

- Biological and physiological variables
- Symptom status
- Functional status
- General health perception
- Overall quality of life
- Oral health related quality of life

This was applied to the current literature review as below:

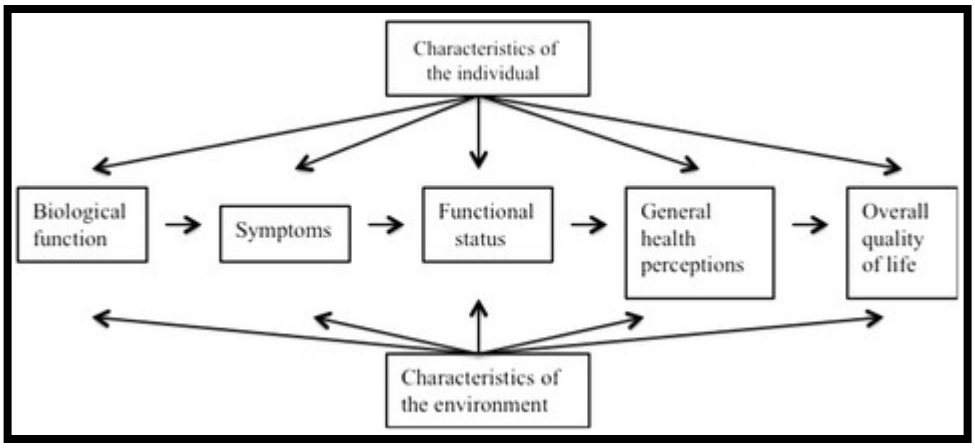

Figure 2-1 The revised conceptual model

2.5 BIOLOGICAL AND PHYSIOLOGICAL VARIABLES IN SJÖGREN'S SYNDROME

2.5.1 *Smell*

1. Physiology of smell

The sense of smell was described as the sentinel of the brain by Critchley (1986). It plays an important role in the safety, quality of life and nutrition, as it determines foods and beverages smelling, and provides a warning bell for hazards detection as in rotted food (Christopher Hawkes and Doty, 2009). The same authors viewed this sense as an indicator of brain function.

The olfactory area is lined with special kind of epithelium, in which its mucous is secreted from specialized mucous secreting glands called ''Bowman's glands''. Whilst the rest of the nasal cavity structures (bony, cartilaginous and turbinates) are covered by ''mucous-secreting respiratory epithelium'' (Menco, 2003).

The mucous membrane in the olfactory area plays significant role in the smell perception of odorant molecules. This is achieved by transferring signals through specialised receptors on the cilia of the lining epithelium to the brain centres (Imamura and Hasegawa-Ishii, 2016). The process includes two actions: first, the transfer events of odours to the nasal neuroepithelium, and second, the processing of these information into the brain, especially the olfactory bulb and the higher brain centres (Breer, 2008).

The general somatic innervation of the nose, especially the lining mucosa is derived from the trigeminal cranial nerve (CN V), while the involuntary autonomic nerve supply comes from the sphenopalatine ganglion. Additionally, the upper part of the nasal cavity is supplied by branches of the nasociliary nerve, whereas the posterior part is nourished by branch of the maxillary nerve (nasopalatine nerve) (Sinnatamby, 2006).

2. Odour coding mechanism

Odorant molecules are usually classified into hydrophobic and lipophilic particles with different binding affinities that lock onto the smell receptors (Amoore, 1967). The main function of these molecules, is to pass the aqueous barrier of the nasal mucosa, an activity which in some cases assisted by soluble protein molecules called ''odorant binding

proteins'' (Briand et al., 2002). Therefore, this mechanism is highly influenced by the amount of mucosa wetness in the nasal cavity.

Some odours are similar in their chemical structures but exert different smell. Moreover, odorants can be recognized by more than one receptor, while on other occasions, a single receptor is able to differentiate a variety of other odours (Christopher Hawkes and Doty, 2009). Thus, it is still unclear to explain the olfactory system works. But generally, it can be pointed out to important structure named amygdala, which is responsible to process the olfactory signals (Hudry et al., 2001). The amygdala is located in the anterior temporal lobe of the brain (ibid), which can be activated by pleasant and intense odours (Zald and Pardo, 1997, Anderson et al., 2003). The amygdala has a considerable input from the olfactory bulb, and it is connected to a number of brain parts (basal ganglia, orbitofrontal cortex, thalamus and hypothalamus). The piriform cortex, which is located in the anteromedial temporal lobe in the brain, together with the amygdala react in accord to the valence, intensity and memory of an odour, to be processed later by another centre, mainly the orbitofrontal cortex; in which finally represented by specific smell sensation to an odour (Christopher Hawkes and Doty, 2009).

3. Types of smell dysfunction

Smell dysfunction was described and classified into different terminologies in accord to their severity and the way of perception. Table 2-3 highlights each term with a brief definition.

Table 2-3: Definitions of smell disorder terms by Hawkes (2002), p:50

Term	Definition
Anosmia	Loss of the sense of smell
Hyposmia or microsmia	Decline of smell sensation
Dysosmia	Impairment of the sense of smell
Parosmia or troposmia	Dysfunction due to specific stimulus
Phantosmia	Impairment when there is no external stimulus
Cacosmia	Unpleasant smell
Torquosmia	Burning type of distortion
Hyperosmia	Increased sensitivity of smell sensation
Osmophobia	Certain smells dislike
Heterosmia	Same smell for all odors applied
Presbyosmia	Deterioration of the sense of with age

4. Factors influencing the acuity of Smell

- **Diseases**

A number of common diseases can have a negative impact on smell function. These diseases vary from simple cold to neurodegenerative disorders. Christopher Hawkes and Doty (2009) categorized in a list the main types of diseases that affect the quality of smell including SS (Table 2-4). There are only a few studies providing evidence of the effect of SS on smell (Henkin et al., 1972, Weiffenbach and Fox, 1993, Porter, 2010). These studies provided valuable assessments and results but did not attempt to relate the change in smell function to the degree of dryness.

Table 2-4: List of the main types of diseases that have an impact on olfaction by Christopher Hawkes and Doty (2009), p:117

Disease	Type
Local nasal infection	Polyps, allergic rhinitis, sinusitis, common cold, influenza, AIDS, prion disease, fungal infection.
Head injury	Usually in the posterior or lateral part of the head.
Epilepsy	Olfactory aura, complex partial seizure
Migraine	Before, during or after attack
Multiple sclerosis (MS)	During relapse or in advanced stages.
Tumors and inflammatory diseases	Nasopharyngeal carcinoma, Wgener's granulomatosis, olfactory groove meningioma or neuroblastoma, facial Paget disease, **Sjögren's Syndrome**
Endocrine	Diabetes, Addison's disease, Cushing and Klinefelter syndromes, pseudohypoparathyroidism, Kallman syndrome, septo-otic dysplasia
Neurodegenerative	Parkinson's disease, Alzheimer's disease, dementia

- **Age**

The effect of ageing on the quality of olfaction after the sixth decade of life is generally agreed, but this is not clear in relation with gender. Kamel et al. (2009) found a negative correlation between smell and age in pSS patients compared with controls. Although the authors attributed the smell dysfunction to dryness in pSS group, there was no attempt to measure the severity of mucosal dryness, neither subjectively nor objectively. Bhattacharyya and Kepnes (2015) conducted a self-assessment cross-sectional survey for smell disorders on 142 million of American adults, and observed that 10.6% of the participants reported increasing prevalence of smell dysfunction with increasing age. The cause of anosmia was also attributed to the environmental factors, which has an accumulative damaging effect on the nasal epithelium throughout life (Christopher Hawkes and Doty, 2009, Doty and Kamath, 2014). The same authors as well as Doty et al. (1984),

Doty et al. (1996) and Hummel et al. (2007), have referred the impairment of the smell function to the ageing effect on the reduction rate of protein synthesis, reduced intramucosal blood flow and high mucus viscosity in the olfactory epithelium.

- **Gender**

Women score slightly higher on identification tasks at all ages (Doty et al., 1984, Hummel et al., 2007). However, unlike age, the evidence in the literature suggests that gender does not have a direct impact on smell dysfunction. These observations were also supported by Kern et al. (2014) findings, where a lack of association was shown between gender and smell dysfunction. Hayes and Jinks (2012) presented evidence, which showed that both age and sex do not seem to have influence on olfaction, despite the more accurate guessing of women to the correct odour than men ($p=0.001$).

- **Smoking**

Studies on animals showed that the exposure to volatiles that come from burning tobacco, could damage the olfactory neuroepithelium. Vanscheeuwijck et al. (2002) have described the pathology of the upper respiratory tract epithelium in a study that used rats to expose ''nose-only'' to either fresh air or mainstream cigarette smoke. There was noticeable basal cell hyperplasia, squamous metaplasia and goblet cell hyperplasia in the study group of rats. Perhaps due to the fact that hyper activity of the respiratory epithelium is a protective response, there is hardly ever anosmia seen with smoking persons.

Although Hayes and Jinks (2012) found that smoking affect odorants threshold levels of olfaction, recent observations on patients with Parkinson's disease (PD) by Lucassen et al. (2014), refuted that assumption. Hayes and Jinks (2012) suggested that the quality of smell identification sense is associated with the duration of smoking history. Doty et al. (1984), Frye et al. (1990) and Sharer et al. (2015) believe that there is a considerable difference in the smell identification test scores, between smokers and non-smokers when age is adjusted.

- **Pollution**

Attention has been recently focused on the impact of environmental pollution on olfaction, between rural and city residents. For example, a study by Hudson et al. (2006) compared the olfactory function between residents of Mexico city, which has high ambient air pollution, and residents of the state of Tlaxcala; a region that is geographically similar to Mexico city, but with low air pollution. It was concluded that the city "long-term'' residents have impaired sensation of olfaction compared with the "long-term'' residents of Tlaxcala state. The state's subjects were able to detect the smells of orange and coffee at lower concentrations, more than those of the city participants. Although the study did not provide a strong evidence of the olfactory epithelium damage by pollution, this research succeeded in demonstrating a significant difference in the olfactory function between subjects live in rural dwellings, and those live in polluted conurbations. Especially, after adjusting for the influential variables, such as age, altitude, socioeconomic levels of participants, climate and having the same administrator to carry out the study. Findings by Hudson et al. (2006) were the first to show the effect of air pollution on olfaction. More studies, later on, were able to support the previous findings, and showed that the accumulative effect of environmental factors have a negative impact on olfaction (Christopher Hawkes and Doty, 2009, Sorokowska et al., 2013, Guarneros et al., 2013, Doty and Kamath, 2014).

- **Medications**

In comparison with taste, most medications have little effects on smell. Long-term consumption of certain drugs might have an impact on olfactory quality function. Little evidence is available to support this. Most of the available evidence are based on personal reports, and thus no quantitative comparisons have been carried out. Hawkes and Doty (2009) suggested that the disease itself could cause smell dysfunction, instead of the medication used for treating it. Whereas two studies reported that some kinds of antihypertensive therapeutics, especially calcium channel blockers, have high percentage of side effects on both smell and taste function (Deems et al., 1991, Doty et al., 2003). Deems et al. (1991) who conducted a study on 750 patients in Pennsylvania University in the US, attributed the reason to the impairment of "electro-olfactogram'' impulse

transmission, which is a calcium-mediated mechanism to the olfactory bulb (Restrepo et al., 1990). Hawkes (2002) mentioned that lipid lowering agents, antibiotic, antifungal, antithyroid, antidepressant, antiepileptic and nasal decongestant, can also have an adverse impact on olfaction.

Welge-Lussen et al. (2004) and her team have successfully proved that the intranasal local anaesthesia, is capable of reducing olfaction acuity temporarily, but unable to abolish its activity (Welge-Lussen, 2004). Despite the fact that this study was conducted on 20 participants only, it presents evidence of the effect of local anaesthetization on the neurology of olfaction. Hence, subjects complaining from smell disorder after surgical operations, should consider the impact of the general anaesthesia used in the operation, and may allow its effect to resolve spontaneously.

- **Head trauma**

Head injury is one of the commonest causes for olfactory dysfunction. In a recent systematic review by Schofield et al. (2014), the negative impact of head injury was reported. The review highlights the finding of 25 studies on the effect of head injury on olfaction; although the review considered language and publication restriction, the scientific value of the study cannot be hidden. According to Jafek et al. (1989) explained the reason of the traumatic brain injury impact on olfaction from neurological point of view. The authors believed that the problem is due to the damage of the olfactory nerve fibres that emerge from the cribriform plate, in their pathway to enter their destination in the olfactory bulb. The skull does not necessarily need to fracture in order to inversely affect olfaction. A blow or even a whiplash could be sufficient to cause smell dysfunction (Delank and Fechner, 1996).

- **Congenital abnormalities**

Congenital anosmia is a very rare condition, where individuals experience complete loss of smell sensation since birth. It was believed that the condition is solely due to olfactory bulb agenesis (Qu et al., 2010), but recent studies indicated the presence of gene mutations, that have a significant role in the transduction of olfactory signals to the brain (Moya-Plana et al., 2013, Karstensen et al., 2015). This gene mutation is X-linked chromosome, which is

dominantly found in males and mainly transmitted by male to male; but has also been occasionally observed in females by Chen et al. (2013b).

5. Measurement of smell

There are numerous tests described in the literature for the assessment of patients' ability to smell. Identification tests that are used in clinics rely on the patients' ability to identify odours, whilst threshold tests rely on the ability to detect low concentrations of odours. Identification tests are the most widely used and can be self-administered sometimes as in the University of Pennsylvania Smell Identification Test-40 (UPSIT-40) (Doty et al., 1984). The test consists of scratch and sniff of 40 odorants, and a shorter version of 12-item is also available for quick clinical screening purposes (Doty et al., 1996). If smell dysfunction is detected by the shorter version, further assessment is usually recommended.

Other commonly used smell identification test is the Sniffin' Sticks Test (SST) which has been developed by Kobal et al. (1996). The test comprises of multiple pen-like devices, each of which has a particular odorant. The patient will recognize smells through 16 sticks and should choose the relevant option from the four choices provided (forced choice test) in a separate sheet. The reliability of this test is less than that of the full UPSIT but it is comparable to the shorter version of it. Later on, an extended version of SST called TDI index has been developed by Ahne et al. (2000) to be more reliable, which was tailored to assess the three main elements of the chemosensory smell function, these are threshold, identification and discrimination (where patients have to determine which of the sticks smells differently) via 48 sticks which requires long time to be conducted and professional trained supervision compared to the ordinary identification version of SST and UPSIT.

6. Review of the research showing smell dysfunction in patients with Sjögren's Syndrome

PSS patients frequently report olfactory disorders and only a few studies looked at the problem in these patients. In a pioneering study by Henkin et al. (1972), a high percentage (90%) of smell dysfunction was found in SS patients. The authors attributed the results to the dryness of the nasal mucosa that was reported by 92% of the patients. Although this

study provided evidence of the smell dysfunction in these patients, they recruited a rather limited number of mixed syndromes: 11 secondary SS, 14 sicca syndrome, two SLE and two pSS patients only who were diagnosed based on clinical judgement. Similarly, a study by Kamel et al. (2009) reported significant deterioration of smell function (43%) and suggested that the deficit in olfaction was because of the nasal mucosa dryness in pSS patients and suggested that the reported impaired quality of life was influenced by the smell dysfunction. They also reported that the smell was adversely associated with age in pSS patients. Although the study used the reliable AECG criteria in diagnosing pSS patients, the main weakness in this study being the small sample size of the patients recruited (n=28).

Four more studies in the literature have compared the smell function in SS patients but no attempt was made to investigate whether the smell was associated with the severity of the mucosal dryness. In a clinical trial by Rasmussen et al. (1986) who evaluated the sensitivity to the odour of coffee in 36 SS patients, has failed to demonstrate a deficit of the smell function in pSS patients. Another small Chinese study by Su et al. (2015b) that assessed the smell identification by the sniffin sticks in 15 SS subjects and 32 patients with burning mouth syndrome (BMS). The study reported no significant difference between the two groups (SS=10.7, ±3.5, BMS=11.8 ±2.6, p=0.21), although reporting lower smell scores in SS patients compared with BMS subjects. A recent small study by Rusthen et al. (2017) reported significant olfactory disorder in 31 pSS patients compared with 33 healthy controls. The authors argued that the reason for the smell dysfunction in pSS patients was the systemic inflammatory process associated with the syndrome, which contradicts findings of a previous study where no significant association was found between the impairment of olfactory performance and the inflammatory markers of the syndrome activity (Weiffenbach and Fox, 1993).

There is contradiction in the literature not only on the association of the smell dysfunction in SS, but also on its aetiology.

2.5.2 *Taste*

1. Physiology of taste

Taste buds are distributed mainly over the tongue, and to a lesser extent on the pharynx and the oesophagus. Each taste bud consists of cluster of receptors in which they aggregate to form swellings or tiny prominences called papillae, which are divided into four types named after their grouping pattern: circumvallate, foliate, filiform and fungiform. A central pore is located at the apex of each bud to permit the entry of fluids, hence, moisture plays an important role in its function. The large fungiform together with circumvallate papillae are found on the root of the tongue. The foliate papillae are found on the posterolateral margins of the tongue, and the filiform papillae are spread on the dorsal surface of the tongue.

Multiple pathways serve the nerve supply of the tongue; therefore, it is unlikely to have a complete taste loss. The four cranial nerves that supply the tongue are V, VII, IX and X. The common touch, temperature and pain sensation through the anterior two thirds of the tongue is fed by trigeminal nerve (V) by its lingual branch. The posterior third, along with the surrounding soft palate, are supplied by glossopharyngeal nerve (IX), and the taste sensation of the anterior two thirds, is perceived by the chorda tympani, a branch from the facial nerve, which also contains secretomotor fibers that supply the sublingual and submandibular salivary glands (Sinnatamby, 2006). The chorda tympani conveys taste stimuli from the taste buds to the brain centres. Experts are of the opinion that if a lesion or neuropathy damages the nerves that are responsible on taste can cause hypogeusia, and where a damage affects the salivary glands, mouth dryness and in turn compromised taste function may occur (Malaviya and Ramu, 1981, Spector and Stark, 1983, Okuda et al., 1994, Hashimoto et al., 2012). These findings need to be supported by further studies, and a study with SS would help.

2. Types of taste dysfunction

Taste dysfunction is reflected in various terms, which explain the severity of each abnormality according to the individual perception. Table 2-5 illustrates each term with brief definitions.

Table 2-5 Taste abnormalities definitions by Hawkes (2002), p: 125.

Term	Definition
Ageusia	Loss of the sense of taste
Hypogeusia or microgeusia	Decline of taste sensation
Dysgeusia	Distortion of the sense of taste
Parageusia	Taste distortion due to specific stimulus
Phantogeusia	Taste distortion with no stimulus
Cacogeusia	Unpleasant taste
Torquegeusia	Burning taste
Hypergeusia	Increased taste sensitivity
Gustatophobia	Certain taste dislike
Heterogeusia	Same taste for all tastants applied
Presbygeusia	Reduction of taste sensation with age

3. Factors that Influence taste sensation

Several factors are known to affect the quality of taste perception. The following review will consider the main factors that are thought to mostly affect the taste function.

- **Diseases**

There is a number of diseases and conditions known to have adverse effect on the taste sensation (Table 2-6). These diseases varied from simple infections to neurodegenerative dysfunction. Hawkes (2002) enlisted the commonest diseases associated with taste disorders where SS was included. In Yamamoto et al. (2009), it was found that taste buds atrophy is noticeable in SS patients due to decreased salivary flow rate. The study relied on a digital microscope only in its investigations, with no attempt to test the function of the sense of taste in this study group. Another study by Enger et al. (2011) pointed to the effect of pSS on taste alteration in 49% of pSS patients with high oral distress ($p<0.001$) out of 177 patients. Although the response rate of this study was good (72%), the results were not confirmed objectively. However, in this area of research, there is no publication examined the change in taste perception to the degree of oral dryness in pSS patients, which is known to be part of the syndrome.

Moreover, it has been recently reported by Nagai et al. (2015), that depression is inversely correlated with the sweet taste threshold ($r=-0.472$, $p=0.031$). This supports the relation between mental health status and taste perception. Similar findings were reported by Karita et al. (2012) and Naudin et al. (2015), who all agreed that taste acuity perception depends, to some degree, on the mental health status of patients.

There is evidence showing that Parkinson's disease, chronic hepatitis C, and HIV have an adverse impact on taste sensation (Shah et al., 2009, Musialik et al., 2012, Raja et al., 2013). Deems et al. (1991) found that dysgeusia was reported in higher percentage of patients suffering from upper respiratory tract infection and nasal sinus diseases compared with other conditions. Therefore, in the current project we excluded participants with any disease other than SS, with possible impact on taste. The following table, which is quoted

from Hawkes (2002), highlights the commonest diseases that have an impact on the taste perception.

Table 2-6 The commonest diseases that have negative impact on taste perception, by Hawkes (2002).

Diseases	Type
Tumors	Middle ear tumor, jugular foramen tumor
Trauma	Petrous bone fracture, neck injury damaging glossopharyngeal nerve, cortical trauma, orbitofrontal cortex injury
Surgical procedure	Bilateral thalamotomy, laryngectomy, neck radiation, middle ear surgery, tracheal intubation
Vascular disorder	Lateral medullary syndrome, pontine hemorrhage, internal carotid artery dissection
Systemic disease	Type I & II diabetes, cystic fibrosis, renal failure, familial dysautomia, primary amyloid, Cushing's disease, cretinism, cranial arteritis, **Sjögren's syndrome**
Infection	Bell's palsy, viral encephalitis, influenza, leprosy, periodontitis, glossitis, Guillan-Barre syndrome, AIDS
Deficiency states	B3 and B12, vitamin A, zinc
Psychiatric	Depression, schizophrenia
Developmental	Congenital facial hypoplasia

- **Age and gender**

The influence of age and gender on the sense of taste has been explored in a number of studies. Mojet et al. (2001) reported significant loss of taste threshold in older people ($p<0.003$), but the gender did not contribute to the taste loss. Similar findings by Ng et al. (2004) who reported that taste threshold of older subjects (0.414, ±0.366, $p=0.001$) was significantly higher than that of young (0.084 ±0.057, $p=0.001$) and middle aged participants (0.082, ±0.076, $p=0.001$). Findings by Suchecka et al. (2012) also concluded that the intensity of the salt taste response decreases with ageing process, especially over the age of 50. The study pointed to a gender discrepancy, in that women were more able to recognize salt taste compared with men ($p=0.05$). However, others did not support the above assumption, but found that age does not have an adverse effect on taste acuity

(Mojet et al., 2003, Mojet et al., 2005, Kamel et al., 2009). Further investigations are needed to resolve the above contradictions.

- **Medications**

Many drugs are excreted in saliva, and hence, it is envisaged that drugs can impair taste function either by adversely affecting the neural transduction mechanism of the taste buds or by presenting the drug's taste itself (Henkin, 1994). However, Henkin, 1994 believed that taste dysfunction could be restored after therapy termination, while effects that continue to persist might necessitate treatment to alleviate the symptoms. Nevertheless, and according to Hawkes (2002), who deemed that the disease itself could cause the adverse effect on the taste perception, rather than the drugs used in its alleviation. It has been shown that the drugs used to treat diseases such as asthma, muscular spasm, depression, sleeping problems and cardiovascular diseases, can cause mouth dryness and affect taste perception (Casaburi et al., 2002, Godara et al., 2011, Suliburska et al., 2012). Notably, it is thought that zinc deficiency which is caused by prolonged injection of β-lactam antibiotics for the treatment of some diseases, has also a negative impact on taste sensitivity (Jones et al., 1987). However, Negoro et al. (2004), presented different observation, in which serum zinc that is measured in SS patients, in comparison with sicca sufferers does not significantly correlate with their taste sensitivity. This finding partially agrees with that of the systematic review by Nagraj et al. (2014), who found very low quality evidence of the impact of the zinc supplement on taste function.

- **Smoking**

The effect of smoking on taste perception has been studied and conflicting findings were obtained. A study was conducted in 1961 by scientists from South Africa, who recruited 156 medical students, half of whom were smokers Krut et al. (1961). The study concluded that the taste acuity of smokers did not significantly differ from that of non-smokers for sweet, sour and salt, while the perception of tasting bitter was the worst among smokers. This can be attributed to the prolonged practice of the habit. This finding was confirmed by others who believed that taste perception was not affected neither in smokers nor non-smokers

in their study groups (Shah et al., 2009, Konstantinidis et al., 2010). Asim Mustafa Khan et al. (2016) reached to a different conclusion and found that smoking has a negative impact on taste perception in a group of 30 smokers compared to 30 non-smokers.

It was anecdotally believed that taste returns to normal after smoking cessation. This could be due to the recovered function of the taste buds that were damaged by smoking; however, detailed studies are needed to confirm this belief.

- **Head trauma**

Head trauma has an impact on taste perception since it could damage the brain lobules that expresses taste sensation. Paul J. Schechter and Henkin. (1974) together with Daniel A. Deems et al. (1991), reported altered and decreased taste acuity after head trauma. Participants in their studies performed poorer than normal subjects.

- **Irradiation**

Irradiation could significantly worsen taste function and decreases the subjective taste sensation of patients (Saito et al., 2002, Caputo et al., 2012, McLaughlin and Mahon, 2014). This could be due to the fact that cancer patients who are subjected to radiotherapy and/or chemotherapy, are prone to having poor oral health, psychological status and hence negatively impact the nutritional status, where all of which impact the perception of different senses. In addition, this group of patients are known to have xerostomia caused by radiotherapy (Paterson et al., 2015), that can compromise taste perception.

4. Measurement of taste

The gustatory function of the taste buds was often examined by presenting a variety of aqueous solutions with different concentrations to test subjects (Henkin et al., 1963). However, this approach has several limitations, the main one being the water content that may create environment different from the natural oral circumstances for patients with dry mouth syndrome. In addition, aqueous solutions possess sensitive response to shelf life and room temperature. Therefore, a number of tests that do not rely on aqueous solutions for taste stimulation was developed. These tests comprised of either chewable dried taste

tablets of the four basic taste stimuli (sweet, sour, salt and bitter) (Ahne et al., 2000), or cellulose-based filter papers which impregnated with different concentrations of each tastant (Mueller et al., 2003). Although these approaches have met the requirement of long shelf life, some limitations were found and should be mentioned. The main of which being that the tablets have to be chewed therefore the possibility of regional taste assessment of the tongue is not applicable. For the impregnated filter paper strips, there are reservations about the celluloid texture of the strips, which may not be helpful in testing patients with dry mouth syndrome, but regional taste testing of the tongue is applicable with this test.

The Electrogustometer (EGM) is the only quantitative method available to date for the assessment of the neural function of the taste sensation performed by chorda tympani nerve. The device was first introduced by Krarup (1958), and is widely used in neurological departments for the regional mapping of the neuronal taste sensation thresholds which is expressed in decibels (dB) (Miller et al., 2002, Berling et al., 2011). Ellegard et al. (2007) advised to use the machine as a complementary procedure to the gustatory tests rather than been used as a replacement for them. Using gustatory and neuro-electrogustometry tests provides full picture for the taste function process. One limitation of the EGM worth to be mentioned that the patient may respond to the common sensation, which is supplied by the trigeminal nerve rather than responding to the sensory stimulation by the chorda tympani. However, the sensory threshold of the trigeminal receptors is higher than that for chorda tympani (Miller et al., 2002, Stillman et al., 2003).

5. Review of the research showing taste dysfunction in patients with Sjögren's Syndrome

There is only a few evidence in the literature of the taste function in SS patients. A hypothesis was proposed by Henkin et al., 1972 which stated that the scarcity of saliva lead to a deficit in the ability of transferring signals to the taste buds. The authors also concluded that the dryness of oral mucosa raised the chance of promoting oral microbial infections that usually disturbs taste sensation and recognition. The study was the first that demonstrated taste disorder in 90% of 29 tested patients with SS. Although they provided evidence of the taste impairment in this group of patients, authors of the study assessed

oral dryness by clinical inspection rather than by objective assessment. Additionally, patients were not diagnosed using reliable criteria as the study was conducted before any diagnostic criteria were developed. Moreover, authors of the study reported insufficient objective evidence to establish the diagnosis of SS, therefore, the result of the study may not be applied on SS patients. Henkin and colleagues findings were refuted later by a study performed by Weifenbach et al. (1995), who reported no significant difference of the taste function between SS patients compared with healthy controls, and no impact of saliva scarcity was found on taste. The study appeared to be more reliable than that of Henkin et al., 1972 in its design and number of patients recruited, although they did not apply valid diagnostic criteria.

A decade later, a Japanese study by Negoro et al. (2004) reported 18% taste dysfunction among SS patients, which is lower than that reported previously (Henkin et al., 1972). The study emphasized the impact of oral dryness on the quality of the sense of taste but reported no effect on the neurosensory threshold of taste. Another research by Gomez et al. (2004), showed that all SS patients and matched healthy controls, were able to detect and recognize the four basic tastes (sweet, salty, sour, and bitter) at suprathreshold concentrations. However, SS patients exhibited varied degrees of dysgeusia compared with controls. Mild dysgeusia was observed only for the sweet and salt tasting ability in the SS group, but severe dysgeusia in sour and bitter was recorded compared with controls. The study, however, found no correlation between the scarcity of saliva and the deficit in tasting ability in pSS patients, in agreement with Weiffenbach et al. (1995).

Kamel et al. (2009) concurred Henkin et al. (1972) and Negoro et al. (2004) in suggesting a correlation between oral dryness and taste dysfunction in SS patients, and was the first to assess the impact of taste dysfunction on the QoL of patients. Kamal's study further reported that taste is a robust function throughout the life and that it is not influenced by age, a finding that strongly contradicts others who found that taste was deteriorated with aging process (Gomez et al., 2004, Suchecka et al., 2012). The study found a significant reduction in the QoL of pSS patients (n=28) compared with the healthy controls (n=37), and

referred this reduction to the chemosensory impairment of the smell and taste functions together. About 70% of pSS patients of the same study were suffering from hypogeusia. However, salivary flow rate measurement was not employed equally for all participants. Therefore, reporting a correlation between oral dryness and taste impairment may not be applicable in pSS patients. Kamel and colleagues have also studied the relation between the functions of the smell and taste in pSS patients, and reported a strong correlation between both functions. Kamal's findings supported previous study by Dzaman et al. (2005) who concluded that individuals with smell impairment had problems in correctly identifying the basic tastes. However, other studies believed that the sense of smell is not correlated with that of taste (Stinton et al., 2010, Fasunla et al., 2012, Ros et al., 2012, Chen et al., 2013a). Although the study used the reliable criteria of AECG in diagnosing patients, the low number of population employed did not allow for formal hypothesis testing, which is a general weakness of all of the above-mentioned studies. Therefore, the evidence in the literature regarding the correlation between both senses is unclear.

A recent small study on 31 pSS patients who were diagnosed by AECG criteria, reported poor olfactory and gustatory function that are not correlated with the depletion of salivary secretion (Rusthen et al., 2017). The study also reported impaired oral health quality and referred the reason of the oral health problems to the taste impairment, burning sensation of tongue and halitosis. The same study reported weak association between gustatory function with age, medications or disease duration, but a strong correlation with olfactory function in pSS patients However, with the limited number of patients recruited for the study, this argument may not be reliable.

Over all, the studies agreed that taste dysfunction is prominent in SS patients but the association with the oral dryness or smell impairment remains disputed.

2.6 SYMPTOMS STATUS

2.6.1 Dryness of the mucosa and xerostomia

Since it was firstly described by Henrik Sjögren, the most overwhelming symptoms described by patients is the oral dryness, which is also known by xerostomia. Hyposalivation in Sjögren's Syndrome occurs due to the lymphatic infiltration of the salivary glands that leads to functional destruction (Gerli et al., 1997). With the hypofunction in the salivary glands, a depletion of saliva and its natural lubricative and protective constituents are prone to unfavourable consequences. The change in saliva quantity and quality may affect the hard tissues as well as the soft tissues and their related functions. By moistening chewed-up food, saliva helps in conveying food particles to be analysed by taste buds, in a manner that facilitates transduction by ion channels and/or specific protein receptors, to transmit taste signals to the thalamus, insula and orbitofrontal cortex in the brain. Taste quality coding, relies upon the response of neurons, and the way they are evoked with certain tastes (Kaplan and Baum, 1993). Without saliva, none of the aforementioned activities would take place. Additionally, the lack of saliva precipitates Candida infection, which in turn has a negative impact on the taste perception (Sakashita et al., 2004).

2.6.2 Definition of xerostomia

Xerostomia is the subjective feeling of oral dryness where salivary glands impairment may or may not be associated with the problem. Xerostomia is more common in middle-aged people and has been shown to affect the oral health quality of sufferers (Locker, 2003, Ikebe et al., 2005).

2.6.3 Measurement of xerostomia

- **Xerostomia inventory**

This is an 11-item scale to measure the severity of xerostomia, which is the subjective sensation of chronic mouth dryness that has a great impact on QoL (Hahnel et al., 2014). The Xerostomia Inventory (XI), was firstly developed and validated by Thomson et al., in 1999 and was subjected to further validation in the following year (Thomson WM et al., 2000). The XI provides five numerical options of responses that range from "never" to "very

often" giving a scale to the oral dryness, rather than classifying sufferers into either xerostomic or non-xerostomic as proposed by previous tools (Fox et al., 1987, Narhi, 1994). In 2011, Thomson et al proposed a modification of the scale to a shorter version (Summated Xerostomia Inventory (SXI) consisting of five items validated in a multicentre study (Thomson et al., 2011). Hahnel et al. (2014) validate this tool for clinical and research purposes successfully. The study was a single-centre but involved subjects from different ethnic origins who had consistent results. The convergent validity of SXI with the global oral health question used in the study, demonstrated very good to excellent correlation (r=0.6-0.8) with Chronbach's alpha value of 0.7. Although the shortened version of the inventory was validated and shown to be a reliable tool, it was deemed to be lacking in questions relevant to our project objectives, and therefore the full list of the original XI questions was used in the current study.

2.6.4 Review of the research showing xerostomia in patients with Sjögren's Syndrome

The dysfunction of salivary glands could precede autoimmunity process in SS (Nikolov and Illei, 2009). However, xerostomia is not an exclusive symptom of SS and other conditions such as smoking and medicines intake can cause hyposalivation (Porter and Scully, 2000, Rad et al., 2010). Additionally xerostomia is subjective to the individual's tolerance and adaptation for oral dryness (Scully and Felix, 2005, Ramos-Casals et al., 2012).

Studies on the salivary constituent in patients with SS showed that with the reduced rate of salivation, the protein concentrations and some bacterial species such as Streptococcus and Veillonella were significantly increased in saliva of SS patients compared with matched-controls (Eliasson et al., 2005, Siddiqui et al., 2016).

Investigating the oral manifestations in 55 patients with dry mouth syndrome including SS, revealed increased symptoms of angular cheillitis, lip dryness, ulcerations and aphthae appearing on the patients' oral mucosa (Blochowiak et al., 2016).

Hyposalivation can be assessed via measuring salivary flow rate; however, patient-reported xerostomia was considered as a significant indicator for SS in a large cohort of 2046 SS

patients. The study also suggested to consider patient-reported xerostomia in SS classification as it represents patients' own perspective about the severity of the syndrome (Billings et al., 2016).

Xerostomia is the subjective sensation of oral dryness, while hyposalivation is the objective assessment for oral dryness when the unstimulated salivary flow rate (UWSR) is less than 0.1 mL/min (Jorkjend et al., 2004, Villa et al., 2015). van der Putten et al. (2011) found that item two and four of XI were significantly correlated with hyposalivation in a group of residents at nursing home in Netherlands. Although the sample size was selective and limited, this association added extra importance to the validity of XI. The opposite was the case with findings by Minicucci et al. (2013), who concluded that XI was not ($p>0.1$) correlated with the salivary flow rate in menopausal women, presuming that there was no evidence in the literature of a correlation between xerostomia and hyposalivation. Nevertheless, the unique sensation of mouth dryness felt by xerostomic patients or people suffering from low salivary flow rate has one outcome, which reflects a negative impact on individual's QoL (Cho et al., 2013). The latter is a Korean study to investigate the determinants of the European League against Rheumatism SS Patient Report Index (ESSPRI)*, in comparison with other clinical parameters. Cho et al. (2013) used XI to compare the impact of xerostomia on QoL in two groups, pSS patients and non-SS sicca participants. The researchers found that XI scores correlated significantly with several components of the SF-36 in the non-SS group, and no correlation was found between both scales in the pSS group. Nevertheless, the ESSPRI and XI were significantly correlated with each other in both tested groups. The latter correlation added further support to XI, since that ESSPRI was deemed by Cho et al. (2013) to be a disease specific for pSS patients. Other studies presented more evidence of a correlation between XI and the OHRQoL when assessed by OHIP-14 (Willumsen et al., 2010).

*ESSPRI: is a specific index to measure the severity of pSS symptoms

2.7 FUNCTIONAL STATUS

2.7.1 Sexual functioning

1. Definition of sexual functioning

Sexuality is a complex process of physical and emotional reaction during the sexual response cycle. According to definition by the National Health Service (NHS), any problems occur during any phase of the sexual response cycle, is known by the sexual dysfunction (SD). SD can include loss of desire, loss of arousal, problems with orgasm, and pain during sex. Women are more likely to suffer from SD (32%) than men (23%) (Nicolosi et al., 2006), which is an aspect that affects the QoL of individuals. It was recognised that SD in patients with rheumatic diseases including SS can be referred to a number of factors (multifactorial) including mucosal dryness, rather than being attributed to a particular reason (Tristano, 2012). However, little was published about the subject, which could be due to the sensitivity of the problem.

2. Measurement of sexual functioning

- **Female Sexual Function Index**

This study explores variety of clinical aspects of the impact of pSS on patients. However, it was not feasible to cover each aspect with its assessing tool holistically in the literature review and hence it was decided to choose the most reliable and widely used assessing tool. The Female Sexual Function Index is a self-reporting scale known by FSFI, which was developed by Rosen et al. (2000) to measure the female sexual function through six domains via 19 items. These domains are desire, arousal, lubrication, orgasm, satisfaction and pain; where higher scores indicate better sexual functioning from a total of 36 points (ibid). Its psychometric properties were tested by different studies and with different language versions. It was agreed by number of studies, that the scale has a good validity and reliability, excellent internal consistency, adequate test-retest reliability and good discriminant validity (Rosen et al., 2000, Meston, 2003, Sidi et al., 2007, Chang et al., 2009, Sun et al., 2011, Takahashi et al., 2011, Ghassamia et al., 2013, Filocamo et al., 2014, Lee et al., 2014, Ryding and Blom, 2015, Crisp et al., 2015, Kalmbach et al., 2015). The scale was also used as a gold standard to validate newly developed or translated questionnaires (Corty

et al., 2011, Herbenick et al., 2011, Momenimovahe et al., 2015), which added more weigh to its usefulness.

There have been several studies that used FSFI in the assessment of the sexual activity in patients with rheumatic diseases (Tseng et al., 2011, El Miedany et al., 2012, Shahar et al., 2012, Ferreira Cde et al., 2013, Anyfanti et al., 2013, Anyfanti et al., 2014, Frikha et al., 2014, Coskun et al., 2014); where converged conclusions were drawn from these studies, which suggested that SD was strongly present in patients with rheumatic diseases. However, findings by Tseng et al. (2011) contrasted the aforementioned studies, and reported similar rates of SD in females with Systemic Lupus Erythematosus (SLE) and healthy controls. In the same study, particular number of SLE patients who developed SS, were not significantly different from those without it. These conflicts need to be resolved.

Females' SD is commonly associated with anxiety and depression in rheumatic patients; this was described in a group of pSS patients by van Nimwegen et al. (2015). The authors of the study believed that pSS patients recorded significant lower scores than healthy controls in FSFI ($p<0.001$) in domains of arousal, desire, lubrication, orgasm and pain. Therefore, the reduced scores of FSFI could be a good indicator for depression and anxiety in rheumatic patients.

Another study by Priori et al. (2015) which has also used FSFI in assessing the quality of sexual life in pSS patients. The study found that the scale was a useful tool in evaluating vaginal dryness status after treatment prescription, such as oral pilocarpine and cemiveline, which are both potent in alleviating oral dryness (Vivino et al., 1999, Petrone et al., 2002). Priori and colleagues further concluded that the affected mental health status, represented by high scores of the mental health assessment tool, was inversely correlated with lower scores of FSFI. This finding was in line with others (van Nimwegen et al., 2015), and shed light on the negative impact of SD on the mental health well-being.

An attempt to shorten and modify the original scale was carried out in 2010, to be more practical for clinical settings. Isidori et al. (2010) abridged the scale from its full version of 19 items to six items only that was called FSFI-LL, to indicate women's lifelong sexual

function. The shortened version demonstrated accurate results with high sensitivity (0.93%) and specificity (0.94%). The new version was also tested by Burri et al. (2010) and was shown to have good reliability and validity. However, the authors recommend the abridged scale for clinical use as well as for studies with limited time coverage, as it provides brief information.

3. Review of the research showing sexual dysfunction in patients with Sjögren's Syndrome

The fact that the female to male ratio in pSS patients is 9:1, supports the theory that female hormones may play a key role in the pathogenesis of this syndrome. Skopouli et al. (1994) reported a significant difference in the presence of dyspareunia in 40% of premenauposal SS patients (n=51) in comparison with 3% of premenauposal healthy controls. However, the authors believed that half of SS patients in the study had potential dyspareunia, which originated from trauma or inflammatory process that might occur in other organs as a consequence of the syndrome. Marchesoni et al. (1995) found that vaginal dryness and dyspareunia occurred in 61% and 55% of SS patients (n=36) versus 39% and 33% of healthy controls respectively, with significant difference between the two groups. Nevertheless, authors did not find a correlation between lacrimal or oral dryness with the sexual activity in SS patients. Likewise, Mulherin et al. (1997) suggested that dyspareunia was present in SS patients (n=11) several years prior to the appearance of oral or ocular symptoms. However, the classification criteria used to diagnose SS patients was not rigorous enough, and this can be referred to the fact that the AECG criteria was not yet released at that time. The results of the aforementioned studies were refuted by Valtysdottir et al. (2003) who argued that there was no correlation between sexual activity and decreased vaginal lubrication in SS patients (n=21). The authors found that the psychological factors had stronger influence on sexuality than physical determinants. Additionally, the study reported that the decrease in the serum DHEA-S, which is noticed to reduce in SS patients, associated with the decrease in mental well-being and that the latter affects the sexual activity. Hartkamp et al. (2008) contradicted the above findings, and reported that DHEA does not have a role in the course of SS female patients compared with placebo group.

Goodwin (1997) and Frikha et al. (2011) assumed that any disease associated with chronic fatigue syndrome, might have a negative influence on the marital relationships represented by sexual and shared events. The study was conducted with sample size of 131 partners, in which the females reported higher scores of fatigue compared to their spouses. Another study by (Blazquez et al., 2015b) on females with chronic fatigue syndromes including SS, reported more avoidance in the sexual activities, less satisfaction and less communications in the SS patients, and referred the reason to the fear of pain due to the decrease in lubrication. However, the study relied on subjective measures and no objective tests were carried out. Furthermore, although recruiting a large sample size of 615, the sample was not representative of the Spanish population, as the authors recruited patients from one hospital in one city in Spain. Additionally, assessment of medications and mental status was not taken into account. Moreover, they recruited women only, despite of their attempt to investigate SD in conditions that are seen in men. However, the study contributed in supporting number of the very few studies that correlated between SD in fatigued patients.

There are only few studies looking at the SD in a well-defined pSS study group identified in accordance to the American-European diagnostic criteria. A case-control study by van Nimwegen et al. (2015) investigated the impact of pSS on the sexual function in relation to the mood status of female patients. Authors of the study reported that women with pSS had lower FSFI scores (Median FSFI=20.6) with worse mood status than controls (Median FSFI=30.3). Although the study has a limitation of selection bias for sexually active patients only, it represents a recent evidence in this field. Findings of another study by Priori et al. (2015), supported the latter in which pSS female patients showed impaired sexual function. The study demonstrated an inverse correlation between FSFI with age and HADS separately. The authors made efforts to examine the impact of the symptoms and activity of the disease subjectively and objectively on the sexual function, and found that SD was influenced by vaginal dryness and interfered with QoL. The latest study in this field was from Turkey by Isik et al. (2016), who investigated pSS women's satisfaction with their sexual life. The authors found that pSS patients (n=46) had significantly impaired sexual function and low satisfaction of their sexual activity compared to age and sex-matched controls (n=47). The

authors referred the SD to the age, vaginal dryness and impaired physical and emotional function due to the disease. Despite the relatively small sample size, authors put efforts in matching the groups by excluding patients with severe systemic diseases or complications, and patients who were using antidepressants or diuretics, to eliminate the unfavourable impact on patients' sexual life.

Looking at the studies that assessed SD in other rheumatic diseases in an attempt to assess the problem in similar debilitating conditions, El Miedany et al. (2012) proved that SD is a common problem in patients suffering from RA. However, the main weakness in this study was the lack of controls for comparison. Ferreira Cde et al. (2013) looked at the same problem in a number of RA, where authors of the study attributed the reason for SD to the autoimmune effect of the syndrome and the medications used for its remedy. Nevertheless, no clinical evidence was provided to support these findings. In the same research field, Abdel-Nasser and Ali (2006) and Josefsson and Gard (2012), referred the reason of SD in RA patients, to the physical disability and fatigue. Another study on RA group by Shahar et al. (2012) concluded that the disease activity has a direct impact on the severity of SD, which supports the latter findings.

In the same context, a relatively old study by Bhadauria et al. (1995) referred the reason for SD in patients with Systemic Sclerosis to the chronic inflammatory process of the disease. The study used comprehensive questionnaire, which was especially designed to assess the gynaecologic manifestations. This questionnaire was not validated, and there was no reference to its contents in the publication. Additionally, no control group was used for comparison. However, the performed clinical vaginal evaluation for part of the recruited subjects, added some importance to the study.

In a case control study to assess SD in SLE female patients by Tseng et al. (2011), it was concluded that patients had similar rates of sexual activity with that of controls. However, although the response rate of participants was high (92% patients, 73% controls), authors used Chinese translation of FSFI, which has not been validated. The study found that 30% of SLE patients had SS and this did not alter or aggravate FSFI scores, compared with SLE

group without SS. Authors attributed these results to the activity of SLE that was not affected by secondary SS. However, it cannot be confirmed that secondary SS does not have an effect on sexual life. Therefore, in order to develop a proper conclusion concerning the impact of secondary SS on SD, a study that compares SD in patients with different autoimmune diseases complicated by SS would help.

4. Neurological manifestations

Peripheral neuropathy (PN) is one of the common symptoms of the syndrome, occurring in 20% of pSS patients (Svein I. Mellgren et al., 1989 , Govoni et al., 1999, Ramos-Casals et al., 2008, Pavlakis et al., 2011, Jamilloux et al., 2014). The neurological manifestations (NM) may present in a variety of forms such as trigeminal neuropathy, sensory neuropathy with ataxia and radiculoneuropathy (Mori et al., 2005). It is thought that the peripheral nervous system (PNS) is the most predominantly involved in pSS compared with the central nervous system (CNS) (Chai and Logigian, 2010, Gono et al., 2011), whereas Teixeira et al. (2013) believed that both PNS and CNS have similar frequency of involvement in the course of pSS. Although the exact cause for this aspect in SS is still not completely understood, there are studies have shown that neurological symptoms are associated to anti-Ro and anti-La antigens, and is not related to vitamin B12 deficiency (Scofield et al., 2012). This finding challenges the general belief that low vitamin B12 has an effect on the integrity of the nervous system.

Another study by Agmon-Levin et al. (2012) concluded that vitamin-D low levels is correlated with PN in pSS patients. It has been reported that vitamin-D supplement has a noticeable role in the alleviation of neuropathic symptoms in diabetic patients (Valensi et al., 2005, Lee and Chen, 2008). It was anticipated to get similar outcome when this supplementation is given to pSS patients. However, a randomized control trial is needed to provide evidence for this.

Different suggestions have been considered for the relief of NM. Rist et al. (2011) recommended the use of intravenous immunoglobulin therapy, to reduce the severity of the symptoms; although this treatment has the benefit of avoiding the prolonged use of

immunosuppressive agents, its high cost should be considered. Rituximab and corticosteroids have also been proved useful (Seve et al., 2007, Rist et al., 2011, Jamilloux et al., 2014). It was observed by Jamilloux et al., (2014) that the increase in corticosteroids administration in pSS patients, is associated with the severity of the NM symptoms. This study has also observed that the increase in B-cell proliferation correlates with the severity of NM. There are no studies to date of the association between NM and the acuity of smell and/or taste perception in pSS patients.

2.8 GENERAL HEALTH PERCEPTION

2.8.1 Fatigue and depression

1. Definition of fatigue and depression

Fatigue is one of the most common symptoms in SS and can interfere with QoL. It was described as a combination of the impairment of both somatic (voluntary) and mental efficacies, so that the deterioration of both components is a consequence of its manifestation (Meijer et al., 2009). Fatigue is one of the symptoms of depression that is defined by the loss of energy and is listed in the *Diagnostic and Statistical Manual of Mental Disorders* criteria (The manual was published by the American Psychiatric Association that covers all categories of mental health disorders). Therefore, fatigue and depression occur together in the majority of patients (Targum and Fava, 2011).

Depression is the state of low mood that is used in many senses such as state of grief, demoralization, low self-esteem and pessimism (Snaith, 1987). This state has been shown to be most likely to respond to a tailored psychotherapy as well as pharmacotherapy (Jobst et al., 2016).

2.8.2 Measurement of depression

- **Hospital anxiety and depression scale**

A number of questionnaires developed for the assessment of individuals' mental health status. This included questionnaires tailored to assess depression only such as Beck Depression Inventory and Patient Health Questionnaire (PHQ-9) (Beck et al., 1961). Other

instruments have the bonus of assessing anxiety and depression as the two emotional components of an individual, such as the Hospital Anxiety and Depression Scale (HADS). This self-administered scale was designed in 1983 by Zigmond and Snaith to assess the level of anxiety and depression that patients might experience due to physical sickness (Zigmond, 1983). This questionnaire comprised of 14 items, which are easy to read and answer. Half of the items refers to anxiety assessment (HADS-A) and the rest to depression assessment (HADS-D), so that the two dimensions of anxiety and depression are constructed. In this tool, there are four scoring levels for each question, which are ranged from zero to three depending on the severity of the condition. This means that each question has a total of four choices, so that subjects do not have a middle option to choose. A final score of 0-7 for each subscale represents non-cases, scores range of 8-10 indicate doubtful cases, whereas a score of 11 or more represent certain clinical anxiety and/or depression (Zigmond, 1983). Bjelland et al. (2002) believed that HADS has comprehensive screening properties for each of its domains. This was also supported by a French study, which confirmed HADS ability to detect symptoms of anxiety and depression in group of working people Bocerean and Dupret (2014). However, the sample size recruited in this study was not representative, as only workers in the major companies were considered in this survey; but the high response rate of 95% from a total of 20992 participants who fully completed HADS, is noteworthy.

Differently, a meta-analysis by Norton et al. (2013), contradicted findings of the latter two studies, by showing that the scale does not serve as a good detector between symptoms of anxiety and depression. Data of the study were drawn from studies selected for inclusion in a systematic review by Cosco et al. (2012). Both studies argued that the scale provides only a general distress assessment. However, results by both studies are questionable, due to the language restriction considered and the low response rate (39%).

Both anxiety and depression were sought to be investigated in the current project. HADS, as a measure of depression showed validity, reliability, sensitivity, specificity simplicity, speed, ease of use that assesses both symptoms together in one questionnaire and good psychometric properties with different language versions (Fatt et al., 2007, Honarmand and

Feinstein, 2009, Annunziata et al., 2011, Reda, 2011, Wang et al., 2011, Muller et al., 2012, Roberge et al., 2013, Haugan and Drageset, 2014).

HADS was used as a gold standard to validate other similar instruments in a number of studies. The most recent being the validation of the German version of Mother-Generated Index (MGI) where HADS was used as a validity indicator (Grylka-Baeschlin et al., 2015). Another study by Helvik et al. (2011) confirmed that HADS performs well discrimination between its two subscales with proper internal consistency of 0.78 and 0.71 for anxiety and depression respectively. This has also been supported in study by Watson et al. (2014), where a validation of three mood assessing tools [Beck Anxiety Inventory (BAI), Beck Depression Inventory-II (BDI-II) and HADS] was conducted on a group of multiple sclerosis (MS) patients. The study concluded that HADS demonstrated high sensitivity and specificity for both of its domains: Anxiety (90%, 77%) and Depression (92%, 81%) respectively, with an optimum cutoff score of 11. While for BDI-II and BAI a sensitivity of 85% and 80%, and a specificity of 76% and 46% were demonstrated for both scales respectively; at an optimum cutoff score of 23 (for BDI-II) and 10 (for BAI). These figures disclose the slightly better trend of HADS, in comparison with the rest of the scales in the same study.

HADS was also used with patients suffer from autoimmune diseases such as rheumatoid arthritis (RA) (Chatzitheodorou et al., 2008, Aras et al., 2013) and pSS (Valtysdottir et al., 2003, Bowman et al., 2004a, Stevenson et al., 2004, Inal et al., 2010, Gandia et al., 2014). Moreover, it was also used in studies that focused on assessing the mental health well-being in patients with oral problems, olfactory and sexual dysfunction (Ni Riordain et al., 2010, Irani et al., 2010, Silva et al., 2012, Watrowski and Rohde, 2014, Azevedo et al., 2014). The studies' findings support HADS effectiveness in evaluating the mental health status in these study groups. More specifically, this scale was used in measuring the mood status of pSS female patients, in relation with the quality of sexual life (van Nimwegen et al., 2015, Priori et al., 2015). The latter two studies found that HADS had inverse correlation with the impaired sexual activity in pSS patients. This indicates that the scale was measuring what it was meant to measure.

2.8.3 Measurement of fatigue

- **Visual analogue scale**

This scale is a psychometric rating tool, arranged in a continuous linear manner to measure the intensity or the subjective outcome of a condition, which is frequently used in clinical and epidemiologic research. The scale is abbreviated to VAS that usually consists of a horizontal line of a fixed length of 100 mm, with ends oriented from the worst on the left to the best on the right. It has been used in a number of studies and under different topics, the most widely known is pain VAS (Huskisson, 1974, Price et al., 1983) and xerostomia VAS (Dry mouth VAS) (Pai et al., 2001), which were both validated successfully. Furthermore, VAS was effectively used to assess the level of fatigue in pSS patients (Harboe et al., 2009, Norheim et al., 2012), however, a limitation of having a unidimentional nature was pointed out. The authors recommend using a multidimensional scale instead, so that more information could be obtained. However, another three trials by Mariette et al. (2004), Mariette et al. (2015) and Salom et al. (2015) valued the scale in reflecting the success of the treatment targeted towards pSS patients. Similarly, there are very supporting findings for the strong correlation between VAS and other validated instruments, such as EULAR Disease Activity Index (ESDAI), ESSPRI, SF-36, the Multidimensional Assessment of Fatigue (MAF) ($p<0.001$) (Ibn Yacoub et al., 2012, Lendrem et al., 2014, Pertovaara and Korpela, 2014).

2.8.4 Review of the research showing fatigue and depression in patients with Sjögren's Syndrome

Patients suffering from almost all rheumatic disorders normally experience fatigue, hence, with the consequential depression a direct impact on quality of life was observed (Barendregt PJ1 et al., 1998, Segal et al., 2008, Ng and Bowman, 2010). Fatigue is also thought to be one of the most important reasons to seek medical treatment by SS sufferers (Barendregt, 1998). It is an important and simple indicator for pSS activity, compared with other laboratory tests such as antinuclear antibody (ANA), extractable nuclear antigen panel (ENA) and erythrocyte sedimentation rate (ESR) (ibid).

A study by Meijer et al. (2009) showed that patients with secondary SS (n=50) had worse physical functioning and health related QoL (HRQoL), when compared with pSS (n=185) sufferers. This finding is questionable, as the sample size recruited for secondary SS was not comparable to that of pSS patients. Given that, the associated rheumatic disease with secondary SS patients was most frequently RA and/or SLE, and that each disease has its own impact on the associated SS. These complications might exert different effect and burden on the physical activity of the patient that cannot be generalized for secondary SS sufferers. Consequently, this finding contrasts with Sutcliffe et al. (1998) who found no difference between groups of pSS and secondary SS associated with SLE in terms of functional status.

Another study proposed a significant positive correlation between fatigue and depression in a comparison between pSS and RA female patients (Barendregt PJ1 et al., 1998). The study reported no significant difference between the two groups in terms of depression, but only for the dimensions of general and mental fatigue. It was asserted that pSS subjects recorded higher scores on those dimensions than RA patients, indicating a worse status, but no meaningful differences. Indicating that when depression was adjusted in this study, no significant difference was found between the two study groups.

It is easy to understand that chronic fatigue has a direct impact on the patients' psychological status and hence their QoL (Ng and Bowman, 2010). However, in a cohort study conducted in the USA, Segal et al. (2008) proposed a higher percentage of fatigue experienced in 67% of pSS patients, while depression was found in only 32% of subjects suffering from fatigue. In the same context, another study argued that depression and fatigue are in the forefront among other symptoms of pSS that force women to visit physicians more frequently than controls, and to retire early as well (Westhoff et al., 2012). While in a case-control study, it was reported that women with pSS recorded a low to mild, but significant decrease in their physical capacity compared to the healthy controls, who were age and sex matched (Strombeck et al., 2003). However, Bowman et al. (2004a) had comparable results with that of Strombeck et al., although the study did not assume an association between fatigue and depression in pSS patients.

In reviewing the literature, it became apparent that the correlation between fatigue and depression has been studied extensively.

2.9 QUALITY OF LIFE

Despite of being dated back since 1964, when the expression ''quality of life'' was firstly used by President Lyndon B. Johnson in his speech in the Square Garden in New York (Johnson, 1964). It remains difficult to explain what "Quality of Life" exactly means. The term is commonly used to describe the health status (physically, psychosocially, well-being, life satisfaction and happiness) based on the importance of these elements to the individual him/herself (Barofsky, 2012). Later on, the WHO has defined the term as individuals' perceptions of positions in their life, in terms of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.

Therefore, it can be inferred that the term is used to describe individual's perspective of life subjectively. It is an outcome that is known as debilitating but not life threatening for patients (Iacopino, 2010). As if there is a group of people diagnosed with different diseases, treated with variety of medications and came from miscellaneous cultural backgrounds, their definition to QoL might be different, depends on their ability to cope with the problems they encountered. Thus, the term "Quality of Life" is considered as ''multi-criteria'' as well as ''type-dependent'' expression (McCall, 1975).

2.9.1 Measurement of quality of life

In the new global health concept, measuring QoL became important for some systemic disease experiences. In this context, there has been increasing number of studies that assess the QoL of patients with different diseases, including SS. A number of authors measured QoL in variety of ways in accordance with the research requirements. Hence, different instruments were developed and used for this purpose, such as the Short Form (SF-36) of the Medical Outcome and the brief form of the World Health Organization Quality of Life (WHOQOL-BRÉF) (Barendregt PJ1 et al., 1998, Bowman et al., 2004a, Champey et al., 2006, Bowman et al., 2007, Goodchild et al., 2008). The following review sheds light on the questionnaire that has been chosen to achieve the current projects' targets.

2.9.2 Review of the research showing quality of life in patients with Sjögren's Syndrome measured by WHOQOL-BRÉF

The questionnaire is self-administered to measure the level of general QoL in the previous two weeks. It is a comprehensive instrument that measures four facets of life domains (physical health, psychological, social relationship and environment) by a total of 26 items, where higher scores indicate better QoL (Bowman et al., 2004a, WHO, 1998). The scale was originally designed as a 100-item measure by the World Health Organization (The World Health Organisation, 1995), which later was shortened to be WHOQOL-BRÉF (Skevington et al., 2013). The former is ideal to be used in clinical trials or larger studies, as it allows global and detailed assessment of the QoL for individuals, but in some instances, it was thought impractical to be answered by participants. For this reason, the shortened form of WHOQOL-BRÉF was developed to provide full-scale, yet, brief assessing instrument for the QoL. The WHOQOL instruments in general, are very useful in epidemiological studies, which allow assessment of the nature of the disease. The instruments can also provide evaluation of the impact of the health problem subjectively, to help assess how this problem impairs different aspects of the person's life (WHO).

The psychometric properties of the WHOQOL-BRÉF was assessed by Skevington et al. (2013), who found that the instrument performs well with good validity and reliability. The authors believe that the instrument's performance, being cross-culturally sensitive and a multilingual scale put the instrument at the forefront of the tools that measure QoL. Another study by Taylor et al. (2004) examine the psychometric properties of this scale on a randomly selected group with rheumatoid arthritis (RA), in comparison with healthy controls. It was found that the instrument has adequate psychometric properties and internal consistency ($\alpha>0.80$) in each domain, except the social, where poor internal consistency was recorded. The test-retest reliability was adequate, which indicates acceptable stability (interclass correlation coefficient >0.70). However, the relatively low response rate (59%) was observed as a weakness in the study. As individuals who failed to return the questionnaires, might have worse QoL than respondents.

In a study by Castro et al. (2014), where a comparison between two instruments was conducted, it was found that WHOQOL-BRÉF was more suitable than the Short Form, 36 (SF-36), in assessing QoL in a group of Brazilian old women. This was reported after comparing the validity and reliability of the two instruments in this study group. Although both tools were reliable and valid in assessing QoL for research and clinical uses, WHOQOL-BRÉF possesses special properties in evaluating QoL changes of the group studied. Researchers observed that WHOQoL-BRÉF prioritises assessment of ageing process and peoples' perspectives on QoL from their points of view; in addition, it does not focus on the physical impairments as the SF-36 does.

The instrument was used in assessing and comparing QoL in a number of autoimmune diseases including SS by Bowman et al. (2004a), Goulia et al. (2010) and Hyphantis et al. (2011). The results of these studies were in line with the previous findings in which patients with RA, pSS and SLE had reduced QoL when compared with healthy controls (Sutcliffe et al., 1998, Strombeck et al., 2003, Tensing et al., 2001, Rostron et al., 2002, Bowman et al., 2004a, Belenguer et al., 2005, Stewart et al., 2008, Baturone et al., 2009, Segal et al., 2009). However, the cross-sectional design used in the three aforementioned studies has the disadvantage of providing a snapshot of a selected population at a certain time, regardless of the individuals' status assessment before and after the time of data collection. Hence, this design provides information of association only, rather than a hypothesis testing (Hennekens C and Buring J, 1987). Therefore, a longitudinal study and surveillance of the QoL, could provide a comprehensive evaluation of the patients' life quality.

The questionnaire was also used with a well-defined group of pSS patients, alongside other instruments to examine the relation between QoL and the mental health status (Inal et al., 2010). The results of this study presented comprehensive assessment of QoL by using two measures: WHOQOL-BRÉF and SF-36; which supports findings by Bowman et al. (2004b). The SF-36 measures HRQoL from the medical point of view, while the WHOQOL-BRÉF assesses the QoL from individuals' perception which helps in epidemiological surveys. Several limitations were identified in this study, including that the exact component that

contributes to the impairment of HRQoL in pSS patients was beyond the scope of the study. Moreover, the deficit of the impact of therapeutic agents on QoL in these patients was not considered. Additionally, the study assessed the degree of mood disorders on cases only, which does not help in providing a reliable conclusion.

2.10 ORAL HEALTH RELATED QUALITY OF LIFE

2.10.1 Definition of oral health related quality of life

The oral health related QoL (OHRQoL) is a multidimensional construct that represents subjective evaluation of individual's oral health perception. This perception reflects self-comfort when eating, sleeping, and pursuing social interaction. It also shows individual's self-esteem and satisfaction with respect to personal oral health (Rockville, 2000, Sischo and Broder, 2011).

2.10.2 Measurement of OHRQoL

A number of questionnaires are available to assess the oral health status including the General Oral Health Assessment Index (GOHAI) (Atchison and Dolan, 1990), and Oral Health Literacy Assessment (OHLA) for adults (Naghibi Sistani et al., 2014). However, the most popular, widely used questionnaire for the assessment of oral health quality is Oral Health Impact Profile-14 (OHIP-14).

2.10.3 Review of the research showing OHRQoL in patients with Sjögren's Syndrome

The OHIP-14 is a self-reporting instrument that measures the oral health outcomes from patient's perception that may affect their well-being. It also provides a theoretic framework of the social impact of oral disorders (Slade, 1997). Originally, it was developed as a 49-item questionnaire (full OHIP) after a number of approaches to measure the impact of the oral health problems on patients' perception. It was adapted from the WHO classification of impairments by Locker in 1988 (Gilson et al., 1975, Slade, 1997, Locker, 1988). The full OHIP comprised of seven dimensions, these are physical pain, functional limitation, physical disability, psychological discomfort, psychological disability, social disability and handicap. Later on, a shortened version of OHIP-14 was developed with respect to a subset of two questions for each one of the seven dimensions of the full OHIP (Slade, 1997a). The

shortened form has a good validity, reliability and precision compared to the full OHIP when both were used in a cross-sectional study in South Australia (Slade, 1997a). This was also supported by Fernandes et al. (2006), Baker et al. (2006), Stenman et al. (2012), Khalifa et al. (2013) and Nikbin et al. (2014), who all approved its good validity, reliability, appropriate internal consistency and discriminant validity.

The shortened version was used in a number of studies, in which the impact of dryness and salivary hypofunction on OHRQoL was tested subjectively. Additionally, it was also shown that the index was sensitive in measuring the level of OHRQoL in xerostomic patients (Ikebe et al., 2007, Busato et al., 2009, Cho et al., 2012, Nikbin et al., 2014, Benn et al., 2015).

More specifically, the questionnaire was used in assessing OHRQoL of pSS patients (Enger et al., 2011, Mumcu et al., 2013). Enger and colleagues confirmed that the instrument has a high internal reliability (0.94) in assessing the OHRQoL for all its items. The scale was validated in a general dental practice in the UK by Fernandes et al. (2006), whom found that the scale had a good level of validity and reliability. It was also validated in several languages and was shown that the scale has acceptable reliability and validity (Navabi et al., 2010, Roumani et al., 2010, Stenman et al., 2012, Papagiannopoulou et al., 2012, Leon et al., 2014). Being used with pSS patients, in a UK cohort, has encouraged applying the scale in the current project.

It could be debated that the General (formerly Geriatric) Oral Health Assessment Index (GOHAI) is a better instrument for assessing OHRQoL for the current project, as it has good psychometric properties, better response rate and ability to differentiate between the less damaged parts compared with OHIP-14 (Hassel et al., 2008). Nonetheless, a study conducted by Locker D (2001), which compared between both instruments, reported that none of the scales was superior to the other in assessing OHRQoL. The study has also found that they were equal at predicting life satisfaction and psychological well-being in this study group. Moreover, Cronbach's alpha was found to be higher in OHIP-14 than GOHAI, which means better internal consistency and reliability. In the same context, Rodakowska et al. (2014) found that both instruments were correlated strongly with each other when applied

on a group of old Polishes aged 55 and over, who were recruited by means of convenience sampling. Although the sampling process was set at 90% type two error, it does not represent rigorous findings as the convenience sampling method was based on collecting data from people who were easily reached, hence, this had the benefit of serving the views of specific group and not the entire population. Provided that the use of the first translated version of the Polish OHIP-14 that had not been validated might have biased the results. Nevertheless, a study by Nikbin et al. (2014) on a group of Iranian diabetic patients, had settled the matter, by asserting that OHIP-14 was better than GOHAI in diagnosing oral disorders.

OHIP-14 has been, as yet, used in a number of papers since the time of its development, with variety of study groups under different disorders, and with different languages, which supports its validity and reliability.

In conclusion, the literature review revealed that there is insufficient information on the effect of dryness on smell, taste and sexual function and whether the impairment of these senses has an effect on QoL of patients.

2.11 Hypothesis development

From the above review, it was concluded that:

- PSS is prevalent worldwide and a remarkable increase in its incidence has been observed recently.
- SS Patients are affected by fatigue, joint pain and neuropathy, however, the most common, and overwhelming symptom is the dryness of the mucosal linings.
- The literature is scanty in studies that relate the severity of mucosal dryness with the function of the related organs, in particular, smell, taste and sexuality and whether an existing dysfunction can compromise patients' life quality.
- The literature is conflicted on whether the smell and taste functions are correlated with each other.

- There is lack in studies that investigate the aetiology of the taste function in pSS patients and whether it is related to the mucosal dryness or to neurosensory impairments.

In conclusion, the literature review revealed that there is insufficient information on the effect of dryness on smell, taste and sexual function and whether the impairment of these senses has an effect on QoL of patients. A systematic review was conducted to test the hypothesis that the mucosal dryness has an impact on the functions of the smell, taste and sexuality in pSS patients, as described in more details in the following chapter.

The aims of this project were as follows:

1. To assess the functions of the smell, taste and sexuality in women with pSS,
2. The consequences of the impairment of these functions may have on the QoL and mental health well-being.
3. To investigate whether the severity of the mucosal dryness in pSS patients, is associated with the deterioration of the functions of the smell, taste and sexuality.

CHAPTER 3: SYSTEMATIC REVIEW AND META-ANALYSIS

We reviewed the literature systematically for evidence on whether mucosal dryness affects the function of smell, taste, sexuality or quality of life in primary Sjögren's women. The methodology for the systematic review was registered with PROSPERO in 2015 (Al-Ezzi M. et al., 2015) and the date submitted to the Journal of Modern Rheumatology was on 07th Aug 2016 revised on 29th Sep 2016 and accepted on 13th Oct 2016 (Al-Ezzi et al., 2016) (Appendix 26).

3.1 Introduction

Primary Sjögren's Syndrome (pSS) is a systemic autoimmune rheumatic disorder of unknown origin, affecting women nine times more commonly than men (Fox, 2005). 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 (Rasmussen et al., 1986, Jacobsson et al., 1992, Marchesoni et al., 1995).

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 (Henkin et al., 1972, Porter, 2010). 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 (Negoro et al., 2004). 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 (Skopouli et al., 1994, Marchesoni et al., 1995, Mulherin et al., 1997, Cirpan et al., 2007). An evidence was presented of the association between oral symptoms and vaginal dryness in Sjögren's patients (Mulherin et al., 1997). Other studies suggested that dryness and dyspareunia

could adversely impact the sexual well-being of women with pSS (van Nimwegen et al., 2015, Priori et al., 2015). 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.

3.2 Methods

A prospective protocol was registered (PROSPERO number CRD42015024354) (Al-Ezzi M. et al., 2015). This review was performed using recommended methods and reported in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement.

3.3 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, falvour, 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 to diagnose for pSS patients. 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.

3.4 Data extraction and quality assessment

All titles and abstracts for relevant studies were screened, and a final selection for full text papers was conducted. Reasons for exclusion were documented (Appendix 20). Full texts of eligible studies were independently read and data were extracted by two reviewers (MA) and (NP). The two authors discussed the outcome, any disagreements were resolved by consensus. The following data was extracted: study characteristics (authors, year of publication, title, country of the study, study design); population characteristics (patients' 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 of cross-sectional design by Herzog et al. (2013) to meet the study's criteria (Appendix 21). 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 studies' quality in terms of three criteria: Participant' selection, comparability, exposure and outcome assessment.

3.5 Meta-analysis

Standardised mean differences (SMD) and a confidence interval (CI) of 95% were calculated for continuous data. A random–effect model was applied to reduce heterogeneity in combining studies' data in order to get an overall SMD. Heterogeneity was evaluated via Tau^2, Chi^2, df and I^2 at a *p*-value of ≤ 0.05. Overall effect was assessed using Z score 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 (Higgins JPT, 2011). We contacted the authors by email to obtain additional data for the meta-analysis. The correlation of smell, taste, sexual function, quality of life and mental health well-being with pSS was evaluated using Review Manager meta-analysis software (version 5.3; Cochrane Collaboration, Copenhagen, Denmark).

3.6 Results

3.6.1 Study selection

Final searches were undertaken in April 2016 and a total of 2767 articles were initially identified using the search strategy in five search engines. An overall agreement between reviewers achieved 99%. After reviewing titles and/ or abstracts, it was noticed that there is no article studied the effect of dryness on the three elements together (smell, taste and sexuality) in Sjögren's patients. Therefore, our search strategy has been focused on studying the effect of pSS on each element separately and on the general quality of life and mental health well-being. Fifty three studies were deemed relevant and selected for full text assessment. Of which, five articles fulfilled the criteria and were selected for qualitative and quantitative (meta-analysis) assessment. A flowchart based on PRISMA statement, shows the process of articles selection in

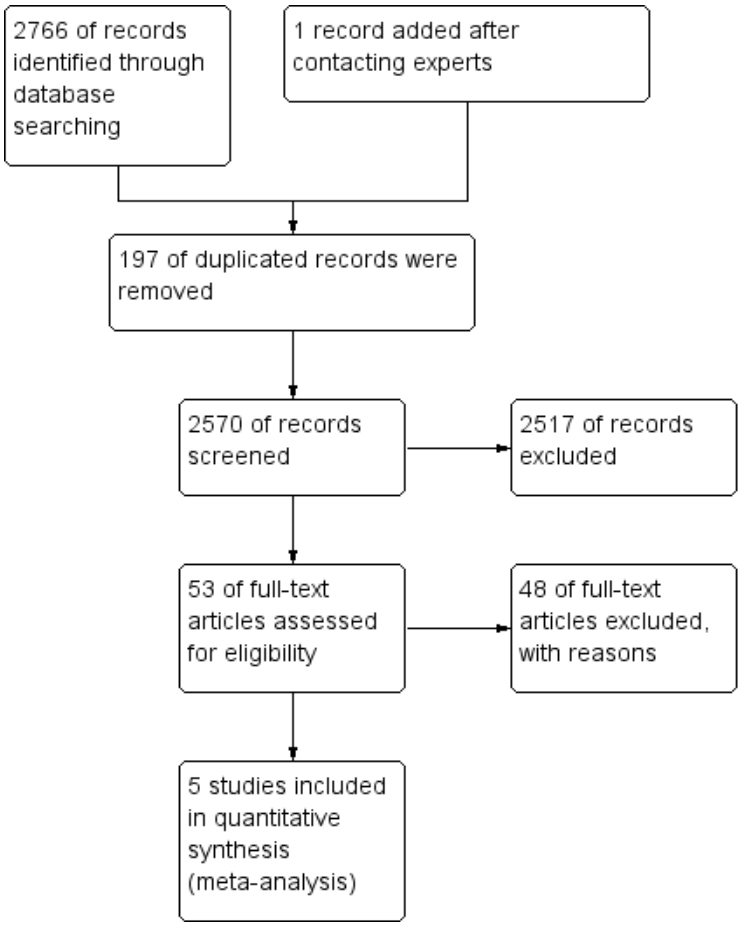

Figure 3-1. Studies selection process

3.6.2 Study characteristics

The characteristics of the five included studies for the current review are presented in table 3-1. Evidence of quality assessment of these studies ranged between moderate to high (Table 3-2; Figure 3-2). One study assessed the impact of pSS on smell and taste, with a total of 65 participants (Kamel et al., 2009), and three studies evaluated the impact of pSS on sexuality, with a total of 201 participants (Ugurlu et al., 2014, Priori et al., 2015, van Nimwegen et al., 2015). Three studies (Bongi et al., 2013, van Nimwegen et al., 2015, Priori et al., 2015) evaluated the impact of sexual dysfunction on mental health well-being by using the Hospital Anxiety and Depression Scale (HADS), and one study (Ugurlu et al., 2014) assessed the impact of sexual dysfunction on mental health well-being by using Beck's Depression Inventory (BDI), with a total of 249 and 313 participants to meta-analyse anxiety and depression respectively. Four studies (Kamel et al., 2009, Bongi et al., 2013, van Nimwegen et al., 2015, Priori et al., 2015) 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 et al. (2013) assessed the sexual function by different instrument modified from Hill questionnaire with no data displayed, therefore, this study has not been included in the meta-analysis.

Table 3-1 Characteristics of the five included studies

Reference	Country of publication	Study design as stated in the	Screening	Participants in analysis	Mean age	Mean years of disease duration	Outcome	Summary of study
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
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
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
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
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 3-2 Quality assessment of the included studies measured by Modified Newcastle Ottawa Scale (M-NOS)*

Studies	Selection						Comparability	Exposure			Outcome		Evidence quality
	Case definition	Represent-ativeness of cases	Selection of controls	Controls definition	Sample size	Outcome was not at start of study		Ascertain-ment of exposure	Same ascertain-ment for cases & controls	Non-response rate	Outcome - assessment	Statistical analysis	
Kamel et al 2009	⋆	-	-	-	-	⋆	⋆⋆	⋆	⋆	-	⋆	⋆	High
Bongi et a2013	⋆	-	-	⋆	⋆	⋆	⋆	-	-	-	⋆	⋆	Moderate
Ugurlu et a 2014	⋆	-	-	⋆	-	-	⋆⋆	-	⋆	-	⋆	⋆	Moderate
Nimwegen et al 2015	⋆	-	⋆	⋆	⋆	-	⋆⋆	-	⋆	-	⋆	⋆	High
Priori et al 2015	⋆	⋆	-	⋆	-	⋆	⋆⋆	-	⋆	⋆	⋆	⋆	High

0-3 poor; 4-7 moderate; 8-11 high; 12-15 very high

* See appendix 3.

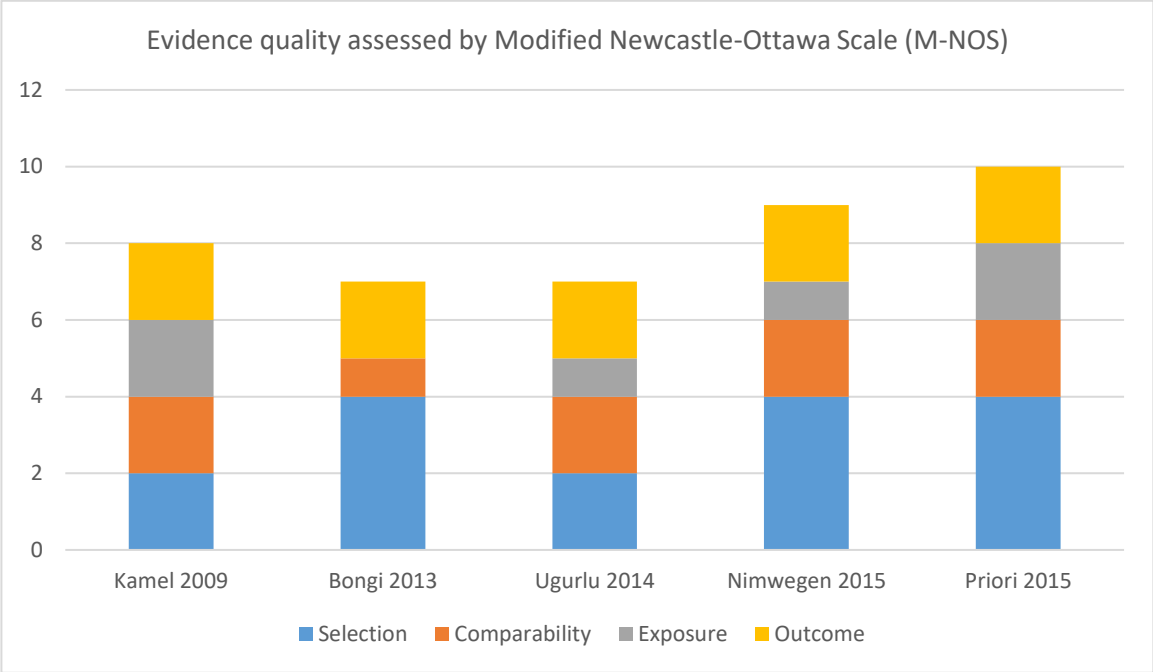

Figure 3-2 Quality assessment of the included studies measured by Modified Newcastle Ottawa Scale (M-NOS)

3.6.3 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 employed equally for all participants, therefore, information about the relation between the impaired chemosensory perception and the degree of salivary glands dysfunction, was not reported. In terms of the correlation between both senses, authors of the study found that smell function was positively correlated with that of taste ($r=0.35$, $p=0.004$). The study also proved that age was adversely associated with smell thresholds ($r=-0.252$; $p=0.04$), whilst no impact was found on taste dysfunction ($r=-0.15$, $p=0.236$). Results of this study may not be applied to the female population of Sjögren's patients, as there was 11% males recruited 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; therefore, there will be no meta-analysis for these elements in this review.

3.6.4 Sexual function

Sexual function has been measured by FSFI in three included studies (Ugurlu et al., 2014, van Nimwegen et al., 2015, Priori et al., 2015), and was compared between pSS patients (102 patients) and healthy controls (99 participants). Random-effect 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 - -0.43), Arousal (P<0.00001, SMD=-0.93, 95% CI=-1.22 - -0.64), lubrication (P<0.00001, SMD=-1.07, 95% CI -1.37 - -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 - -0.51), total FSFI (P<0.00001, SMD=-0.93, 95% CI=-1.22 - -0.64).

3.6.5 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 (Kamel et al., 2009, Bongi et al., 2013, van Nimwegen et al., 2015, Priori et al., 2015) 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 of combining domains' scores, 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).

3.6.6 Mental health well-being

Mental health well-being has been measured by HADS in four included studies (Bongi et al., 2013, Ugurlu et al., 2014, van Nimwegen et al., 2015, Priori et al., 2015) 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. 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 3-3).

Table 3-3 Summary of the meta-analysis of included studies

Outcome	Number of studies	SMD	95% CI	I^2
Smell impairment	1	-0.78	-1.29, -0.27	NA
Taste impairment	1	-1.01	-1.54, -0.49	NA
Total sexual dysfunction	3	-0.93	-1.22, -0.64	0%
Physical component summary/ QoL	4	-1.28	-1.65, -0.90	55%
Mental component summary/ QoL	4	-0.83	-1.27, -0.40	70%
Anxiety	3	0.61	0.02, 1.20	80%
Depression	4	0.79	0.43, 1.15	57%

NA: not applicable.
See appendix 4.

3.6.7 Publication bias and subgroup analysis

As the number of the included studies in each subgroup is less than ten, funnel plot and subgroup analysis were not possible to conduct.

3.7 Discussion

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

Of the studies that met our inclusion criteria, Kamel et al. (2009) was the only study that measured the effect of pSS on the smell and taste and quality of life in pSS patients. The remaining eligible studies (Bongi et al., 2013, Ugurlu et al., 2014, van Nimwegen et al., 2015, Priori et al., 2015) assessed the impact of sexual dysfunction on quality of life of pSS patients.

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 (Vitali et al., 2002). 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.

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 (Bongi et al., 2013, Ugurlu et al., 2014) to high (Kamel et al., 2009, van Nimwegen et al., 2015, Priori et al., 2015). 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. Not 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 to healthy controls. However, sexual problems tend to be associated with more than one element with this syndrome including age, joint pain, fatigue as well as vaginal dryness.

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, the 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 influencing 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 (Snaith RP, 1994, Brennan et al., 2010) therefore, we concluded that pSS has significantly increased anxiety and depression levels in pSS patients compared to controls.

3.8 Limitations of this study

The limited number of studies available for the meta-analysis 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 SS 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.

3.9 Conclusion

With this systematic review and meta-analysis we present evidence of the multidimensional impact of pSS on patients' well-being. Further work is required to look at the effect of the syndrome on the senses of smell and taste and hence on QoL.

CHAPTER 4: METHODOLOGY

4.1 Introduction

This study followed a matched case-control design, to investigate the impact of pSS on the senses of smell and taste, and sexual activity in female patients in the UK. The study was sponsored by Queen Mary University of London (QMUL), and was funded by the Ministry of Higher Education & Scientific Research in Iraq, as part of the Chief Investigator's PhD fulfilment.

4.2 Aims of the project

The aim of this study was to assess the impact of pSS on the smell, taste and sexual functions of female patients (primary hypothesis), and on various QoL aspects (General QoL, oral health related QoL and mental health well-being) (secondary hypothesis). The models used were to obtain data to achieve the primary objectives, which were for hypothesis testing, and the secondary objectives, which were for exploratory testing.

4.3 Objectives

4.3.1 Primary objectives (Hypothesis testing)

1. To compare the smell function in pSS group vs healthy volunteers group.
2. To compare the gustatory function in pSS group vs healthy volunteers group.
3. To compare the neurosensory threshold of taste in pSS group vs healthy volunteers group.
4. To compare the sexual function in pSS group vs healthy volunteers group.
5. To compare the general QoL in pSS group vs healthy volunteers group.
6. To compare the oral health related quality of life in pSS group vs healthy volunteers group.
7. To compare the mental health well-being in pSS group vs healthy volunteers group.

4.3.2 Secondary objectives (Exploratory testing).

8. To evaluate the impact of smell, gustatory and sexual functions on QoL and mental health well-being in pSS patients.
9. To investigate whether the acuity of the smell and gustatory function are correlated with each other.
10. To study the correlation of the degree of the smell function to the severity of oral dryness in pSS group.
11. To study the correlation of the degree of the taste function to the severity of oral dryness in pSS group.
12. To investigate the correlation of gustatory function to the neurosensory threshold of taste in pSS group.
13. To investigate whether oral dryness is correlated with the self-reported vaginal dryness in pSS group.
14. To investigate the impact of the self-reported vaginal dryness on the sexual function in pSS patients.

4.4 Ethical approval

An application to the Integrated Research Approval System (IRAS) was submitted on 11th November 2015 (IRAS project ID: 186276). A meeting with The Research Ethics Committee (REC) of London Bridge was scheduled on the 16th December 2015, where a number of minor amendments were requested. After implementing the Committee's suggestions, an ethical approval was obtained on the 10th of February 2016 (Reference number 15/LO/2064).

4.5 Participants

4.5.1 Eligibility criteria

- **Patients**

1. Female patients aged 18 years or older, males were excluded because pSS is a predominantly female syndrome.

2. Patients with a confirmed diagnosis of primary SS for a minimum of three months, in accordance to the revised American-European diagnostic criteria (Vitali et al., 2002).

3. Patients with the capacity to provide informed consent as defined by the Mental Capacity Act 2005 (The National Archives, 2017).

4. Patients who are able to understand verbal explanations and written information in English, with the support of the researcher, if needed.

- **Healthy volunteers**

1. Sex matched individuals aged 18 years or older, males were excluded as pSS is a predominant female syndrome.
2. Individuals with the capacity to provide informed consent as defined by the Mental Capacity Act 2005 (The National Archives, 2017).
3. Individuals who are able to understand verbal explanations and written information in English, with the support of the researcher, if needed.

4.5.2 Exclusion criteria

- Past head, neck and/or lower abdomen radiation treatment.
- Past chemotherapy treatment.
- History of having chronic salivary gland disease or swelling.
- Pregnancy or breast-feeding.
- Individuals with secondary SS.
- The presence of confounding signs and symptoms due to other systemic diseases such as asthma, sinusitis, nasal polyps, flu, and cold.
- The presence of oral conditions that are deemed to interfere with smell and taste, such as Candidiasis and Lichen planus.
- Uncontrolled diabetic patients.
- Significant dental problems.
- Staff, colleagues and dental students at Barts and the London school of Medicine and Dentistry.
- Individuals who withhold consent.

4.5.3 Patients

Three routes for patients' recruitment were followed in this study:

1. Patients approached on clinic in the Multidisciplinary Sjögren's clinic at the Institute of Dentistry, with information of the study.
2. Patients identified from the Research Clinical Database (RCD) of the Multidisciplinary Sjögren's clinic at the Institute of Dentistry in Whitechapel, and the Rheumatology clinic at Mile End Hospital. A database of 337 rheumatic patients was screened. Patients on the database were consented in the past to be contacted for research purposes in future. Eligible patients were defined as women diagnosed with pSS according to the American European Consensus Group (AECG) criteria (Vitali et al., 2002) (Appendix 1). If patients' diagnosis was unclear on the database, the blood test results as well as the consultants' letters were reviewed on the Care Record Service (CRS) to support the diagnosis. Postal invitations modified from Dillman methodology (Dillman, 2007) were sent to 122 eligible patients identified by this rout.
3. The project was advertised on the British Sjögren's Syndrome Association (BSSA) website, and interested pSS members were volunteered to take part.

4.5.4 Healthy volunteers

Healthy volunteers were recruited for comparison from the general population, by advertising the project in the Institute of Dentistry. Sex-matched healthy volunteers were recruited by advertising the project via posters, recruiting leaflets and information sheets. The advertising materials were placed in the lifts and the main entrance of the Institute of Dentistry as well as in clinic 6. Recruiting leaflets and information sheets were given to individuals who expressed interest in the study, before the consent form was signed. A ratio of one to one was used in recruiting patients and healthy volunteers.

4.6 Recruitment

4.6.1 Setting

The study was based in the Multidisciplinary Sjögren's Clinic, 2nd floor, Clinic 6, at the Institute of Dentistry, Barts Health Trust in Whitechapel East London. Both of the Institute of Dentistry and Barts Health Trust are major health service providers in the UK.

4.6.2 Procedures

During the period between 2nd March and 30th November 2016 recruitment process took place. The patients' and volunteers' status determined the exposure in the study. Eligible patients were sent a postal invitation pack, with detailed information of the research project (Appendix 5 and 7). A response form (Appendix 6) along with a stamped self-addressed envelope were included in the invitation pack. If patients did not show interest to take part in the study, they were not contacted again. If the research team received no response form, patients were contacted by phone to ensure whether they received the invitation. Otherwise, another invitation letter was sent if patients agreed. If they refused to participate, contacting them was suspended.

Patients, who sent back a response form wishing to take part in the study were contacted to arrange an appointment. On the visit day, patients were consented (Appendix 9) and asked to fill out the questionnaires and to undergo the clinical tests. If patients failed to attend to the appointment, they were contacted to arrange another appointment scheduled at their convenience. Patients, who failed to attend twice were not contacted again. Figure 4-1 summarises the process of recruiting patients from the CRD.

As for patients, interested healthy individuals were consented (Appendix 10) and asked to attend for one day visit at the Institute of Dentistry, to answer the questionnaires and to undergo the clinical tests (Figure 4-2).

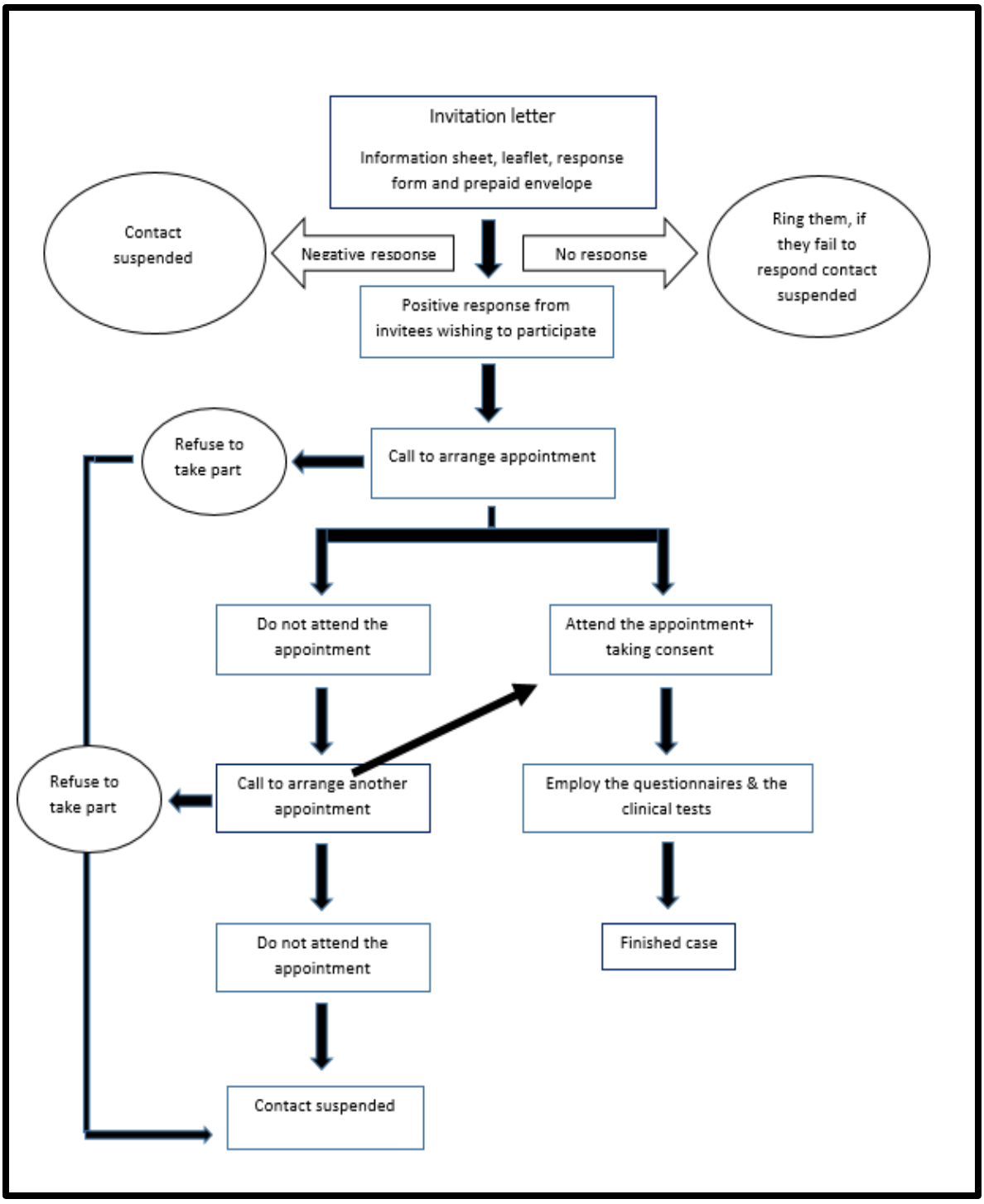

Figure 4-1 Flow chart illustrates the recruitment of pSS patients identified from RCD, modified from Dillman method

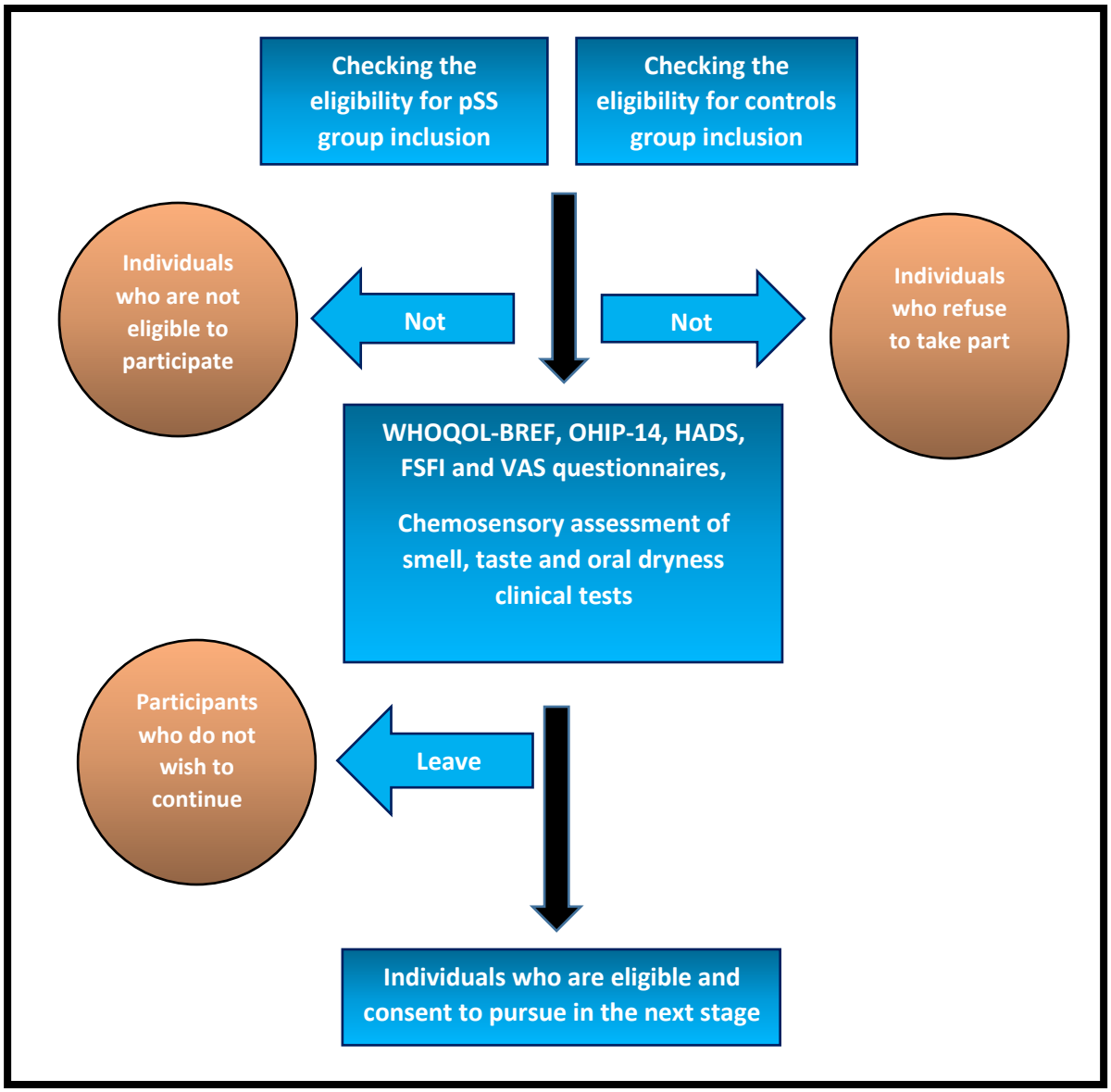

Figure 4-2 Flow chart illustrates the study stages

4.7 Test re-test reliability of the clinical measures

Reliability of the clinical tests was assessed in the study. Nine healthy participants underwent the test-retest evaluations of the smell, gustatory function and neurosensory threshold assessment tests. Cronbach's alpha showed good to excellent reliability (Cronbach's alpha = 0.862, 0.752 and 0.942 respectively).

4.8 Predictors

- Unstimulated salivary flow rate (USFR).
- Stimulated salivary flow rate (SSFR).
- Clinical oral dryness score (CODS).
- Item number 11 of the Xerostomia Inventory (XI) of the severity of nasal dryness.
- Self-reported vagina dryness.

4.9 Outcomes:

1. Smell function.
2. Gustatory function.
3. Neurosensory threshold.
4. Sexual function.
5. General quality of life.
6. Oral health-related quality of life.
7. Mental health well-being.

4.10 Potential confounders

- Age
- Smoking
- Alcohol intake
- Mouthwash
- Appliances
- Betel leaves
- Medicines
- Fatigue
- Disease duration

4.11 Data sources

The details of assessment methods for each variable of interest in the study were described in tables 4-1, 2 and 3.

Table 4-1 Predictors assessment

Predictors	Clinical assessment	Questionnaires	Groups
Nasal dryness	--	Item 11 of XI in the CRF[1]	Patients and volunteers
Oral dryness	USFR, SSFR and CODS	XI in the CRF[1]	Patients and volunteers
Vaginal dryness	--	CRF[2]	Patients

1: Appendix 16, page 10; appendix 17, page 7.
2: Appendix 16, page 10.

Table 4-2 Outcomes assessment

Outcomes	Clinical assessment	Questionnaires	Groups
Smell function	UPSIT	Item 1 of VAS[1]	Patients and volunteers
Gustatory Function	TST	- Items 3,4,5,6 and 7 of VAS[1] - Item 2 of OHIP-14[2]	Patients and volunteers
Neurosensory threshold	EGM	--	Patients and volunteers
Neuropathy	--	Questions 1-4 in the CRF[3]	Patients
Sexual function	--	FSFI[4]	Patients and volunteers
General quality of life	--	WHOQoL-BRÉF[5]	Patients and volunteers
Oral health related quality of life	--	OHIP-14 Item 2 of VAS[1]	Patients and volunteers
Mental health well-being	--	HADS[6]	Patients and volunteers

1: Appendix 15
2: Appendix 12
3: Appendix 16, page 8.
4: Appendix 14.
5: Appendix 11.
6: Appendix 13.

Table 4-3 Confounders assessment

Confounders	Clinical tests	Questionnaires	Groups
Age	--	CRF[1]	Patients and volunteers
Fatigue	--	- Item 8 of VAS[2] - CRF[3]	Patients and volunteers
Smoking	--	CRF[4]	Patients and volunteers
Alcohol	--	CRF[4]	Patients and volunteers
Mouthwash	--	CRF[4]	Patients and volunteers
Betel leaves	--	CRF[4]	Patients and volunteers
Medicines	--	CRF[5]	Patients and volunteers

1: Appendix 16 and 17, page 2.
2: Appendix 15.
3: Appendix 16, page 7.
4: Appendix 16 and 17, page 4.
5: Appendix 16 and 17, page 5.

4.12 Description of the clinical tests:

4.12.1 Smell identification test

Smell function was assessed by the University of Pennsylvania Smell Identification Test (UPSIT) from Sensonics (Doty et al., 1984). This test is a forced choice test for the quantitative assessment of the sense of smell, which was developed by Doty and others in 1984. The test comprises of a standardized 40-item which distributed into four booklets, each booklet has ten boxes of embedded microencapsulated odours with four different choices provided for each box. Subjects had to scratch each box with the provided pencil and to sniff the released smell, then to tick one of the appropriate options provided on the relevant page of the booklet (Figure 3-3). A score was then calculated for the final recognition of each subject.

A special version of this test was ordered to match the British cultural norms. According to the manual of the test, females were categorized based on their scores to:

35 – 40 Normal.
31 – 34 Mild microsmia.
26 – 30 Moderate microsmia.
19 – 25 Severe microsmia.
06 – 18 Total anosmia.

However, in the current study a cut off point for smell dysfunction for all participants was given at ≤30.

Figure 4-3 University of Pennsylvania Smell Identification Test (UPSIT)

4.12.2 Taste tests

A: Taste strips test

The gustatory function in the anterior two thirds of the tongue was assessed by the validated Taste Strips Test (TST) from Burghart Medical Technologies, Wedel, Germany (Mueller et al., 2003, Kamel et al., 2009). The test comprised of paper strips, each strip comes in a length of eight cm, and a width of one cm. The strips were previously soaked in one of the basic taste solutions: Sweet, sour, salt and bitter (Figure 4-4). The taste solutions were prepared with four different concentrations for each tastant, ranged from highest to lowest concentration as follows (Mueller et al., 2003):

- Sweet: 0.4, 0.2, 0.1, 0.05 g/ml sucrose.
- Sour: 0.3, 0.165, 0.09, 0.05 g/ml citric acid.
- Salt: 0.25, 0.1, 0.04, 0.016 g/ml sodium chloride.
- Bitter: 0.006, 0.0024, 0.0009, 0.0004 g/ml quinine hydrochloride.

Figure 4-4 Taste Strips Test (TST)

The strips were placed for 10 seconds on three places of the anterior two thirds of the tongue; these were the right, left and the tip. Subjects were asked to recognize the taste of each strip irrespective of the taste intensity. Subjects were advised to rinse with water after testing with each strip and a confirmation was sought that the previous taste was cleared, to eliminate the overlap between tastes. The correct taste identification was scored as one point on a scoring sheet (Appendix 23). A total score of less than nine points was considered hypogeusia as per the test's manual.

B: Electrogustometer

The neurosensory threshold of taste was assessed quantitatively by electrogustometer (EGM) from Sensonics (Krarup, 1958). The device also known by TR-06 Rion (Tokyo, Japan) (Figure 4-5). Subjects were familiarised with the equipment after explaining how it works and the kind of the taste sensation it stimulates. The device sends faint electrical current via the metal sticks to the tongue that stimulates taste, and a lesser chance of tingling sensation. The device has two poles, the cathode which was usually placed on the wrist or neck of participant, while the anode represented by a metal stick that was put on the tongue (Sham et al., 2007). The metal stick was put on the same places that were tested by the TST, these were right, left and the tip of the anterior two thirds of the tongue. Two centimetres

space was allowed between the borders of the tongue and the tested place. The duration of the current that was applied on each place of the tongue was fixed on 1.5 seconds.

Participants were notified before applying the metal stick on the tongue, and were advised to ignore the tingling they could feel on the tongue. Subjects were requested to only report the taste sensation or a change in a taste they feel by the current's stimulation. When subjects feet the taste, they were instructed to raise their hands or to click on the buzzy button provided, so the readings were recorded for each threshold of perception (Sham et al., 2007). A threshold was defined as the point at which an individual can detect a specific stimulus, or identify any change of stimulus of a test (Gescheider, 1997).

Single staircase technique (tow up/one down) that was adopted from Miller et al. (2002) and Deeb et al. (2010) was employed in this study. The technique includes starting out at the 0.0 dB with three times attempts of bringing the machine on and off, and subject had to identify when there was, or was not stimulus generated. If all the three sets of pairs at this level were correct, then move down in single step (e.g. from 0 dB to -2 dB). If a miss-identification occurred at any point before achieving the three sets of pairs, move up two steps, (e.g. from 0 to 4.0) and repeat. Continued moving up two more steps until three sets of pairs are obtained correctly, and then move down in a single step to achieve the minimum threshold. When same point of correct identification was obtained at least twice, a taste threshold value was marked. If there was no response to the highest value of stimulus, threshold was recorded as 34 dB. The threshold was identified on a particular plot paper for each participant (Appendix 18).

Normal range of neurosensory threshold of taste in the anterior 2/3 of tongue, was accepted at <8 dB (Sone et al., 2001, Negoro et al., 2004), and was considered as abnormal threshold when values exceeded 30 dB (Ellegard et al., 2007).

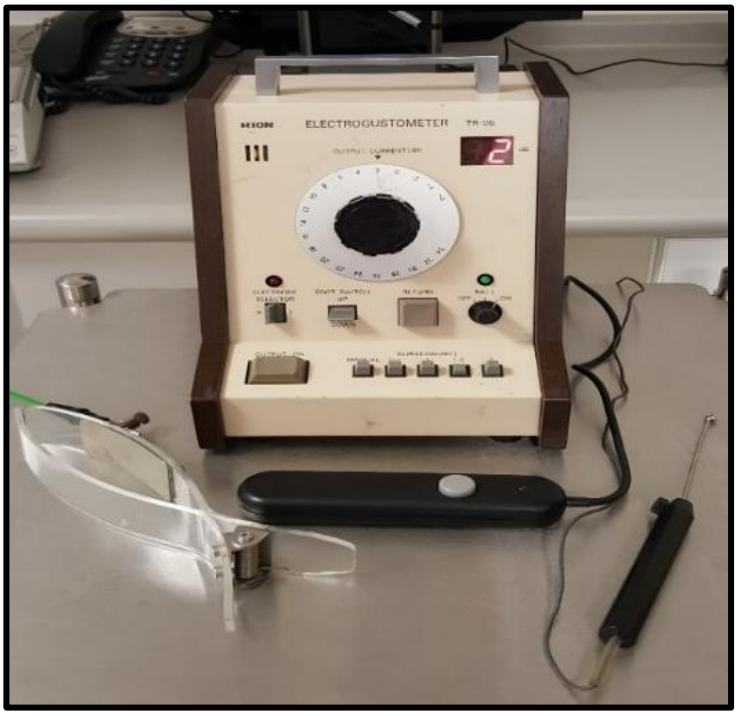

Figure 4-5 The electrogustometer for the neurosensory assessment of the taste

4.13 Oral dryness assessment

4.13.1 Unstimulated salivary flow rate

The test was described by Navazesh (1993) for unstimulated whole salivary flow rate (USFR). Participants were asked to spit out for five minutes into a pre-weighed disposable screw capped bottle. The amount of saliva was calculated per minute rate. A value of ≤ 1.5 ml of saliva in 15 minutes (i.e. ≤ 0.1 ml/min) was considered as the cutoff point of the unstimulated whole salivary glands function (Speight et al., 1992, Vitali et al., 2002).

4.13.2 Stimulated salivary flow rate

The test was described by Navazesh and Christensen (1982) for stimulated whole salivary flow rate (SSFR). Participants were asked to chew for five minutes a piece of same size and weight of sugar free paraffin wax pellets (CRT Paraffin, Ivoclar Vivadent), and spit the produced saliva in a pre-weighed screw capped bottle during chewing time. A significant dryness is defined by a cutoff point rate of ≤ 0.6 ml/min of the stimulated whole salivary glands function (Bookman et al., 2011).

4.13.3 Clinical oral dryness score

This assessing tool is also known as the Challacombe scale, which comprised of 10 items, for the clinical assessment of the severity of mouth dryness (Osailan et al., 2012) (Appendix 16 page 11, appendix 17 page 8). The scale was one of the routinely used instruments in the Multidisciplinary Sjögren's clinic. Mild dryness was indicated to scores ranged one to three. Moderate dryness was referred to scores ranged four to six, and sever dryness when the score ranged seven to ten.

4.14 Description of the questionnaires

4.14.1 World health organisation quality of life-BRÉF

The questionnaire, also known as WHOQoL-BRÉF, was used to assess the general quality of life (QoL) in the previous two weeks period by 26 items. The first question assessed the self-perceived QoL, "How would you rate your quality of life?" whilst the second question assessed satisfaction with health "How satisfied are you with your health?". The first two questions, were given a maximum score of five, to indicate the best QoL. The remaining 24 items assessed individuals' QoL in four domains; physical health, psychological, social relationships and environment. The items were rated on a Likert scale of one to five in each domain score. Raw domain scores were transformed to a 0-100 score according to guidelines (World health organisation, 1996). The higher the score, the better QoL was perceived. A cut-off value of <60 indicating poor/unsatisfactory QoL was used (Silva PAB, 2014). The questionnaire was checked for uncoded items and if applicable, participants were requested to complete the form. When more than 20% of data was missing, the questionnaire was considered invalid (Appendix 11).

4.14.2 Oral health impact profile-14

The questionnaire, also known as OHIP-14, was used to assess the oral health related QoL within the last twelve months period. This assessing tool comprised of fourteen items distributed into seven domains. The domains were functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability and handicap. Responses were given on a five rating scale: 0=never, 1=hardly ever, 2=occasionally, 3=fairly often, 4=very often. According to David Locker and Quiñonez (2009)

the prevalence of oral health problems were estimated by calculating the percentage of respondents reporting one or more impacts of "Fairly often" or "Very often". Extent of oral health problems were calculated by counting the number of items reported "Fairly often" or "Very often". Severity was calculated by summing the scored 14 items (range 0 – 56) to obtain the total score of a participant, where a higher score denotes worse oral health QoL (Locker D, 2001, Willumsen et al., 2010). The mean of items that comprised a domain, was calculated to obtain each domain score (Anneloes E. Gerritsen et al., 2012). The questionnaire was checked for uncoded items and if applicable participants were requested to complete the form. The assessment was considered invalid when responses of more than 20% of data were missing (Appendix 12).

4.14.3 Hospital anxiety and depression scale

The questionnaire, also known as HADS, was used to assess the mental health status in the previous week. This assessing tool comprised of two domains, anxiety (HDAS-A) and depression (HADS-D). Each domain consists of seven items, with four coded responses that range from zero to three. A simple final sum for each domain was given to the final domain scoring value. A score ranged from zero to seven indicates normal mental health status. A cut-off point of 8≤ denotes a borderline case of mental impairment (Snaith RP, 1994). The questionnaire was checked for uncoded items and if applicable participants were requested to complete the form. The assessment was considered invalid when responses of more than 20% of data were missing (Appendix 13).

4.14.4 Female sexual function index

The questionnaire, also known as FSFI, was used to assess the sexual activity in the previous three months period. This assessing instrument comprised of 19-item distributed into six domains, these were desire, arousal, lubrication, orgasm, satisfaction, and pain. Each domain has a certain number of items with coded options, the sum of the codes of each domain was multiplied by the domain's factor described on the FSFI website (Bayer Ag, 2017). The total score of the questionnaire is 36, where higher scores denote better sexual function. A cut-off value of ≤26.55 was adopted from (Wiegel et al., 2005) to identify subjects who are at risk of sexual dysfunction. The questionnaire was checked for uncoded

items and if applicable participants were requested to complete the form. The assessment was considered invalid when responses of more than 20% of data were missing (Appendix 14).

4.14.5 Visual analogue scale

This self-rating questionnaire was used to assess the acuity of smell, gustatory function, oral health related quality of life and fatigue. The cut-off value was arbitrarily specified at <50 for poor rating, over a 100 graded scale (Appendix 17).

4.14.6 Xerostomia inventory

This questionnaire was used for the self-assessment of oral dryness in the previous four weeks through 11 items. The questions were asked to all participants during taking the medical history. Each item has a five-coded options rated on a Likert scale ranging from one to five, in which 1 being “never” and 5 being “very often”. The self-ratings were summated to give a total score of 55, to indicate the severity of oral dryness. Higher scores denote sever oral dryness (Appendix 16, page 10; appendix 17, page 7).

4.15 Clinical research form

A Case Report Form (CRF) was designed to collect the required information from all participants. Each participant in the study received a CRF based on being in either the patients or healthy volunteers group:

4.15.1 CRF for patients

Collected information of the following:

1. Participants’ demographics: This included information of age, sex, address, employment, have a partner, education and ethnicity. For the definition of the latter, information from the Office for National Statistics were used (Office for National Statistics, 2017)(Appendix 16, pages 2-4).

2. Questions about life style (smoking, pan chewing and alcohol intake) (Appendix 16, page 4).

3. Questions about the use of mouthwashes (Appendix 16, page 4).
4. Questions about the existence of oral appliances (partial and/or complete denture or orthodontic appliance) (Appendix 16, page 4).
5. Questions about the medical history and medications (Appendix 16, page 5).
6. Clinical and laboratory Investigation results related to pSS diagnosis, obtained from the Clinical Records System (CRS), including results of: Ro, La, ANA, ENA, Ultra sound of the salivary glands and Lip biopsy (Appendix 16, page 5-7) and Schirmer test (Appendix 13, page 9).
7. Questions about fatigue (Appendix 16, page 7).
8. Questions to assess neuropathy status of pSS patients (Appendix 16, page 8).
9. Description of the extra oral examination (Appendix 16, page 8).
10. Open-ended question on whether there was any other aspect in which pSS affected patients' QoL that was not covered in the survey. These questions were established based on clinical experience of specialists in the Neurology Department at the Royal London Hospital, Barts Health Trust (Appendix 16, page 10).
11. Self-perceived assessment for severity of mouth dryness by using Xerostomia Inventory (XI) (Appendix 16, page 8).
12. The clinical assessment of oral dryness using the clinical oral dryness score (CODS) (Appendix 16, page 11).
13. Results of the research clinical tests that were ethically approved for the study which included results of salivary flow rates (Appendix 13, page 9 of), smell, taste and neurology of taste (Appendix 16, page 12).

4.15.2 CRF for healthy volunteers

Contained the following:

1. Participants' Demographics: This included information on age, sex, address, employment, have a partner, education and ethnicity. For the definition of the latter,

information from the Office for National Statistics were used (Office for National Statistics, 2017) (Appendix 17, page 2-4).

2. Questions about life style (Smoking, pan chewing and alcohol) (Appendix 17, page 4).
3. Questions about the use of mouthwashes (Appendix 17, page 4).
4. Questions about the existence of oral appliances (partial and/or complete denture or orthodontic appliance) (Appendix 17, page 4).
5. Questions about the medical history and medications (Appendix 17, page 5).
6. Description of the extra oral examination (Appendix 17, page 5).
7. Results of the research clinical tests that were ethically approved for the study, which included results of salivary flow rates (Appendix 17, page 6), smell, taste and neurology of taste (Appendix 17, page 9).
8. Self-perceived assessment for severity of mouth dryness by using Xerostomia Inventory (XI) (Appendix 17, page 7).
9. The clinical assessment of oral dryness using the clinical oral dryness score (CODS) (Appendix 17, page 8).

4.16 Bias

Bias was avoided in the current study by ensuring the following:

- One researcher committed participants' recruitment, clinical testing and data collection to eliminate performance bias.
- The number of recruited participants was almost same as the number at the end of the study (two missing per group), this ensured eliminating attrition bias.
- Participants were recruited from different sources to ensure generalisability.
- Questionnaires were checked and the uncoded items were requested to be completed to ensure data accuracy.
- Confounders were identified and controlled by using multiregression analysis.
- Positive and negative results were addressed to eliminate citation bias.

- Patients were identified by the validated AECG criteria to eliminate misclassification of exposure bias.

4.17 Sample size

The sample size calculation was performed using OpenEpi, which is an open source approach, utilised by epidemiologists and others to provide information about sample size and power calculations for different types of study designs. The calculation set the power of the test at 90% and CI at 95% with a ratio of sample size 1 to 1. However, the information that was obtained from the literature on effect size was varied. For instance, the sample size for case-control study, that was obtained based on the mean difference of the smell and taste function in Kamel et al. (2009) study was n=72 and n=6 per group respectively. For sexual function that was based on mean difference in a study by van Nimwegen et al. (2015), the sample was n=59 per group.

It was therefore decided that we use our own data based on a mean difference for smell, taste and sexual function in a pilot study of nine pSS patients and 12 healthy volunteers. The mean score ±SD of the smell for patients=26.7 ±8 and volunteers=34.4 ±3.3 was calculated. Similarly, the mean score of taste for patients=8.3 ±3.3 and volunteers=13.2 ±1.9 and the mean score of sexual function for patients=19.8 ±8.7 and volunteers=28.7 ±4.3 was identified. Nomogram method (Altman, 1982) was used (shown below by dotted line in figure 3-6) to estimate the sample size at power of 90% and level of significance of 5%. Pooled standard deviation of both groups was calculated for smell SD_{pooled}=5.8, taste SD_{pooled}=2.6 and for sexual function SD_{pooled}=6.8. The minimum acceptable mean difference of smell=7.7, taste=4.9 and sexual function=8.9. A large effect size of smell (d=1.3), taste (d=2.6) and sexual function (d=1.3) was found between the groups. Accordingly, a total of 28 subjects (14 cases and 14 healthy volunteers) as was required for the outcomes smell and sexual function, and 25 subjects for the outcome of taste. However, based on benchmarks suggested by Cohen (1988), a moderate effect size of d=7.5 was considered more suitable. A power of 90%, level of significance of 5% and a total of 75 subjects (cases and healthy volunteers) would be required to detect that level of difference (Solid line in figure-6). To consider the possibility of 20% drop out, the sample was inflated to give a

minimum of 90 participants (45 cases and 45 healthy volunteers). The study was powered to address one primary analysis, as is normally recommended for hypothesis testing. Other analyses may be considered exploratory.

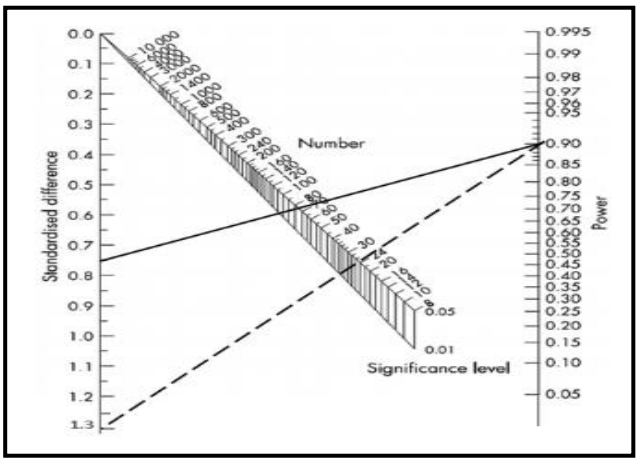

Figure 4-6 Nomogram for calculating the sample size of the study

4.18 Feasibility study

A feasibility study was conducted to determine the project's viability, and the possibility of patients' recruitment within the Multidisciplinary Sjögren's clinic in the Dental Institute/ Whitechapel. Six healthy participants volunteered to take part in this study. A suitable place to conduct the clinical tests was allocated. To ensure confidentiality, a secured place to store participants' data was offered by the Institute of Dentistry.

4.19 Results and observations

- The study worked within the dynamics of the clinic.
- The clinical tests were reflective of participants' perception, and were found affordable by participants.
- Participants answered all the questionnaires without reservation including the FSFI, despite its intrusive nature.
- The clinical tests and the questionnaires were conducted in a reasonable time of one hour.
- The electrogustometer was pain free for participants and was of no discomfort.

4.20 Feedback

1. Participants were not sure how to respond to the VAS.

   Action taken: rewording the questionnaire and adding of descriptive words at each end of the scale to indicate the two extremes of the assessed outcome.

2. A non-native speaker participant was confused between the word bitter and sour, and was reporting the word bitter for sour and vice versa.

   Action taken: Illustrating cards were provided to explain each of the basic tastes, with a relevant picture and descriptive word, to facilitate identifying the tastant by non-native speakers.

4.21 Data analysis

Data were analysed using the latest version of Statistical Package for Social Sciences, IBM Corporation, SPSS Inc., Chicago, IL, USA version-23 statistical software. Quantitative variables were handled as normal and abnormal. Matching of patients and healthy volunteers was addressed by using the variables as confounders in the regression model. The distribution of data was determined via Shapiro-Wilk test, and level of significance was 5%. Residual plots were used to assess quality of regression. Continuous variables were expressed as mean followed by ± standard deviation, and categorical variables were expressed as percent. The following statistical tests were used as follows:

- To examine objectives one to seven, independent t-test, Chi-square and frequency analysis were used. Independent sample t-test was applied to detect the mean difference between patients and healthy volunteers groups. Chi-square and frequency analysis were used to determine the range pattern of dysfunction in each group.
- To examine objective eight, multiregression analysis was used to identify predictors of the quality of life (QoL), and to control for the potential confounding variables. The ENTER method was used for data entry, and the independent continuous variables were the smell, gustatory and sexual functions, whilst the dependent continuous variables in the model were as follows:

- Every domain of the general QoL (Physical, psychological, social and environmental) measured by WHOQoL-BRÉF.
- The total score and each domain of the oral health related QoL measured by OHIP-14 (Functional limitation, physical discomfort, psychological discomfort, physical disability, psychological disability, social disability and handicap).
- Every domain of the mental health well-being (Anxiety and depression) measured by HADS.
- Confounders of smoking, alcohol intake, mouthwash use, appliances, pain relief, Gabapentine, other drugs and fatigue were entered as dichotomous variables. Whilst age and disease duration were entered as continuous variables.
- To examine objective nine, Pearson's correlation and multiregression analysis were used to detect the correlation between the smell (independent continuous variable) and gustatory function (dependent continuous variable). The ENTER method was used for data entry in the regression analysis. Confounders of smoking, alcohol intake, mouthwash use, appliances, pain relief, Gabapentine, other drugs and fatigue were entered as dichotomous variables. Whilst age and disease duration were entered as continuous variables.
- To examine objectives 10 and 11, multiregression analysis was used to predict the smell and gustatory function (dependant continuous variables) from the oral dryness assessment tests (independent continuous variables). The ENTER method was used for data entry. Confounders of smoking, alcohol intake, mouthwash use, appliances, pain relief, Gabapentine and other drugs were entered as dichotomous variables. Whilst age and disease duration were entered as continuous variables.
- To examine objective 12, Pearson's correlation and multiregression analysis were used to detect the association between the gustatory function (dependent variable) and the neurosensory threshold of taste (independent variable). The ENTER method was used for data entry. Confounders of smoking, alcohol intake, mouthwash use, appliances, pain relief, Gabapentine and other drugs were entered as dichotomous variables. Whilst age and disease duration were entered as continuous variables.

- To examine objective 13, frequency analysis was used to determine the rate of the self-reported vagina dryness in the patients group. Binary logistic regression was used to predict the self-reported vagina dryness (dependant variable) from oral dryness measures (independent variable).

- To examine objective 14, multiregression analysis for a subgroup of the sexually active pSS patients was conducted. The analysis was run to predict the sexual function (dependant variable) from the self-reported vagina dryness (independent variable) and to control for the potential confounders. The ENTER method was used for data entry. Confounders of alcohol intake and fatigue were entered as dichotomous variables, whilst age and disease duration were entered as continuous variables.

- To examine other results, Pearson's rank order was used to study the correlation between subjective and objective tests. Multiregression analysis was used to predict oral, nasal and vaginal dryness (dependant continuous variable) from medicines (independent dichotomous variables) taken by patients. The ENTER method was used for data entry.

- To analyse the open-ended questions, frequency analysis was used to determine the rate of each reported symptom by patients.

4.22 Subgroup analysis

A subgroup of sexually active participants was considered in the analysis to detect the impact of the pSS on sexuality.

4.23 Missing data

The missing data was considered few (three missing data in the patients group and two in the healthy volunteers group). Therefore, the need to adjust the results statistically was not deemed necessary.

CHAPTER 5: RESULTS

5.1 Demographics of participants

Out of the 122 invitations that were sent to eligible pSS patients who were selected from RCD, 38 patients were interested and attended the clinic to take part in the study, after being consented. Twenty more patients were recruited on clinic, of which, four dropped out. Fifteen more patients were recruited from BSSA. Excluded patients were those with unconfirmed diagnosis, one from RCD and three from BSSA (Figure 5-1). The attendance rate was 80%, and the overall response rate of contacted patients from RCD was 31.15%. Sixty five healthy volunteers were recruited for comparison, of which, three did not meet eligibility criteria and hence excluded, giving a total of 62 healthy volunteers (Figure 5-2).

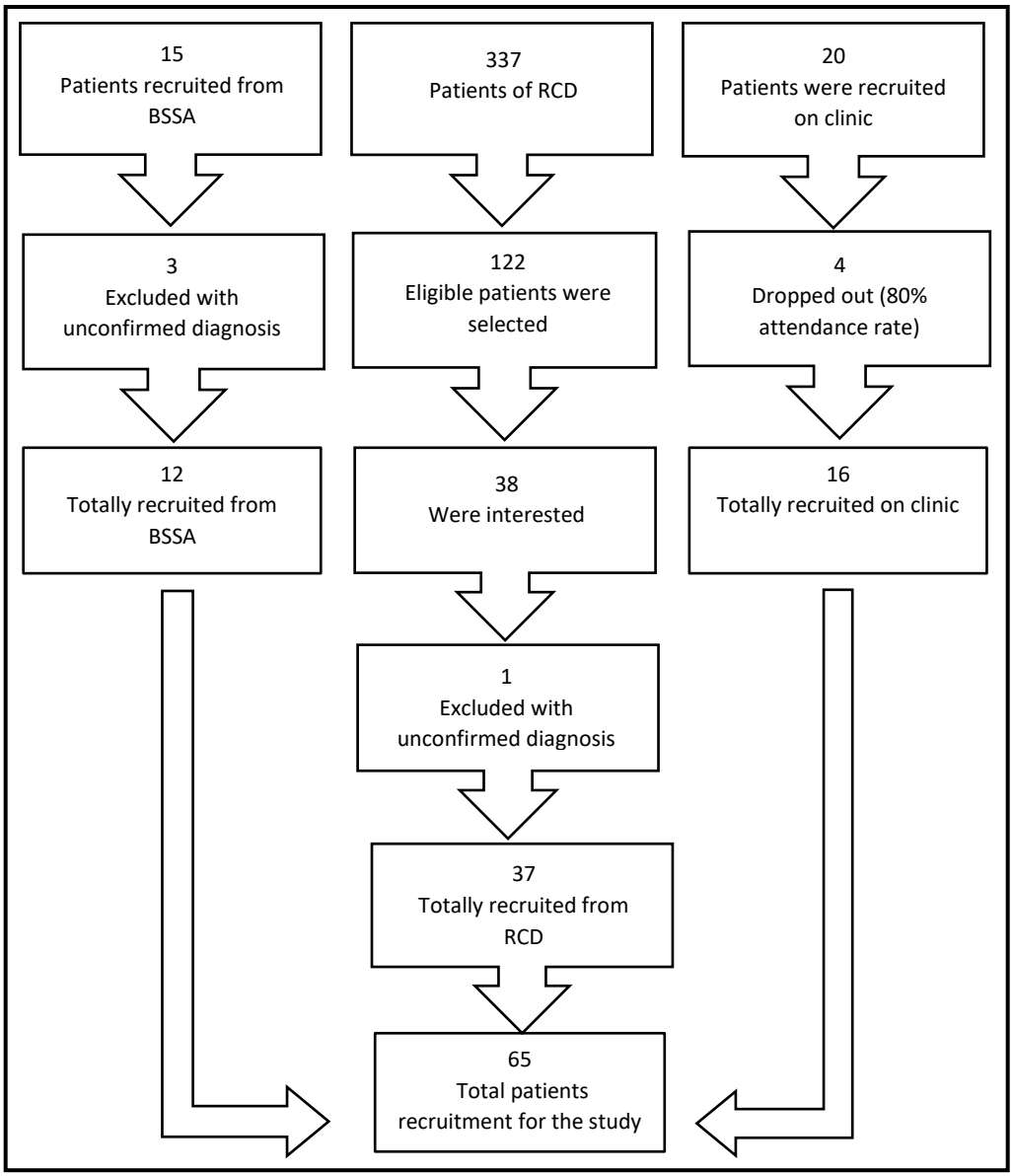

Figure 5-1 Flow diagram illustrates the included and excluded patients from the three routs of recruitment and the final number of enrolled eligible patients

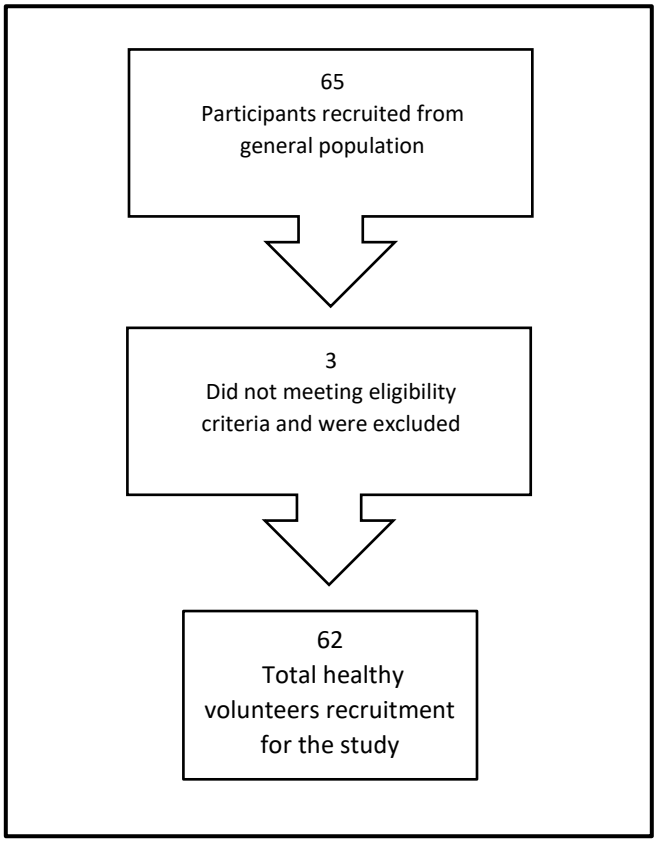

Figure 5-2 Diagram illustrates the recruitment of the healthy volunteers in the study

5.2 Sample description

Sixty five patients and sixty two sex-matched healthy volunteers gave consent and participated in the study. The advantage of recruiting more participants than that obtained from power calculation was high power of multivariate regression analysis, to avoid spurious or false statistical significance due to over drafting. All literate with different levels of educational attainment with age mean, (±SD) of patients 59.03 ±12.75 (Patients' age range 24 – 83 years) and healthy volunteers 43.04 ±14.84 (Volunteers' age range 21 – 93 years). Ethnicity of patients included 69.23% of White background and 10.76% black, 13.84% Asian, 1.53% mixed or multiple background and 4.61% other ethnic group. Ethnicity of the healthy volunteers constructed 46.77% White background and 8.06% black, 20.96% Asian, 19.35% mixed or multiple background and 4.83% other ethnic group. Retired patients and controls were 53.84% and 9.67% respectively. Employed patients (30.76%) and healthy volunteers (69.35%) were higher than unemployed (15.38% and 19.35% respectively) (Table 5-1).

Patients attended the clinic from outside London constituted 33.84% versus 66.15% from London. The latter was distributed to the west (16.27%), east (72.09%) and north London (11.62%). Volunteers attended from outside London 6.45% versus 93.54% from London of which 41.37%, 51.72% and 6.89% were recruited from southwest, east and north London respectively.

Table 5-1 Characteristics of patients and healthy volunteers.

Characteristics	**Patients n=65**	**Volunteers n=62**	**Total n=127**
Age	**Mean (95%)** 59 (55.8-62.1)	**Mean (95%)** 43 (39.2-46.8)	**Mean (95%)** 51 (48.4-54)
Ethnicity	**N (%)**	**N (%)**	**N (%)**
White UK	41 (63)	14 (22)	55 (43)
White others	4 (6)	14 (22)	18 (14)
White total	45 (69)	28 (45)	73 (57)
Mixed	1 (1)	4 (6)	5 (3)
Asian	9 (13)	13 (20)	22 (17)
Black	7 (10)	5 (8)	12 (9)
Other	3 (4)	12 (19)	15 (11)
Partner			
Yes	45 (69)	43 (71)	88 (70)
No	20 (31)	19 (31)	39 (31)
Education			
Primary	1 (1)	2 (3)	3 (2)
Secondary	23 (35)	11 (17)	34 (26)
Tertiary	41 (63)	49 (79)	90 (70)
Monthly income			
£500-£1000	7 (10)	7 (11)	14 (11)
£1000-£2000	18 (27)	19 (30)	37 (29)
more than £2000	33 (50)	26 (41)	59 (46)
preferred not to say	5 (8)	10 (16)	15 (11)
Missing	1 (1)	0	1 (0.7)
Employment			
Employed	20 (30)	43 (69)	63 (49)
Unemployed	10 (15)	12 (19)	22 (17)
Retired	35 (53)	6 (9)	41 (32)
Missing	0	1 (1)	1 (0.7)
Smokers	4 (6)	4 (6)	8 (6)
Alcoholics	31 (47)	23 (37)	54 (42)
Betel leaves takers	0 (0)	2 (3)	2 (1)
Mouthwash users	41 (63)	32 (51)	73 (57)

5.3 PRIMARY OUTCOME RESULTS

5.3.1 Objective 1: To compare the smell function in pSS group vs healthy volunteers group

All patients (n=65) and all healthy volunteers (n=62) underwent the smell test. The smell function was statistically significantly impaired in pSS group (30, ±7.087) compared with healthy volunteers group (33.95, ±4.806). The mean difference was 3.9 and 95% CI=1.8 - 6.1 (Table 5-13). Individuals with hyposmia constructed 41.5% (n=27/65) of pSS patients vs 24.1% (n=15/62) healthy volunteers. Only 7.3% (n=10) of pSS group who self-assessed their smell quality using VAS, were aware of the loss of their smell acuity.

5.3.2 Objective 2: To compare the gustatory function in pSS group vs healthy volunteers group tested by TST

1. Total gustatory function score

Sixty three patients and 60 healthy volunteers underwent the TST. The average of the three sites of the tongue (Tip, right and left) of the taste function was statistically significantly impaired in pSS group (8.3, ±3) compared with healthy volunteers group (12.6, ±2.1). The mean difference was 4.3 and 95% CI=3.3–5.2 (Table 5-13). Individuals with hypogeusia constructed 54% (n=34/63) of pSS group vs 8.3% (n=5/60) of the healthy volunteers group. Patients' self-assessment of their taste quality using VAS, revealed that 21.9% (n=14) were aware of the loss of their taste acuity.

2. Regional gustatory function score

The function of taste was statistically significantly affected on the three tested places of the anterior 2/3 of the tongue in the patients group, compared to the healthy volunteers group. The right side scored statistically significantly lower in patients (7.9, ±3.6) compared with healthy volunteers (12.9, ±2). The left side of the tongue scored statistically significantly lower in the patients group (7.5, ±3.6) compared with healthy volunteers groups (12.1, ±3.2). The tip of the tongue scored statistically significantly lower in the patients group (9.5, ±3.3) compared with healthy volunteers group (12.8, ±2.2), although both were within the normal range score (Table 5-2).

Table 5-2 Comparison of the regional taste function of the tongue tested by TST between pSS patients and healthy volunteers

Tested site	Mean* Patients, n=63 Healthy volunteers, n=60	Mean difference (95% CI)	p-value
Tip	9.5 12.8	3.2 (2.2–4.2)	< 0.05
Right	7.9 12.9	5 (3.9–6)	< 0.05
Left	7.5 12.1	4.5 (3.3–5.8)	< 0.05
Total**	8.3 12.6	4.3 (3.4-5.2)	< 0.05

*Normal taste function of ≥9 in 0–16 scale

** See table 4-2

In the patients group, there was no significant difference in the results obtained from both laterals of the tongue (Mean difference=0.4, 95% CI=0.8–1.6). However, the difference between the tip and each lateral of the tongue was statistically significant, where the mean score of the tip was the highest (9.5, ±3.3) (Table 5-3). In the healthy volunteers group, there was no statistical significant difference between the three tested places of the tongue (Table 5-4).

Table 5-3 Comparison of the regional taste function of the tongue tested by TST in the patients group

Tested site	Mean* Patients, n=63	Mean difference (95% CI)	p-value
Right	7.9	0.4	0.5
Left	7.5	(0.8–1.6)	
Right	7.9	1.6	0.01
Tip	9.5	(0.3–2.8)	
Left	7.5	2	< 0.05
Tip	9.5	(0.7–3.2)	

*Normal taste function of ≥9 in 0–16 scale

Table 5-4 Comparison of the regional taste function of the tongue tested by TST in the healthy volunteers group

Tested site	Mean* Healthy volunteers, n=60	Mean difference (95% CI)	p-value
Right	12.9	0.8	0.1
Left	12.1	(0.1–1.8)	
Right	12.9	0.1	0.6
Tip	12.8	(0.6–0.9)	
Left	12.1	0.6	0.1
Tip	12.8	(0.3–1.6)	

*Normal taste function of ≥9 in 0–16 scale

3. The four basic tastes scores

According to the TST manual, the whole mouth tasting ability is represented by examining of the tip of the tongue, and the comparisons were as follow:

- **Sweet**

The ability to taste sweet was statistically significantly impaired in pSS group (2.8, ±1.1) compared to healthy volunteers group (3.6, ±0.7). The mean difference between the groups was 0.7 and 95% CI=0.4–1.1 (Table 5-5).

- **Sour**

There was statistical difference in the ability to taste sour in pSS group (2.3, ±0.9) compared to healthy volunteers group (2.7, ±0.8). The mean difference between groups was 0.4 and 95% CI=0.1–0.7 (Table 5-5).

- **Salt**

The ability to taste salt was statistically significantly impaired in pSS group (1.6, ±1.2) compared to healthy volunteers group (3.4, ±0.7). The mean difference between groups was 1.1 and 95% CI=0.7–1.1 (Table 5-5).

- **Bitter**

The ability to taste bitter was statistically significantly impaired in pSS group (1.6, ±1.2) compared to healthy volunteers group (3.1, ±0.9). The mean difference between groups was 0.9 and 95% CI=0.5–1.3 (Table 5-5).

The ability to taste sour, salt and bitter differed statistically significantly (p=0.00) from the ability to taste sweet, but not significantly with each other.

Table 5-5 Comparison of the whole mouth testing of the four basic tastes between pSS patients and healthy volunteers

Taste category	**Mean*** Patients, n=63 Healthy volunteers, n=60	**Mean difference (95% CI)**	**p-value**
Sweet	2.8 3.6	0.7 (0.4–1.1)	< 0.05
Sour	2.3 2.7	0.4 (0.1–0.7)	< 0.05
Salt	2.2 3.3	1 (0.7–1.1)	< 0.05
Bitter	2 3	0.9 (0.5–1.3)	< 0.05

*Range score of each taste is 0-4

4. The rate of identifying the lowest concentration of each taste

The number of patients, who were able to identify each of the four basic tastes at the lowest concentrations, was statistically less than that of healthy volunteers (Table 5-6).

Table 5-6 Comparison of identifying rate of the lowest concentration of each taste between patients and healthy volunteers

Taste category	**Tip** Patients Healthy volunteers	**p-value**	**Right** Patients Healthy volunteers	**p-value**	**Left** Patients Healthy volunteers	**p-value**
Sweet	39.7%, n=25/63 78.3%, n=47/60	< 0.05	38.1%, n=24/63 78.3%, n=47/60	< 0.05	33.3%, n=21/63 73.3%, n=44/60	< 0.05
Sour	7.9%, n=5/63 16.7%, n=10/60	0.1	7.9%, n=5/63 25%, n=15/60	< 0.05	6.3%, n=4/63 18.3%, n=11/60	< 0.05
Salt	14.3%, n=9/63 51.7%, n=31/60	< 0.05	6.3%, n=4/63 33.3%, n=20/60	< 0.05	3.2%, n=2/63 45%, n=27/60	< 0.05
Bitter	9.5%, n=6/63 35%, n=21/60	< 0.05	6.3%, n=4/63 46.7%, n=28/60	< 0.05	14%, n=9/63 40%, n=24/60	< 0.05

5.3.3 Objective 3: To compare the neurosensory threshold of taste in pSS group vs healthy volunteers group

1. Total neurosensory threshold score

Sixty three patients and 61 healthy volunteers underwent the EGM test. The total score of the neurosensory threshold was three times higher (p=0.00) in pSS group (5.7, ±8.4, n=63) compared to healthy volunteers group (-0.4, ±6.6, n=61). The mean difference was 6.1 and 95% CI=3.4–8.8, where highest mean score indicates worse function (Table 5-13).

2. Regional neurosensory threshold score

- **Right side (Right patients-right healthy volunteers)**

The neurosensory threshold on the right side of anterior 2/3 of the tongue was statistically significantly impaired in the pSS group (7.4, ±10.5) compared with that of the healthy volunteers group (-0.1, ±6.5). The highest mean score indicates worse function.

- **Left side (Left patients-left healthy volunteers)**

Similarly, the neurosensory threshold of the left side of the tongue was statistically significantly impaired in the pSS group (6.2, ±10.3) compared with that of the healthy volunteers group (-0.6, ±6). The highest mean score indicates worse function.

- **Tip of the tongue (Tip patients-tip healthy volunteers)**

The neurosensory threshold on the tip of the tongue was less affected by the syndrome than the laterals of the tongue. Furthermore, the neurosensory threshold of the tip of the tongue was statistically significantly impaired in the patients group (3.7, ±10.3) compared to the tip of the tongue in the healthy volunteers (-0.8, ±7.5) (Table 5-7).

In a comparison between the neurosensory thresholds of the three tested places of the tongue in each group, there was no statistical significant difference between the right and left, right and tip, left and tip in the patients and healthy volunteers separately (Tables 5-8 and 5-9).

Table 5-7 Comparison of the regional neurosensory threshold of taste tested by EGM between pSS patients and healthy volunteers

Tested site	Mean* Patients, n=64 Healthy volunteers, n=61	Mean difference (95% CI)	p-value
Tip	3.7 -0.8	4.5 (1.3–7.7)	< 0.05
Right	7.4 -0.1	7.4 (4.3–10.6)	< 0.05
Left	6.2 -0.6	6.9 (3.9–10)	< 0.05
Total	5.7 -0.3	6.1 (3.4–8.8)	< 0.05

*Normal score of neurosensory function of taste <8 in a scale of -6–34

3. Comparison of the regional scores of the tongue

- **Patients**

In the pSS group, there was no difference in the neurosensory threshold when the right and left laterals of the tongue were compared with each other or when the left and the tip of the tongue were compared. However, the mean score of the tip (3.7, ±10.3) was statistically significantly less than the mean score of the right lateral (7.4, ±10.5) (Table 5-8).

- **Healthy volunteers**

In the healthy volunteers group, there was no statistical significant difference in the neurosensory threshold between the three tested sites of the tongue (Table 5-9).

Table 5-8 Comparison of the three places of the tongue tested by EGM in the pSS group

Tested site	**Mean*** Patients, n = 64	**Mean difference (95% CI)**	**p-value**
Right	7.4	1.1	0.5
Left	6.2	(-2.5 – 4.7)	
Right	7.4	3.4	0.05
Tip	3.7	(-7 – 0.2)	
Left	6.2	2.5	0.1
Tip	3.7	(-6.2 – 1)	

Table 5-9 Comparison the three places of the tongue tested by EGM in the healthy volunteers group

Tested site	**Mean*** Healthy volunteers, n=61	**Mean difference (95% CI)**	**p-value**
Right	-0.2	0.5	0.6
Left	-0.7	(-1.7–2.8)	
Right	-0.2	0.9	0.4
Tip	-0.9	(-3.3–1.7)	
Left	-0.7	-0.1	0.8
Tip	-0.9	(-2.6–2.2)	

5.3.4 Objective 4: To compare the sexual function in pSS group vs healthy volunteers group

Forty three percent of the pSS group (n=28) and 67.7% (n=42) of the healthy volunteers were sexually active and therefore were included in the statistical analysis. Out of the sexually active participants, 82.1% of patients (n=23/28) and 33.3% of healthy volunteers (n=14/42) had sexual dysfunction as measured by FSFI. The total score of the sexual function was impaired significantly in the sexually active pSS group (19.1, ±7.7) compared with the sexually active healthy volunteers group (28.4, ±4.9). The mean difference of the total score was 9.3, 95% CI=6–12.6 (Figure 5-3). The percentage rate was calculated for the lowest score in each domain. The lowest scores were determined by the validated scoring system of the FSFI questionnaire.

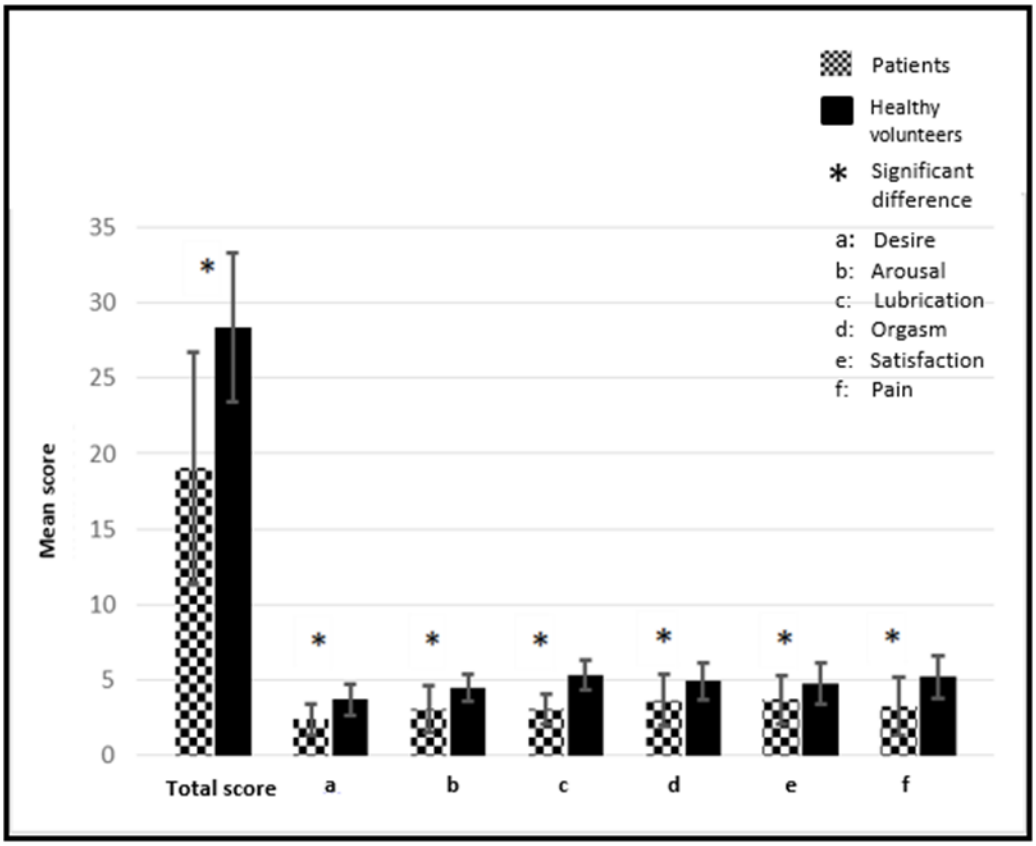

Figure 5-3 Comparison of the mean difference of the total FSFI and each of the six domains between pSS patients and healthy volunteers. Bars indicating SD.

Domain 1: Desire

The sexually active patients had statistically less sexual desire (2.3, ±1) than the sexually active healthy volunteers (3.7, ±1). The mean difference was 1.3 and the 95% CI=0.8–1.8 (Table 5-10).

2. *Domain 2: Arousal*

The sexual arousal in the sexually active patients was statistically impaired in the sexually active patients (3.1, ±1.6) compared to the sexually active healthy volunteers (4.5, ±0.9). The mean difference was 1.4 and the 95% CI=0.7–2 (Table 5-10).

3. ***Domain 3: Lubrication***

The ability to lubricate in a sexual activity was statistically impaired in the sexually active patients (3.1, ±1.5) compared to the sexually active healthy volunteers (5.3, ±0.9). The mean difference was 2.2 and the 95% CI=1.5–2.8 (Table 5-10).

4. ***Domain 4: Orgasm***

The ability to reach orgasm in the sexually active pSS group was statistically less (3.7, ±1.7) compared to the sexually active healthy volunteers group (4.9, ±1.2), the mean difference was 1.3 and the 95% CI=0.5–2 (Table 5-10).

5. ***Domain 5: Satisfaction***

The sexually active patients were statistically less satisfied with their sexual life (3.7, ±1.6) compared to the sexually active healthy volunteers group (4.8, ±1.4). The mean difference was 1.1 and the 95% CI=0.4–1.8 (Table 5-10).

6. ***Domain 6: Pain***

The sexually active patients had more sexual pain (3.3, ±1.9) compared with the sexually active healthy volunteers group (5.2, ±1.4). The mean difference was 2 and the 95% CI=1.1–2.8. Higher scores in this domain denotes the absence of pain (Table 5-10).

Table 5-10 Percentage of the lowest scores of the FSFI domains in each group.

FSFI Domains	pSS patients Sexually active	Healthy volunteers Sexually active	Mean difference (95% CI)	p-value
	Mean Minimal scoring rate, n of minimal scoring	Mean Minimal scoring rate, n of minimal scoring		
Desire (Score range 1.2–6)	2.38 32%, n=9/28	3.7 2.4%, n=1/42	1.3 (0.8–1.8)	< 0.05
Arousal (Score range 0–6)	3.1 0%, n=28/28	4.4 0%, n=42/42	1.3 (0.7–2)	< 0.05
Lubrication (Score range 0–6)	3.1 3.6%, n=1/28	5.2 0%, n=42/42	2.1 (1.5–2.7)	< 0.05
Orgasm (Score range 0 – 6)	3.6 0%, n=28/28	4.9 0%, n=42/42	1.2 (0.5–2)	< 0.05
Satisfaction (Score range 0.8–6)	3.7 0%, n=28/28	4.7 0%, n=42/42	1 (0.3–1.7)	< 0.05
Pain (Score range 0–6)	3.2 6.7%, n=2/28	5.2 2.4%, n=1/42	1.9 (1.1–2.7)	< 0.05
Total score	19 82.1%, n=23/28	28.3 33.3%, n=14/42	9.23 (6–12.6)	< 0.05

5.3.5 Objective 5: To compare the general QoL in pSS group vs healthy volunteers group

The self-perceived assessment of the general QoL measured by the first global question "How do you rate your quality of life?" of the questionnaire, was statistically significantly lower in pSS group (3.5, ±0.9) compared to that of the healthy volunteers group (4.3, ±0.5), with a mean difference of 0.8 and 95% CI=0.6–1.1. Similarly, the second global question that assesses individual's satisfaction of health "How satisfied are you with your health?" was statistically significantly lower in pSS group (2.8, ±0.9) compared with healthy volunteers group (4.1, ±0.7) with a mean difference of 1.2 and 95% CI=0.95–1.5.

1. *Domain 1: Physical*

Patients' physical life quality was statistically significantly impaired (55.4, ±19) compared with healthy volunteers group (80, ±12.7). The mean difference was 24.7 and 95% CI=19–30.3 (Table 5-13).

2. *Domain 2: Psychological*

Psychologically, patients were statistically significantly affected (61.8, ±15.6) compared with healthy volunteers group (73.7, ±11.7). The mean difference was 11.8 and 95% CI=7–16.7 (Table 5-13).

3. *Domain 3: Social*

The social domain was statistically significantly impaired in the patients group (61.6, ±20) compared with healthy volunteers group (73.6, ±17.2). The mean difference was 11.9 and 95% CI=5.2–18.8 (Table 5-13).

4. *Domain 4: Environmental*

Patients' environmental life quality was statistically significantly affected (69.5, ±16.1) compared with that of the healthy volunteers group (75.6, ±12.8). The mean difference was 6 and 95% CI=1–11.2 (Table 5-13).

5.3.6 Objective 6: To compare the oral health related quality of life in pSS group vs healthy volunteers group

The total score of OHIP-14 assessing tool was statistically significantly higher in pSS group (20.4.7, ±11) compared with healthy volunteers group (6.7, ±6.6). Higher scores denotes worse OHRQoL. The mean difference was 13.7 and 95% CI=10.5–16.9. Table 5-11 illustrates the prevalence, extent and severity of the oral health problems in the study's population.

Table 5-11 The prevalence, extent and severity of self- perceived oral health problems in the pSS and healthy volunteers groups

Variable	pSS group N=65	Healthy volunteers group N=61	95% CI	P-value
Prevalence (%)	69.2%	14%	0.4–0.7	< 0.05
Extent (mean score)	2.6	0.3	1.6–3.2	< 0.05
Severity (mean score)	20.4	6.7	10.5–16.9	< 0.05

1. *Domain 1: Functional limitation*

The oral function was statistically significantly impaired in the pSS group (1.5, ±1.1) compared with healthy volunteers group (0.1, ±0.4). The mean difference was 1.4 and 95% CI=1.1–1.7 (Table 5-12).

2. *Domain 2: Physical discomfort*

The physical discomfort was statistically significantly higher in the pSS group (1.8, ±1) compared with healthy volunteers group (0.8, ±1.2). The mean difference was 1 and 95% CI=0.7–1.5 (Table 5-12).

3. *Domain 3: Psychological discomfort*

The psychological discomfort was statistically significantly higher in the pSS group (1.9, ±1.2) compared with healthy volunteers group (0.9, ±0.9). The mean difference was 1 and 95% CI=0.6–1.4 (Table 5-12).

4. *Domain 4: Physical disability*

The physical disability was statistically significantly higher in pSS group (1.4, ±1) compared with healthy volunteers group (0.4, ±0.6). The mean difference was 0.9 and 95% CI=0.7–1.2 (Table 5-12).

5. ***Domain 5: Psychological disability***

The psychological disability was statistically significantly higher in pSS group (1.5, ±1) compared with healthy volunteers group (0.6, ±0.7). The mean difference was 0.9 and 95% CI=0.6–1.2 (Table 5-12).

6. ***Domain 6: Social disability***

The social disability was statistically significantly higher in pSS group (1, ±0.9) compared with healthy volunteers group (0.4, ±0.6). The mean difference was 0.6 and 95% CI=0.4–0.9 (Table 5-12).

7. ***Domain 7: Handicap***

Patients were statistically significantly more orally handicapped (1, ±1) compared with healthy volunteers group (0.2, ±0.5). The mean difference was 0.8 and 95% CI=0.5–1.1 (Table 5-12).

Table 5-12 Comparison of the OHIP-14 domains between pSS patients and healthy volunteers

OHIP-14 domains Patients, n=65 Healthy volunteers, n=61	**Mean***	**Mean difference (95% CI)**	**p-value**
Functional limitation Patients Healthy volunteers	1.5 0.1	1.3 (1.1–1.6)	< 0.05
Physical pain Patients Healthy volunteers	1.8 0.8	1 (0.6–1.4)	< 0.05
Psychological discomfort Patients Healthy volunteers	1.8 0.8	0.9 (0.6–1.3)	< 0.05
Physical disability Patients Healthy volunteers	1.3 0.4	0.9 (0.6-1.2)	< 0.05
Psychological disability Patients Healthy volunteers	1.5 0.6	0.8 (0.5–1.1)	< 0.05
Social disability Patients Healthy volunteers	1 0.3	0.6 (0.3–0.9)	< 0.05
Handicap Patients Healthy volunteers	1 0.2	0.8 (0.5–1)	< 0.05
Total score Patients Healthy volunteers	20.4 6.7	13.7 (10.5–16.9)	< 0.05

5.3.7 Objective 7: To compare the mental health well-being in pSS group vs healthy volunteers group

1. Anxiety

Patients group was statistically significantly more anxious (8, ±3.8) compared with the healthy volunteers group (5.2, ±3.3). The mean difference was 2.8 and 95% CI = 1.6 – 4.1 (Table 5-13).

2. Depression

Patients group was statistically significantly more depressed (5.9, ±3.8) compared with healthy volunteers group (2.4, ±2.5). The mean difference was 3.5 and 95% CI=2.4–4.7 (Table 5-13).

5.3.8 Summary results of the primary outcomes

The rate of hyposmia in the pSS group was significantly higher (41.5%) than that in the healthy volunteers (24.7%) group. Similarly, hypogeusia was found in 34 patients compared to five in the healthy volunteers. The neurosensory threshold of taste was three times higher in pSS group compared with healthy volunteers group (p=0.00). The number of patients with sexual dysfunction (n=28) was significantly higher than that of the healthy volunteers (n=42). The QoL was significantly impaired, eight times physically (D1), five times psychologically (D2), twice socially (D3) and environmentally. Oral health problems were significantly more in the patients group (69.2%) compared with the healthy volunteers group (14.8%). The mental health well-being was affected, and the number of anxious patients (58.5%) was more than that of the healthy volunteers (21%). Additionally, patients were four times more depressed (p=0.00) than healthy volunteers (Table 5-13).

Table 5-13 Comparison of percentage of the dysfunction rate of the outcome of interest in pSS patients compared with healthy volunteers

Test	pSS group	Healthy volunteers group	Mean difference (95% CI)	P-value	Type of test
Smell function[1]	41.5% (n=27/65)	24.1% (n=15/62)	3.9 (1.8-6)	< 0.05	Clinical
Gustatory function[2]	54% (n=34/63)	8.3% (n = 5/60)	4.3 (3.4-5.2)	< 0.05	Clinical
Neurosensory threshold of taste [3]	31.7% (n=20/63)	9.8% (n=6/61)	6.1 (3.4–8.8)	< 0.05	Clinical
Sexual function[4]	82.1% (n=23/28)	33.3% (n=14/42)	9.2 (5.9-12.6)	< 0.05	Questionnaire
Quality of life[5] Physical domain (D1)	53.8% (n=35/65)	6.6% (n=4/61)	24.7 (18.9–30.3)	< 0.05	Questionnaire
Quality of life[5] Psychological domain (D2)	47.7% (n=31/65)	9.8% (n=6/61)	11.8 (6.9–16.6)	< 0.05	Questionnaire
Quality of life[5] Social domain (D3)	44.6% (n=29/65)	21.3% (n=13/61)	11.9 (5.2–18.7)	< 0.05	Questionnaire
Quality of life[5] Environmental domain (D4)	21.5% (n=14/65)	9.8% (n=6/61)	6 (0.9–11.2)	< 0.05	Questionnaire
Oral health problems[6] (total score)	69.2% (n=45/65)	14.8% (n=9/61)	13.7 (10.5–16.9)	< 0.05	Questionnaire
Mental health well-being[7] Anxiety	58.5% (n=38/65)	21% (n=13/61)	2.8 (1.5–4)	< 0.05	Questionnaire
Mental health well-being[7] Depression	32.3% (n=21/65)	8.2% (n=5/61)	3.5 (2.3–4.6)	< 0.05	Questionnaire

1: Calculated as normal smell function of ≥ 30 in 0 – 40 scale; 2: Normal taste function of ≥ 9 in 0 – 16 scale; 3: Normal score of neurosensory function of taste < 8 in a scale of - 6 – 34; 4: Normal sexual function ≥ 26.5 in a scale of 0-36; 5: Overall QoL ≥ 60 in a scale of 0 - 100; 6: No oral health problems = never, hardly ever and occasionally vs fairly often and very often; 7: Normal HADS scores < 8.

**See tables 3-1, 3-2 and 3-3 of data sources measurement.

5.3.9 Age groups

1. Comparison of two age groups between patients and healthy volunteers

The patients were sub-grouped into two age groups based on menopausal age. A group of 20-50 years and 51-100 years old, which were compared to the corresponding age groups in the healthy volunteers in terms of smell, taste, sexuality, QoL and mental health status. In both comparisons, the pSS group showed worse function compared with the healthy volunteers group. Both age groups comparisons showed that smell did not differ statistically significantly between patients and healthy volunteers, although patients group had lower mean than that of the healthy volunteers group (Tables 5-14 and 5-15). A significant difference was found between patients and healthy volunteers in the 20-50 age group in terms of taste, neurosensory threshold, sexual function, QoL and mental health status. Similarly, significant difference was observed between patients and healthy volunteers in the 51-100 age group in taste, sexual function, QoL (Except the social domain in the WHOQoL-BRÉF) and the mental health status (Table 5-15).

Table 5-14 Comparison of percentage of the dysfunction rate according to the cut-off points of each outcome of interest in the 20-50 years old age group between pSS patients compared with healthy volunteers

Test	20–50 years old		Mean difference (95% CI)	P-value
	pSS group Mean, SD	Healthy volunteers Mean, SD		
Smell[1]	31.2% (n=5/16) 31, ±9	23.4% (n=11/47) 34.4, ±3.7	3.3 (-8.2–1.5)	0.1
Taste[2]	37.5% (n=6/16) 10.2, ±3.2	4.4% (n=2/45) 13.1, ±1.8	2.9 (-4.6- -1.1)	< 0.05
Neurosensory threshold of taste [3]	31.2% (n=5/16) 6, ±8.9	6.5% (n=3/46) -0.7, ±6.4	6.8 (2.6–10.9)	< 0.05
Sexual function[4]	77.7% (n=7/9) 20.5, ±9.5	33.3% (n=13/39) 28.4, ±4.7	7.9 (-15.3- -0.5)	< 0.05
Quality of life[5] Physical domain (D1)	62.5% (n=10/16) 50.1, ±20.7	4.3% (n=2/46) 81.1, ±12.9	31 (-42.6- -19.5)	< 0.05
Quality of life[5] Psychological domain (D2)	37.5% (n=6/16) 60.6, ±15.9	6.5% (n=3/46) 74.4, ±11.5	13.8 (-21.2- -6.4)	< 0.05
Quality of life[5] Social domain (D3)	26.6% (n=4/15) 59.2, ±24	15.2% (n=7/46) 74.5, ±16.7	15.3 (-29.3- -1.2)	< 0.05
Quality of life[5] Environmental domain (D4)	26.6% (n=4/15) 63.8, ±17.5	10.8% (n=5/46) 74.5, ±12.7	10.7 (-19- -2.3)	< 0.05
Oral health problems[6]	43.7% (n=7/16) 16.5, ±8.8	15.2% (n=7/46) 7, ±6.8	9.5 (5.2– 13.8)	< 0.05
Anxiety[7]	81.2% (n=13/16) 9.1, ±3.9	23.9% (n=11/46) 5.3, ±3.1	3.8 (1.9–5.8)	< 0.05
Depression[7]	25% (n=4/16) 6.6, ±5.4	6.5% (n=3/46) 2.3, ±2.2	4.2 (1.3–7.2)	< 0.05

1: Calculated as normal smell function of ≥30 in 0–40 scale; 2: Normal taste function of ≥ 9 in 0–16 scale; 3: Normal score of neurosensory function of taste < 8 in a scale of - 6–34; 4: Normal sexual function ≥26.5 in a scale of 0-36; 5: Overall QoL≥60 in a scale of 0-100; 6: No oral health problems = never, hardly ever and occasionally vs fairly often and very often; 7: Normal HADS scores <8.

**See tables 3-1, 3-2 and 3-3 of data sources measurement.

Table 5-15 Comparison of percentage of the dysfunction rate of the outcome of interest in the 51-100 years old age group between pSS patients compared with healthy volunteers

Test	51-100 years old		Mean difference (95% CI)	P-value
	pSS group Mean, SD	Healthy volunteers Mean, SD		
Smell[1]	44.8% (n=22/49) 29.6, ±6.4	26.6% (n=4/15) 32.4, ±7	2.7 (-6.6-1.1)	0.1
Taste[2]	61.7% (n=29/47) 7.7, ±2.7	20% (n=3/15) 11.2, ±2.2	3.5 (-5.1- -1.9)	< 0.05
Neurosensory threshold of taste[3]	31.9% (n=15/47) 5.3, ±8.5	20% (n=3/15) 0.7,±7.4	4.6 (-0.3-9.5)	0.3
Sexual function[4]	89.4% (n=17/19) 18.3, ±6.7	33.3% (n=1/3) 26.7, ±8.5	8.3 (-17.3-0.7)	0.06
Quality of life[5] Physical domain (D1)	51% (n=25/49) 57.1, ±18.3	6.6% (n=1/15) 76.7, ±11.6	19.5 (-29.6- -9.5)	< 0.05
Quality of life[5] Psychological domain (D2)	42.8% (n=21/49) 62.2, ±15.5	20% (n=3/15) 71.2, ±12.4	9 (-17.8- -0.2)	< 0.05
Quality of life[5] Social domain (D3)	48.9% (n=24/49) 61.7, ±19.8	33.3% (n=5/15) 70.9, ±19.1	9.1 (-20.8-2.4)	0.1
Quality of life[5] Environmental domain (D4)	20.4% (n=10/49) 63.8, ±17.5	6.6% (n=1/15) 74.5, ±12.7	10.7 (-19- -2.3)	< 0.05
Oral health problems[6]	77.5% (n=38/49) 21.6, ±11.4	13.3% (n=2/15) 5.6, ±6	16 (11.4-20.5)	< 0.05
Anxiety[7]	51% (n=25/49) 7.6, ±3.7	13.3% (n=2/15) 4.8, ±3.9	2.8 (0.6-5)	< 0.05
Depression[7]	34.6% (n=17/49) 5.6, ±3.2	13.3% (n=2/15) 2.4, ±3.3	3.2 (1.2-5.1)	< 0.05

1: Calculated as normal smell function of ≥30 in 0–40 scale; 2: Normal taste function of ≥9 in 0–16 scale; 3: Normal score of neurosensory function of taste <8 in a scale of -6 – 34; 4: Normal sexual function ≥26.5 in a scale of 0-36; 5: Overall QoL≥60 in a scale of 0-100; 6: No oral health problems = never, hardly ever and occasionally vs fairly often and very often; 7: Normal HADS scores <8.

**See table 3-1, 3-2 and 3-3 of data sources measurement.

5.4 SECONDARY OUTCOME RESULTS

5.4.1 Objective 8: To evaluate the effect of smell, taste and sexual functions on QoL in pSS patients

A: Impact on general QoL

1. *Physical domain*

The coefficients table shows no significant positive correlation between the sexual function (β=0.2, 95% CI=-0.8–2.1) of the sexually active patients and the physical life quality. Neither smell nor gustatory function impairment had an important effect on the physical domain in the pSS group (Table 5-16).

Table 5-16 Coefficients' table of the impact of the smell, gustatory and sexual functions on the physical domain of the WHOQoL-BRÉF.

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	45.302	53.484		.847	.412	-70.244	160.849
Smell	-.049	.635	-.018	-.078	.939	-1.421	1.322
Gustation*	.099	1.845	.016	.054	.958	-3.888	4.085
FSFI**	.647	.714	.260	.906	.381	-.895	2.190
Age	.236	.446	.158	.530	.605	-.728	1.200
Smoking	-10.498	20.361	-.134	-.516	.615	-54.485	33.490
Alcohol	2.224	9.361	.059	.238	.816	-18.000	22.448
Mouthwash	-4.200	9.748	-.108	-.431	.674	-25.260	16.860
Appliances	6.386	10.484	.142	.609	.553	-16.264	29.036
Pain relief	-6.181	10.490	-.154	-.589	.566	-28.844	16.482
Gabapentin	-11.830	15.865	-.181	-.746	.469	-46.104	22.444
Other drugs	-1.958	9.608	-.054	-.204	.842	-22.716	18.799
Fatigue	-10.056	17.243	-.154	-.583	.570	-47.308	27.196
Dis duration	-.166	.297	-.137	-.558	.587	-.807	.476

R^2=0.35
Dependent Variable: Physical domain
*Gustatory function measured by TST
**FSFI for sexually active patients

2. *Psychological domain*

The coefficients table shows no significant correlation between the sexual dysfunction (β=0.4, 95% CI=-0.4–2.1) of the sexually active pSS patients and the psychological domain of the patients' life quality. The impairment of the smell and gustatory function did not have an important effect on the psychological domain in pSS group (Table 5-17).

Table 5-17 Coefficients' table of the impact of the smell, gustatory and sexual functions on the psychological domain of the WHOQoL-BRÉF

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	33.352	45.120		.739	.473	-64.124	130.827
Smell	.253	.536	.115	.473	.644	-.904	1.410
Gustation*	.146	1.557	.029	.094	.927	-3.217	3.509
FSFI**	.897	.602	.442	1.489	.160	-.404	2.198
Age	.136	.376	.111	.361	.724	-.677	.949
Smoking	-11.015	17.177	-.171	-.641	.533	-48.123	26.093
Alcohol	2.183	7.897	.070	.276	.787	-14.879	19.244
Mouthwash	-5.494	8.224	-.173	-.668	.516	-23.260	12.272
Appliances	-.509	8.845	-.014	-.058	.955	-19.616	18.599
Pain relief	-2.769	8.850	-.084	-.313	.759	-21.887	16.350
Gabapentin	2.437	13.384	.046	.182	.858	-26.477	31.350
Other drugs	5.308	8.106	.179	.655	.524	-12.203	22.819
Fatigue	-2.138	14.547	-.040	-.147	.885	-33.564	29.288
Dis duration	-.072	.251	-.073	-.287	.779	-.613	.469

R^2=0.31

Dependent Variable: Psychological domain

*Gustatory function measured by TST

**FSFI for sexually active patients

3. *Social domain*

The sexual function of the sexually active patients (β=0.6, 95% CI=0.3–3.3), appears to correlate significantly with this domain. The gustatory function (β=-0.2, 95% CI=-5.3-2.3) appears to have negative correlation with this domain but not statistically significant in pSS group. The smell had no important effect on the social life quality in pSS group (Table 5-18).

Table 5-18 Coefficients' table of the impact of the smell, gustatory and sexual functions on the social domain of the WHOQoL-BRÉF

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	37.640	51.502		.731	.478	-73.624	148.904
Smell	.326	.611	.110	.533	.603	-.995	1.646
Gustation*	-1.502	1.777	-.220	-.845	.413	-5.340	2.337
FSFI**	1.860	.688	.679	2.706	.018	.375	3.346
Age	-.052	.430	-.032	-.121	.905	-.980	.876
Smoking	-9.339	19.606	-.108	-.476	.642	-51.696	33.018
Alcohol	.792	9.015	.019	.088	.931	-18.683	20.266
Mouthwash	.720	9.387	.017	.077	.940	-19.559	21.000
Appliances	-1.860	10.096	-.038	-.184	.857	-23.671	19.951
Pain relief	5.403	10.101	.122	.535	.602	-16.420	27.226
Gabapentin	2.399	15.277	.033	.157	.878	-30.605	35.403
Other drugs	7.975	9.252	.199	.862	.404	-12.013	27.963
Fatigue	-11.150	16.604	-.155	-.672	.514	-47.022	24.721
Dis duration	.090	.286	.067	.313	.759	-.528	.708

R^2=0.51
Dependent Variable: Social domain
*Gustatory function measured by TST
**FSFI for sexually active patients

4. *Environmental domain*

The coefficients table shows that the sexual function (β=0.2, 95% CI=-0.7–1.9) and alcohol intake (β=0.2, 95% CI=-10.4–24.2) had correlated with the environmental living quality in the pSS group but not statistically significant. Neither smell nor gustatory function had an important effect on this domain in the pSS group (Table 5-19).

Table 5-19 Coefficients' table of the impact of the smell, gustatory and sexual functions on the environmental domain of the WHOQoL-BRÉF

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	53.897	46.581		1.157	.268	-46.735	154.529
Smell	.137	.553	.060	.248	.808	-1.057	1.331
Gustation*	-.423	1.607	-.081	-.263	.797	-3.895	3.049
FSFI**	.600	.622	.286	.966	.352	-.743	1.944
Age	.137	.389	.109	.352	.730	-.703	.976
Smoking	-11.099	17.733	-.167	-.626	.542	-49.409	27.211
Alcohol	7.134	8.153	.223	.875	.397	-10.480	24.747
Mouthwash	-6.256	8.490	-.191	-.737	.474	-24.598	12.086
Appliances	-.596	9.131	-.016	-.065	.949	-20.322	19.131
Pain relief	-3.654	9.136	-.108	-.400	.696	-23.391	16.083
Gabapentin	8.988	13.817	.163	.650	.527	-20.862	38.838
Other drugs	4.973	8.368	.162	.594	.563	-13.105	23.051
Fatigue	-2.148	15.018	-.039	-.143	.888	-34.591	30.296
Dis. duration	-.143	.259	-.140	-.551	.591	-.702	.416

R^2=0.31

Dependent Variable: Environmental domain

*Gustatory function measured by TST

**FSFI for sexually active patients

B: Impact on oral health related QoL

1. Total score of OHIP-14

Age (β=0.4, 95% CI=0.1–0.6) and alcohol intake (β=-0.3, 95% CI=-12.7–-1.4) were independent variables that had an effect on the oral health quality measured by OHIP-14. Gustatory function did not seem to have an important effect on the total oral health problems (Table 5-20).

Table 5-20 Coefficients' table of the impact of the gustatory function on the total score of OHIP-14

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	-4.024	11.859		-.339	.736	-27.868	19.820
Gustation	.388	.592	.108	.657	.515	-.801	1.578
Age	.378	.135	.437	2.789	.008	.105	.650
Smoking	1.509	6.463	.033	.234	.816	-11.485	14.503
Alcohol	-7.055	2.808	-.322	-2.513	.015	-12.701	-1.410
Mouthwash	5.373	2.971	.239	1.809	.077	-.601	11.347
Appliances	1.542	3.342	.059	.461	.647	-5.178	8.262
Pain relief	-.393	3.093	-.017	-.127	.900	-6.611	5.826
Gabapentin	3.984	5.011	.105	.795	.431	-6.092	14.060
Other drugs	-4.495	3.012	-.214	-1.492	.142	-10.551	1.562
Dis. duration	-.049	.091	-.070	-.542	.591	-.232	.133

R^2=0.27

Dependent Variable: OHIP-14 total

2. Functional limitation

Age (β=0.3, 95% CI=0.0–0.0) and mouthwash (β=0.2, 95% CI=0–1.1) were independent factors that affected the oral health function. The gustatory function did not have an important effect on this domain in the pSS group (Table 5-21).

Table 5-21 Coefficients' table of the impact of the gustatory function on the functional limitation of OHIP-14

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	-.038	1.159		-.032	.974	-2.369	2.293
Gustation*	-.036	.058	-.104	-.631	.531	-.153	.080
Age	.029	.013	.341	2.183	.034	.002	.056
Smoking	.444	.632	.099	.702	.486	-.827	1.714
Alcohol	-.460	.275	-.214	-1.676	.100	-1.012	.092
Mouthwash	.599	.290	.272	2.063	.044	.015	1.183
Appliances	.396	.327	.155	1.211	.232	-.261	1.053
Pain relief	.027	.302	.012	.090	.928	-.581	.635
Gabapentin	-.356	.490	-.096	-.727	.471	-1.341	.629
Other drugs	-.066	.294	-.032	-.225	.823	-.659	.526
Dis.duration	-.004	.009	-.062	-.476	.636	-.022	.014

R^2=0.27
Dependent Variable: Functional limitation
*Gustatory function measured by TST

3. *Physical pain*

Miscellaneous drugs that were grouped as "Other drugs" had the highest effect on the prediction of this domain, however, this variable was not considered as a predicting factor as it consists of a number of drugs with different effects on the body (Table 5-22).

Table 5-22 Coefficients' table of the impact of the gustatory function on the physical pain of OHIP-14

Model	Unstandardized coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interal for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	.655	1.116		.587	.560	-1.588	2.899
Gustation*	-.001	.056	-.005	-.027	.979	-.113	.110
Age	.022	.013	.278	1.722	.092	-.004	.048
Smoking	.642	.608	.154	1.056	.296	-.580	1.865
Alcohol	-.299	.264	-.149	-1.132	.263	-.830	.232
Mouthwash	.465	.280	.226	1.662	.103	-.097	1.027
Appliances	-.358	.314	-.151	-1.140	.260	-.991	.274
Pain relief	.213	.291	.100	.732	.468	-.372	.798
Gabapentin	.391	.472	.113	.830	.411	-.557	1.339
Other drugs	-.673	.283	-.350	-2.373	.022	-1.243	-.103
Dis duration	-.005	.009	-.074	-.551	.584	-.022	.012

R^2=0.22

Dependent Variable: Physical pain

*Gustatory function measured by TST

4. *Psychological discomfort*

Age (β=0.3, 95% CI=0-0) and Gabapentin (β=0.3, 95% CI=0.1–2.2) followed by alcohol intake (β=-0.2, 95% CI=-1.1–0) were independent factors that had affected the psychological discomfort domain. The gustatory function had no important effect on this domain in the pSS group (Table 5-23).

Table 5-23 Coefficients' table of the impact of the gustatory function on the psychological discomfort of OHIP-14

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	-.361	1.239		-.291	.772	-2.851	2.130
Gustation*	.060	.062	.159	.969	.337	-.064	.184
Age	.032	.014	.358	2.294	.026	.004	.061
Smoking	-.102	.675	-.021	-.151	.881	-1.459	1.255
Alcohol	-.609	.293	-.265	-2.077	.043	-1.199	-.019
Mouthwash	.324	.310	.138	1.044	.302	-.300	.948
Appliances	.434	.349	.160	1.243	.220	-.268	1.136
Pain relief	-.193	.323	-.079	-.598	.553	-.842	.456
Gabapentin	1.244	.523	.314	2.377	.021	.192	2.297
Other drugs	-.477	.315	-.216	-1.518	.136	-1.110	.155
Dis duration	-.010	.009	-.132	-1.018	.314	-.029	.009

R^2=0.27

Dependent Variable: Psychological discomfort

*Gustatory function measured by TST

5. *Physical disability*

Age (β=0.4, 95% CI=0-0) followed by alcohol intake (β=-0.2, 95% CI=-1–0) appear to have an effect on patients' oral physical ability in this model. The gustatory function (β=0.2, 95% CI=0–0.1) associated with this domain but not statistically significant (Table 5-24).

Table 5-24 Coefficients' table of the impact of the gustatory function on the physical disability of OHIP-14

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	-.918	1.045		-.878	.384	-3.018	1.183
Gustation*	.072	.052	.233	1.373	.176	-.033	.176
Age	.033	.012	.450	2.794	.007	.009	.057
Smoking	.223	.569	.057	.392	.697	-.921	1.368
Alcohol	-.544	.247	-.289	-2.199	.033	-1.041	-.047
Mouthwash	.386	.262	.200	1.475	.147	-.140	.912
Appliances	-.196	.294	-.088	-.664	.510	-.787	.396
Pain relief	-.070	.272	-.035	-.257	.798	-.618	.478
Gabapentin	-.349	.441	-.108	-.791	.433	-1.237	.538
Other drugs	-.356	.265	-.197	-1.342	.186	-.890	.177
Dis duration	-.006	.008	-.101	-.756	.453	-.022	.010

R^2=0.23

Dependent Variable: Physical disability

*Gustatory function measured by TST

6. Psychological disability

Alcohol intake (β=-0.3, 95% CI=-0.3 - -0.1) appears to be an independent factor that had an effect on this domain in the pSS group. The gustatory function had no important effect on the psychological disability of the oral health quality in the pSS group (Table 5-25).

Table 5-25 Coefficients' table of the impact of the gustatory function on the psychological disability of OHIP-14

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Intervalfor B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	-.040	1.098		-.036	.971	-2.248	2.169
Gustation*	.042	.055	.128	.766	.447	-.068	.152
Age	.024	.013	.305	1.916	.061	-.001	.049
Smoking	-.300	.599	-.072	-.501	.619	-1.503	.904
Alcohol	-.652	.260	-.326	-2.506	.016	-1.175	-.129
Mouthwash	.255	.275	.124	.925	.359	-.299	.808
Appliances	.438	.310	.185	1.416	.163	-.184	1.061
Pain relief	-.305	.286	-.144	-1.066	.292	-.881	.271
Gabapentin	.560	.464	.163	1.206	.234	-.374	1.493
Other drugs	-.326	.279	-.170	-1.169	.248	-.887	.235
Dis duration	-.004	.008	-.062	-.468	.642	-.021	.013

R^2=0.24
Dependent Variable: Psychological disability
*Gustatory function measured by TST

7. *Social disability*

Alcohol intake (β=-0.3, 95% CI=-1–0) appears to have significant effect on this domain. The gustatory function had no important effect on the social disability of the oral health quality in pSS group (Table 5-26).

Table 5-26 Coefficients' table of the impact of the gustatory function on the social disability domain of OHIP-14

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	-.475	1.007		-.472	.639	-2.499	1.549
Gustation*	.033	.050	.114	.662	.511	-.068	.134
Age	.021	.011	.303	1.848	.071	-.002	.044
Smoking	-.423	.549	-.115	-.772	.444	-1.526	.680
Alcohol	-.550	.238	-.309	-2.309	.025	-1.030	-.071
Mouthwash	.402	.252	.220	1.595	.117	-.105	.909
Appliances	.111	.284	.053	.392	.697	-.459	.682
Pain relief	-.133	.263	-.070	-.505	.616	-.660	.395
Gabapentin	.222	.425	.072	.521	.605	-.634	1.077
Other drugs	-.144	.256	-.084	-.563	.576	-.658	.370
Dis duration	.000	.008	-.003	-.023	.981	-.016	.015

R^2=0.2
Dependent Variable: Social disability
*Gustatory function measured by TST

8. *Handicap*

The gustatory function had no important effect on this domain. None of the variables in the model had an independent effect on the outcome (Table 5-27).

Table 5-27 Coefficients' table of the impact of the gustatory function on the handicap domain of OHIP-14

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	-.825	1.150		-.717	.477	-3.138	1.488
Gustation*	.034	.057	.104	.591	.557	-.081	.149
Age	.024	.013	.312	1.861	.069	-.002	.051
Smoking	.168	.627	.041	.267	.790	-1.093	1.428
Alcohol	-.431	.272	-.217	-1.583	.120	-.979	.116
Mouthwash	.303	.288	.149	1.053	.298	-.276	.883
Appliances	.219	.324	.093	.674	.503	-.433	.870
Pain relief	.265	.300	.126	.885	.381	-.338	.869
Gabapentin	.275	.486	.081	.567	.574	-.702	1.253
Other drugs	-.205	.292	-.108	-.703	.485	-.793	.382
Dis duration	.003	.009	.053	.383	.704	-.014	.021

R^2=0.16
Dependent Variable: Handicap
*Gustatory function measured by TST

C: Impact on mental health well-being

1. *Anxiety*

Anxiety appears to be negatively affected by the sexual function of the sexually active patients (β=-0.5, 95% CI=-0.5–0), however, the correlation was not statically significant. Neither smell nor gustatory dysfunction had increased anxiety symptoms in the pSS group (Table 5-28).

Table 5-28 Coefficients' table of the impact of the smell, taste and sexual functions on anxiety assessed by HADS

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	21.460	11.209		1.915	.080	-2.963	45.883
Smell	.055	.144	.103	.385	.707	-.259	.370
Gustation*	-.240	.380	-.193	-.633	.538	-1.067	.587
FSFI**	-.278	.146	-.555	-1.903	.081	-.596	.040
Age	-.093	.091	-.310	-1.023	.327	-.292	.105
Smoking	.714	4.169	.045	.171	.867	-8.370	9.799
Alcohol	-1.153	1.925	-.151	-.599	.560	-5.346	3.040
Mouthwash	.348	2.065	.044	.168	.869	-4.151	4.846
Appliances	.763	2.142	.085	.356	.728	-3.903	5.430
Topical	.715	1.569	.120	.456	.657	-2.704	4.133
Pain relief	-.337	2.165	-.042	-.155	.879	-5.054	4.381
Gabapentin	-.529	3.259	-.040	-.162	.874	-7.630	6.573
Other drugs	-1.980	1.965	-.270	-1.007	.334	-6.262	2.303
Fatigue	-2.113	3.543	-.161	-.596	.562	-9.833	5.607
Dis duration	.006	.061	.024	.095	.926	-.126	.138

R^2=0.39
Dependent Variable: Anxiety
** FSFI for sexually active patients
*Gustatory function measured by TST

2. *Depression*

Depression symptoms seem to be associated with the sexual dysfunction of the sexually active patients (β=-0.5, 95% CI=-0.5–0). However, the correlation was not statistically significant. Neither smell nor gustation dysfunction had important effect on the severity of depression symptoms in pSS group (Table 5-29).

Table 5-29 Coefficients' table of the impact of smell, taste and sexual functions on depression assessed by HADS

Model	Unstandardized Coefficients		Standardized Coefficients	T	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	15.112	10.435		1.448	.173	-7.625	37.849
Smell	-.064	.134	-.118	-.476	.642	-.356	.228
Gustation*	-.007	.353	-.005	-.019	.985	-.777	.763
FSFI **	-.282	.136	-.563	-2.077	.060	-.578	.014
Age	-.041	.085	-.138	-.489	.634	-.226	.143
Smoking	.714	3.882	.045	.184	.857	-7.743	9.171
Alcohol	-.703	1.792	-.092	-.392	.702	-4.607	3.201
Mouthwash	1.038	1.922	.132	.540	.599	-3.150	5.226
Appliances	-.038	1.994	-.004	-.019	.985	-4.383	4.306
Topical	.206	1.461	.035	.141	.890	-2.976	3.389
Pain relief	.956	2.016	.118	.474	.644	-3.436	5.348
Gabapentin	-2.013	3.034	-.153	-.663	.520	-8.624	4.598
Other drugs	-1.865	1.830	-.254	-1.019	.328	-5.852	2.121
Fatigue	.251	3.299	.019	.076	.941	-6.937	7.438
Dis. duration	.023	.056	.094	.405	.693	-.100	.146

R^2=0.47
Dependent Variable: Depression
*Gustatory function measured by TST
** FSFI for sexually active patients

5.4.2 Objective 9: To investigate whether the senses of smell and gustatory function are correlated with each other.

- **pSS group**

In the correlation test between the smell and gustatory function, no significant correlation was found in the patients group (r=0.05, p=0.6) (Figure 5-4).

In the regression model, age (β=-0.0, 95% CI=-0.1–0) followed by pain relief medicines (β=0.2, 95% CI=0.2–3.2) had contributed to the prediction of gustation. Smell did not correlate with gustation in the pSS group (Table 5-30).

Table 5-30 Coefficients' table of the relation of the smell and gustation in the pSS group

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	16.779	2.816		5.959	.000	11.111	22.447
Smell	-.024	.055	-.056	-.440	.662	-.135	.087
Age	-.122	.029	-.507	-4.201	.000	-.181	-.064
Smoking	-1.387	1.607	-.109	-.863	.392	-4.622	1.847
Alcohol	.111	.716	.018	.154	.878	-1.331	1.553
Mouthwash	-1.468	.770	-.234	-1.907	.063	-3.017	.081
Appliances	-1.048	.815	-.145	-1.287	.205	-2.689	.592
Topical	-.476	.605	-.100	-.786	.436	-1.694	.742
Pain relief	1.731	.730	.267	2.370	.022	.261	3.201
Gabapentin	-1.795	1.233	-.170	-1.455	.152	-4.278	.688
Other drugs	1.285	.722	.219	1.779	.082	-.169	2.739
Fatigue	-.115	1.294	-.011	-.089	.929	-2.719	2.489
Dis duration	.025	.023	.130	1.115	.270	-.020	.071

R^2=0.45

Dependent Variable: Total gustatory score.

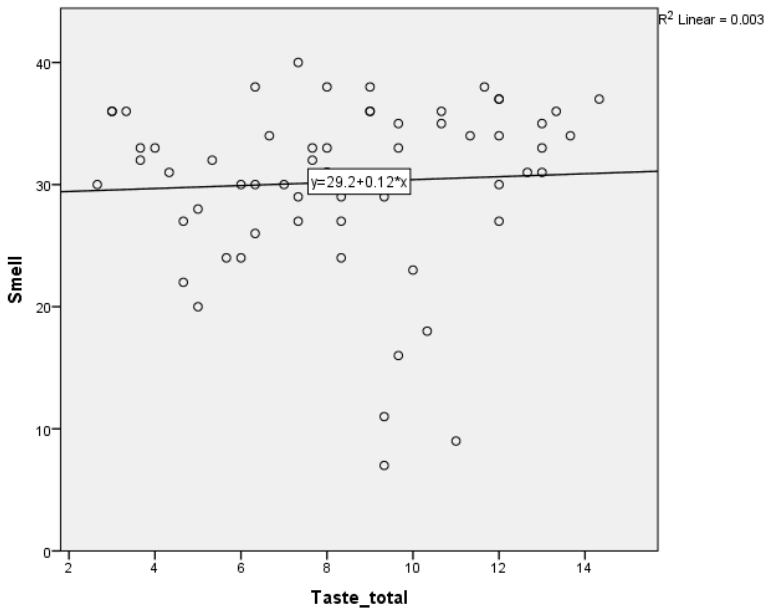

Figure 5-4 Correlation of the smell and the total score of gustatory function in pSS group

- **Healthy volunteers group**

In the correlation test between the smell and gustation, a significant positive correlation was found in the healthy volunteers group (r=0.2) (Figure 5-5). In the regression model, age (β=-0.3, 95% CI=0–0) was independent variable that contributed to the prediction of taste. Smell did not contribute to the prediction of gustation in this group (Table 5-31).

Table 5-31 Coefficients' table of the relation of the smell and gustation in the healthy volunteers group

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	11.765	2.513		4.681	.000	6.724	16.805
Smell	.085	.060	.193	1.409	.165	-.036	.206
Age	-.049	.019	-.342	-2.513	.015	-.088	-.010
Smoking	-.758	1.053	-.089	-.720	.475	-2.870	1.354
Alcohol	-.223	.551	-.051	-.405	.687	-1.329	.882
Mouthwash	.512	.522	.122	.982	.330	-.534	1.559
Appliances	.047	.586	.010	.081	.936	-1.129	1.223

R^2=0.23
Dependent Variable: Total gustatory score

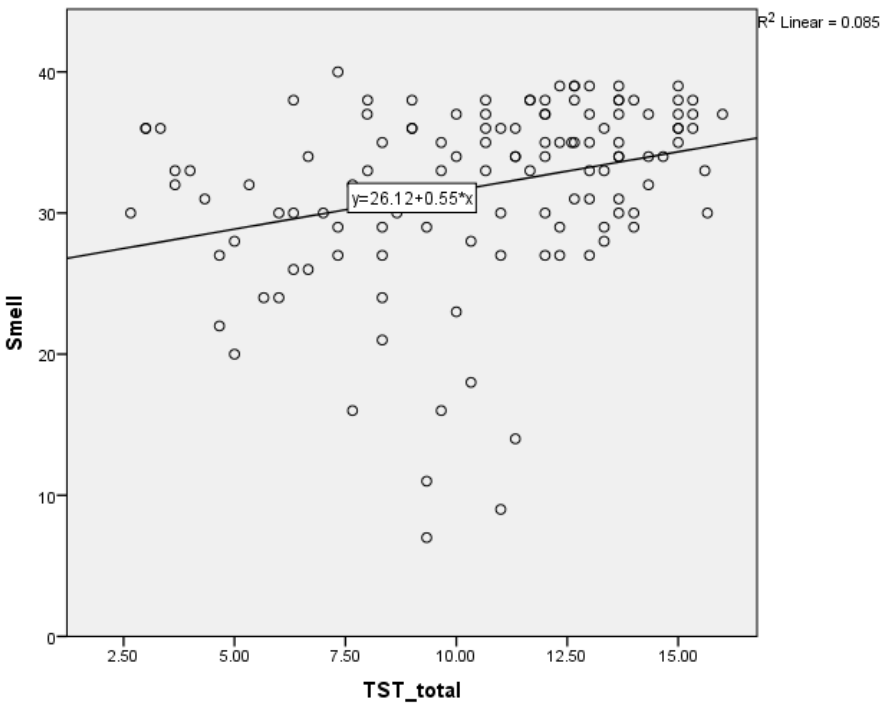

Figure 5-5 Correlation of the smell and taste in the healthy volunteers group

- **Total population**

In the correlation test between the smell and gustation, a significant positive correlation was found in the total population of the study (r=0.29) (Figure 5-6). In the regression model, age (β=-0.5, 95% CI=-0.1–0) was the only variable that contributed to the prediction of taste. Smell did not contribute to the prediction of taste in the total population of the study (Table 5-32).

Table 5-32 Coefficients' table of the relation of the smell and gustation in the total population of the study

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	15.781	1.822		8.664	.000	12.174	19.388
Smell	.048	.041	.089	1.170	.245	-.033	.128
Age	-.116	.017	-.543	-6.892	.000	-.150	-.083
Smoking	-1.040	1.000	-.075	-1.041	.300	-3.020	.939
Alcohol	-.337	.501	-.049	-.672	.503	-1.329	.656
Mouthwash	-.815	.494	-.119	-1.649	.102	-1.794	.164
Appliances	-1.054	.654	-.118	-1.611	.110	-2.350	.242

R^2=0.40

Dependent Variable: Total gustatory score of total population

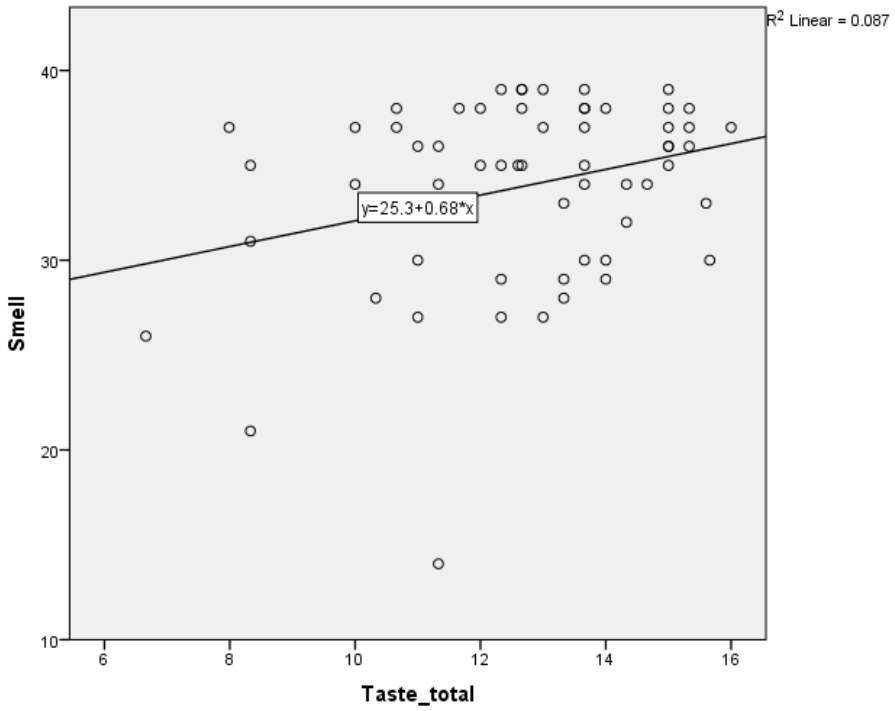

Figure 5-6 Correlation of the smell and gustation in the total population of the study

5.4.3 Objective 10: To study the correlation of the degree of smell function and the severity of oral dryness

The severity of oral dryness that was assessed by USFR, SSFR and CODS had no important contribution to the prediction of smell function in pSS group. The topical medicines appear to have an independent effect on the smell in the three models. Disease duration showed no correlation with the smell function in pSS group (Table 5-33, 34 and 35).

Table 5-33 Coefficients' table of the impact of the USFR on the smell function in pSS group

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	32.452	4.674		6.944	.000	23.078	41.826
USFR	1.931	6.534	.039	.296	.769	-11.174	15.036
Age	-.049	.074	-.088	-.661	.511	-.196	.099
Smoking	-.645	3.858	-.022	-.167	.868	-8.384	7.094
Alcohol	1.628	1.779	.115	.915	.364	-1.939	5.196
Topical	-4.465	1.395	-.406	-3.200	.002	-7.263	-1.666
Dis. duration	.036	.057	.081	.640	.525	-.078	.151

R^2=0.19
Dependent Variable: Smell

Table 5-34 Coefficients' table of the impact of the SSFR on the smell function in pSS group

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	31.204	4.802		6.497	.000	21.571	40.836
SSFR	1.190	1.400	.116	.850	.399	-1.618	3.999
Age	-.041	.074	-.074	-.555	.581	-.188	.107
Smoking	-.814	3.798	-.028	-.214	.831	-8.432	6.804
Alcohol	1.904	1.799	.135	1.059	.295	-1.704	5.512
Topical	-4.288	1.395	-.390	-3.074	.003	-7.085	-1.490
Dis. duration	.042	.057	.094	.738	.464	-.072	.157

R^2=0.2
Dependent Variable: Smell

Table 5-35 Coefficients' table of the impact of CODS on the smell function in pSS group

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	33.548	4.640		7.230	.000	24.237	42.858
CODS	-.205	.485	-.057	-.422	.675	-1.179	.769
Age	-.043	.076	-.078	-.568	.572	-.196	.110
Smoking	-.383	3.830	-.013	-.100	.921	-8.069	7.302
Alcohol	1.535	1.778	.109	.863	.392	-2.033	5.103
Topical	-4.405	1.420	-.400	-3.102	.003	-7.254	-1.555
Dis. duration	.040	.058	.088	.683	.498	-.077	.156

R^2=0.19

Dependent Variable: Smell

5.4.4 Objective 11: To study the correlation of the degree of taste function to the severity of oral dryness

A: Gustatory function in the pSS group

1. Total gustation score

Oral dryness that was assessed by USFR, SSFR and CODS did not correlate with the gustatory function in pSS group. Age, mouthwash and pain relief medicines appeared to have independent effect on the tasting ability in the three models. Disease duration showed no correlation with gustation in pSS group (Tables 5-36, 5-37 and 5-38).

Table 5-36 Coefficients' table of the impact of USFR on the total gustatory function in pSS group

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	16.303	1.924		8.474	.000	12.435	20.172
USFR	-1.816	2.516	-.085	-.722	.474	-6.875	3.243
Age	-.125	.028	-.518	-4.425	.000	-.182	-.068
Smoking	-1.047	1.590	-.083	-.658	.513	-4.244	2.150
Alcohol	-.033	.691	-.005	-.048	.962	-1.421	1.355
Mouthwash	-1.397	.699	-.223	-1.999	.051	-2.802	.008
Appliances	-1.152	.805	-.159	-1.431	.159	-2.772	.467
Pain relief	1.622	.714	.251	2.272	.028	.187	3.058
Gabapentin	-1.879	1.202	-.178	-1.563	.125	-4.296	.538
Other drugs	1.266	.708	.216	1.788	.080	-.158	2.689
Dis. duration	.024	.022	.123	1.104	.275	-.020	.068

R^2=0.44

Dependent Variable: Total gustation

Table 5-37 Coefficients' table of the impact of SSFR on the total gustatory function in pSS group

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	16.206	1.949		8.315	.000	12.287	20.125
SSFR	-.297	.539	-.067	-.550	.585	-1.380	.787
Age	-.125	.028	-.517	-4.380	.000	-.182	-.067
Smoking	-1.208	1.566	-.095	-.772	.444	-4.357	1.941
Alcohol	-.033	.698	-.005	-.047	.963	-1.437	1.372
Mouthwash	-1.361	.697	-.217	-1.952	.057	-2.762	.041
Appliances	-1.134	.807	-.157	-1.404	.167	-2.757	.490
Pain relief	1.705	.717	.263	2.379	.021	.264	3.146
Gabapentin	-1.784	1.194	-.169	-1.494	.142	-4.184	.616
Other drugs	1.348	.719	.230	1.876	.067	-.097	2.794
Dis. duration	.023	.022	.117	1.042	.303	-.021	.067

R^2=0.44

Dependent Variable: Total gustation

Table 5-38 Coefficients' table of the impact of CODS on the total gustatory function in pSS group

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	15.482	1.853		8.358	.000	11.758	19.207
CODS	.122	.217	.079	.564	.576	-.314	.558
Age	-.128	.030	-.530	-4.262	.000	-.188	-.067
Smoking	-1.426	1.583	-.112	-.901	.372	-4.610	1.757
Alcohol	.092	.687	.015	.133	.895	-1.290	1.473
Mouthwash	-1.455	.724	-.232	-2.009	.050	-2.912	.001
Appliances	-1.216	.841	-.168	-1.446	.155	-2.907	.475
Pain relief	1.739	.725	.269	2.399	.020	.282	3.197
Gabapentin	-1.610	1.220	-.153	-1.319	.193	-4.063	.843
Other drugs	1.421	.750	.242	1.895	.064	-.087	2.929
Dis. duration	.022	.022	.114	1.007	.319	-.022	.067

R^2=0.44

Dependent Variable: Total gustation

2. Sweet

The whole mouth tasting ability is represented by examining the tip of the tongue, as per the TST manual instructions. The severity of oral dryness that was tested by USFR, SSFR and CODS did not contribute to the ability to taste sweet in pSS group. Age and pain relief medicines appear to affect the ability of tasting sweet. Duration of the disorder showed no effect on tasting sweet (Table 5-39, 5-40 and 5-41).

Table 5-39 Coefficients' table of the impact of USFR on the sweet tasting ability in pSS group

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	5.126	.817		6.274	.000	3.483	6.769
USFR	-.693	1.069	-.086	-.648	.520	-2.841	1.456
Age	-.031	.012	-.341	-2.604	.012	-.055	-.007
Smoking	.454	.675	.094	.672	.505	-.904	1.812
Alcohol	-.435	.293	-.188	-1.483	.145	-1.025	.155
Mouthwash	-.328	.297	-.138	-1.105	.275	-.925	.269
Appliances	-.344	.342	-.125	-1.006	.319	-1.032	.344
Pain relief	.575	.303	.234	1.897	.064	-.035	1.185
Gabapentin	-.821	.510	-.205	-1.608	.114	-1.847	.206
Other drugs	.076	.301	.034	.251	.803	-.529	.680
Dis. duration	.005	.009	.071	.570	.571	-.013	.024

R^2=0.3

Dependent Variable: Sweet (tip of the tongue)

Table 5-40 Coefficients' table of the impact of SSFR on the sweet tasting ability in pSS group

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	4.992	.829		6.021	.000	3.325	6.659
SSFR	-.047	.229	-.028	-.203	.840	-.508	.414
Age	-.030	.012	-.333	-2.514	.015	-.055	-.006
Smoking	.377	.666	.078	.566	.574	-.963	1.716
Alcohol	-.417	.297	-.180	-1.403	.167	-1.014	.181
Mouthwash	-.310	.297	-.130	-1.045	.301	-.906	.286
Appliances	-.322	.344	-.117	-.938	.353	-1.013	.369
Pain relief	.598	.305	.243	1.960	.056	-.015	1.211
Gabapentin	-.778	.508	-.195	-1.533	.132	-1.799	.243
Other drugs	.092	.306	.042	.302	.764	-.522	.707
Dis. duration	.005	.009	.070	.550	.585	-.014	.024

R^2=0.3

Dependent Variable: Sweet (tip of the tongue)

Table 5-41 Coefficients' table of the impact of CODS on the sweet tasting ability in pSS group

Model	Unstandardized Coefficients		Standardized Coefficients	T	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	4.767	.784		6.078	.000	3.190	6.344
CODS	.066	.092	.112	.721	.474	-.118	.251
Age	-.033	.013	-.364	-2.623	.012	-.059	-.008
Smoking	.285	.670	.059	.425	.672	-1.062	1.633
Alcohol	-.380	.291	-.164	-1.308	.197	-.966	.205
Mouthwash	-.368	.307	-.155	-1.200	.236	-.985	.248
Appliances	-.392	.356	-.143	-1.102	.276	-1.108	.323
Pain relief	.632	.307	.257	2.058	.045	.014	1.249
Gabapentin	-.695	.517	-.174	-1.345	.185	-1.733	.344
Other drugs	.157	.318	.071	.494	.623	-.481	.795
Dis. duration	.004	.009	.058	.455	.651	-.015	.023

R^2=0.31

Dependent Variable: Sweet (tip of the tongue)

3. Sour

None of the oral dryness tests (USFR, SSFR and CODS) contributed to the prediction of the ability to taste sour in the pSS group. Age appears to have an independent effect on tasting sour (Tables 5-42, 5-43 and 5-44).

Table 5-42Coefficients' table of the impact of USFR on the sour tasting ability in pSS group

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	3.598	.665		5.406	.000	2.260	4.936
USFR	.547	.870	.086	.629	.532	-1.202	2.297
Age	-.021	.010	-.294	-2.170	.035	-.041	-.002
Smoking	-.276	.550	-.073	-.502	.618	-1.382	.830
Alcohol	-.238	.239	-.130	-.996	.324	-.718	.242
Mouthwash	.015	.242	.008	.062	.951	-.471	.501
Appliances	-.222	.279	-.102	-.796	.430	-.782	.338
Pain relief	.195	.247	.101	.790	.434	-.302	.691
Gabapentin	-.585	.416	-.186	-1.406	.166	-1.421	.251
Other drugs	.510	.245	.291	2.084	.042	.018	1.003
Dis. duration	.000	.008	-.002	-.018	.986	-.015	.015

R^2=0.26

Dependent Variable: Sour (tip of the tongue)

Table 5-43 Coefficients' table of the impact of SSFR on the sour tasting ability in pSS group

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	3.490	.669		5.219	.000	2.145	4.834
SSFR	.183	.185	.137	.989	.327	-.189	.555
Age	-.020	.010	-.282	-2.080	.043	-.040	-.001
Smoking	-.249	.537	-.066	-.464	.645	-1.330	.831
Alcohol	-.213	.240	-.116	-.887	.379	-.694	.269
Mouthwash	.010	.239	.005	.041	.968	-.471	.491
Appliances	-.206	.277	-.095	-.745	.460	-.763	.351
Pain relief	.158	.246	.081	.641	.525	-.337	.652
Gabapentin	-.604	.409	-.192	-1.476	.146	-1.428	.219
Other drugs	.465	.247	.265	1.885	.065	-.031	.961
Dis. duration	.001	.008	.011	.087	.931	-.014	.016

R^2=0.27

Dependent Variable: Sour (tip of the tongue)

Table 5-44 Coefficients' table of the impact of CODS on the sour tasting ability in pSS group

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	3.511	.629		5.583	.000	2.246	4.775
CODS	.105	.074	.226	1.427	.160	-.043	.253
Age	-.027	.010	-.381	-2.701	.010	-.048	-.007
Smoking	-.335	.537	-.088	-.623	.536	-1.415	.746
Alcohol	-.225	.233	-.123	-.963	.340	-.694	.244
Mouthwash	-.098	.246	-.052	-.399	.691	-.593	.396
Appliances	-.375	.285	-.174	-1.315	.195	-.949	.198
Pain relief	.246	.246	.127	.999	.323	-.249	.741
Gabapentin	-.496	.414	-.158	-1.199	.237	-1.329	.336
Other drugs	.624	.255	.355	2.449	.018	.112	1.136
Dis.duration	-.002	.007	-.033	-.260	.796	-.017	.013

R^2=0.28

Dependent Variable: Sour (tip of the tongue)

4. Salt

The severity of oral dryness that was assessed by USFR, SSFR and CODS did not contribute to the prediction of the salt tasting ability in pSS group. Age showed an independent effect on tasting salt in the three models (Tables 5-45, 5-46 and 5-47).

Table 5-45 Coefficients' table of the impact of USFR on the salt tasting ability in pSS group

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	4.579	.839		5.459	.000	2.893	6.266
USFR	.584	1.097	.069	.533	.597	-1.621	2.790
Age	-.039	.012	-.402	-3.130	.003	-.063	-.014
Smoking	.780	.693	.155	1.125	.266	-.614	2.174
Alcohol	.244	.301	.101	.812	.421	-.361	.850
Mouthwash	-.533	.305	-.214	-1.749	.087	-1.146	.080
Appliances	-.350	.351	-.122	-.997	.324	-1.056	.356
Pain relief	.520	.311	.202	1.671	.101	-.106	1.146
Gabapentin	-.422	.524	-.101	-.805	.425	-1.475	.632
Other drugs	-.130	.309	-.056	-.420	.677	-.750	.491
Dis. duration	.006	.009	.076	.618	.539	-.013	.025

R^2=0.33

Dependent Variable: Salt (tip of the tongue)

Table 5-46 Coefficients' table of the impact of SSFR on the salt tasting ability in pSS group

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	4.772	.850		5.612	.000	3.062	6.481
SSFR	-.014	.235	-.008	-.061	.951	-.487	.458
Age	-.040	.012	-.415	-3.200	.002	-.065	-.015
Smoking	.857	.683	.170	1.255	.216	-.517	2.231
Alcohol	.215	.305	.088	.704	.485	-.398	.827
Mouthwash	-.551	.304	-.221	-1.812	.076	-1.163	.060
Appliances	-.381	.352	-.132	-1.081	.285	-1.089	.328
Pain relief	.508	.313	.197	1.625	.111	-.120	1.137
Gabapentin	-.463	.521	-.111	-.888	.379	-1.510	.584
Other drugs	-.132	.314	-.057	-.421	.676	-.763	.499
Dis. duration	.006	.010	.074	.597	.553	-.014	.025

R^2=0.33

Dependent Variable: Salt (tip of the tongue)

Table 5-47 Coefficients' table of the impact of CODS on the salt tasting ability in pSS group

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	4.931	.803		6.141	.000	3.316	6.545
CODS	-.076	.094	-.124	-.812	.421	-.265	.113
Age	-.036	.013	-.373	-2.750	.008	-.062	-.010
Smoking	.947	.686	.188	1.380	.174	-.433	2.327
Alcohol	.191	.298	.079	.642	.524	-.408	.790
Mouthwash	-.480	.314	-.193	-1.529	.133	-1.111	.151
Appliances	-.284	.364	-.099	-.780	.439	-1.017	.448
Pain relief	.460	.314	.179	1.464	.150	-.172	1.092
Gabapentin	-.552	.529	-.132	-1.045	.301	-1.616	.511
Other drugs	-.221	.325	-.095	-.681	.499	-.875	.432
Dis. duration	.007	.010	.091	.736	.465	-.012	.026

R^2=0.34

Dependent Variable: Salt (tip of the tongue)

5. Bitter

Among the three oral dryness tests (USFR, SSFR and CODS), only the unstimulated salivary flow rate had contributed to the ability to taste bitter in the pSS group. Age and oral appliances were independent factors in the three models (Tables 5-48, 5-49 and 5-50).

Table 5-48 Coefficients' table of the impact of USFR on the bitter tasting ability in pSS group

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	5.862	.737		7.949	.000	4.379	7.345
USFR	-2.060	.964	-.245	-2.136	.038	-3.999	-.121
Age	-.058	.011	-.608	-5.365	.000	-.080	-.036
Smoking	-.803	.609	-.160	-1.318	.194	-2.028	.422
Alcohol	.238	.265	.098	.899	.373	-.294	.770
Mouthwash	-.434	.268	-.175	-1.622	.111	-.973	.104
Appliances	-.789	.309	-.275	-2.555	.014	-1.409	-.168
Pain relief	.274	.274	.107	1.001	.322	-.276	.824
Gabapentin	.012	.461	.003	.025	.980	-.915	.938
Other drugs	.461	.271	.199	1.700	.096	-.084	1.007
Dis. duration	.007	.008	.088	.817	.418	-.010	.024

R^2=0.48

Dependent Variable: Bitter (The tip of the tongue)

Table 5-49 Coefficients' table of the impact of SSFR on the bitter tasting ability in pSS group

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	5.376	.779		6.904	.000	3.811	6.942
SSFR	-.081	.215	-.046	-.375	.709	-.514	.352
Age	-.055	.011	-.578	-4.847	.000	-.078	-.032
Smoking	-1.046	.626	-.208	-1.671	.101	-2.304	.213
Alcohol	.308	.279	.127	1.102	.276	-.254	.869
Mouthwash	-.378	.279	-.152	-1.356	.182	-.938	.182
Appliances	-.710	.323	-.248	-2.200	.033	-1.359	-.061
Pain relief	.333	.286	.130	1.164	.250	-.243	.909
Gabapentin	.144	.477	.034	.302	.764	-.815	1.103
Other drugs	.499	.287	.215	1.737	.089	-.079	1.076
Dis. duration	.007	.009	.087	.764	.448	-.011	.024

R^2=0.43

Dependent Variable: Bitter (tip of the tongue)

Table 5-50 Coefficients' table of the impact of CODS on the bitter tasting ability in pSS group

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	5.025	.731		6.870	.000	3.555	6.496
CODS	.099	.086	.160	1.152	.255	-.073	.271
Age	-.059	.012	-.621	-5.007	.000	-.083	-.035
Smoking	-1.185	.625	-.236	-1.895	.064	-2.441	.072
Alcohol	.365	.271	.151	1.345	.185	-.181	.910
Mouthwash	-.464	.286	-.187	-1.621	.111	-1.039	.111
Appliances	-.812	.332	-.284	-2.446	.018	-1.480	-.145
Pain relief	.382	.286	.149	1.336	.188	-.193	.958
Gabapentin	.269	.482	.065	.559	.579	-.699	1.238
Other drugs	.593	.296	.255	2.001	.051	-.003	1.188
Dis. duration	.005	.009	.071	.625	.535	-.012	.023

R^2=0.44

Dependent Variable: Bitter (tip of the tongue)

B: Gustatory function in the pooled population

Additional regression analyses were added to the Appendices (Appendix 27, page: 339-340) in the thesis, where the outcome was the gustatory function, the control participants were included in the analysis, and the physiological measures (Stimulated Salivary Flow, Unstimulated Salivary Flow and CODS) were entered into the prediction. The severity of oral dryness that was measured by USFR and CODS had significant contribution (β=0.2 and β=0.4 respectively) to the gustatory function of taste in the total population of the study, unlike the SSFR, which had no significant contribution to the taste deterioration in the total population (Appendix 27). Age had moderated the association between the oral dryness and gustation with significant R^2 change (USFR=17%, SSFR=20% and CODS=8%).

C: Neurosensory threshold in the pSS group

The severity of oral dryness that was measured by USFR, SSFR and CODS did not contribute to the prediction of the neurosensory threshold of taste in pSS group. Mouthwash was independent factor on the prediction of the neurosensory threshold in the three models (Tables 5-51, 5-52 and 5-53).

Table 5-51 Coefficients' table of the impact of USFR on the neurosensory function of taste in pSS group

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
Constant)	-1.173	6.349		-.185	.854	-13.945	11.599
USFR	-2.953	8.302	-.048	-.356	.724	-19.655	13.748
Age	.114	.093	.165	1.226	.226	-.073	.301
Smoking	9.844	5.247	.270	1.876	.067	-.711	20.399
Alcohol	-3.726	2.279	-.212	-1.635	.109	-8.310	.859
Mouthwash	6.161	2.306	.343	2.672	.010	1.522	10.801
Appliances	1.392	2.657	.067	.524	.603	-3.954	6.737
Pain relief	-2.666	2.356	-.143	-1.132	.263	-7.405	2.073
Gabapentin	1.347	3.966	.045	.340	.736	-6.632	9.326
Other drugs	-4.454	2.336	-.264	-1.907	.063	-9.153	.246
Dis. duration	-.083	.072	-.149	-1.162	.251	-.228	.061

R^2=0.28

Dependent Variable: EGM total

Table 5-52 Coefficients' table of the impact of SSFR on the neurosensory function of taste in pSS group

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	-1.430	6.421		-.223	.825	-14.347	11.488
SSFR	-.415	1.776	-.032	-.234	.816	-3.988	3.158
Age	.115	.094	.167	1.229	.225	-.073	.304
Smoking	9.566	5.160	.263	1.854	.070	-.815	19.947
Alcohol	-3.707	2.301	-.211	-1.611	.114	-8.336	.923
Mouthwash	6.225	2.297	.346	2.710	.009	1.604	10.845
Appliances	1.437	2.660	.069	.540	.592	-3.915	6.789
Pain relief	-2.541	2.361	-.137	-1.076	.287	-7.292	2.209
Gabapentin	1.508	3.933	.050	.383	.703	-6.404	9.419
Other drugs	-4.334	2.368	-.257	-1.830	.074	-9.099	.431
Dis. duration	-.085	.072	-.152	-1.175	.246	-.230	.060

R^2=0.28
Dependent Variable: EGM total

Table 5-53 Coefficients' table of the impact of CODS on the neurosensory function of taste in pSS group

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	-3.895	6.029		-.646	.521	-16.023	8.234
CODS	.787	.705	.176	1.116	.270	-.632	2.206
Age	.080	.098	.115	.818	.418	-.116	.276
Smoking	8.509	5.152	.234	1.652	.105	-1.856	18.874
Alcohol	-3.313	2.237	-.189	-1.481	.145	-7.812	1.187
Mouthwash	5.524	2.357	.307	2.343	.023	.781	10.267
Appliances	.570	2.737	.027	.208	.836	-4.936	6.075
Pain relief	-2.119	2.359	-.114	-.898	.374	-6.865	2.628
Gabapentin	2.487	3.971	.082	.626	.534	-5.501	10.475
Other drugs	-3.536	2.441	-.210	-1.449	.154	-8.447	1.374
Dis. duration	-.096	.072	-.172	-1.336	.188	-.241	.049

R^2=0.3
Dependent Variable: EGM total

5.4.5 Objective 12: To investigate the association of the gustatory function to the neurosensory threshold of taste in pSS group

Our novel finding in the present study represented in the negative significant correlation between the neurosensory threshold of taste (β=-0.4, 95% CI=-0.2–0) and the gustatory function in the pSS group. Age (β=-0.4, 95% CI=-0.1–0) was independent factor in this model (Table 5-54).

Table 5-54 Coefficients' table of the relation between tasting ability and the neurosensory function of taste in pSS group

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	15.178	1.543		9.838	.000	12.075	18.282
EGM total	-.171	.040	-.478	-4.231	.000	-.252	-.090
Age	-.097	.025	-.403	-3.922	.000	-.147	-.047
Smoking	.369	1.402	.029	.263	.794	-2.451	3.189
Alcohol	-.467	.602	-.076	-.777	.441	-1.678	.743
Mouthwash	-.140	.665	-.022	-.210	.835	-1.477	1.198
Appliances	-.949	.689	-.131	-1.377	.175	-2.336	.438
Pain relief	1.193	.625	.184	1.907	.063	-.065	2.450
Gabapentin	-1.515	1.030	-.144	-1.470	.148	-3.588	.558
Other drugs	.523	.638	.089	.821	.416	-.759	1.806
Dis. duration	.008	.019	.040	.407	.686	-.031	.046

R^2=0.59

Dependent Variable: Total gustatory function

5.4.6 Objective 13: To investigate whether oral dryness is correlated with the self-reported vagina dryness in pSS group

Oral dryness in pSS patients was found in 78.4% (n=51/65) using USFR, 64.6% (n=42/65) using SSFR and 84.6% (n=55/64) using CODS. The self-reported vagina dryness was present in 87% (n=54/62) of pSS patients who answered the question of whether or not they suffer from vaginal dryness. Out of the 28 sexually active pSS patients, 26 (92.8%) reported vagina

dryness, one patient declined to answer, and one patient reported no vagina dryness. The sexually inactive patients were 37, out of which, 75.6% (n=28) reported dry vagina.

In terms of the association between the severity of oral dryness and the self-reported vagina dryness, the unstimulated (β=0.7, 95% CI=12.9- -11.5) and stimulated (β=-0.4, 95% CI=2– -2) salivary flow rate appear to associate with vaginal dryness. However, this association was not statistically significant (Tables 5-55 and 5-56). No important association was found between CODS (β=0, 95% CI=0.4- -0.4) and vaginal dryness in pSS group (Table 5-55).

Table 5-55 Variables in the equation of a logistic regression between USFR and the self-reported vagina dryness in pSS group

Variables		B	S.E.	Wald	df	Sig.	Exp(B)	95% CI for EXP(B)	
								Lower	Upper
Step 1	USFR	.726	3.528	.042	1	.837	2.066	.002	2081.22
	Age	-.005	.034	.021	1	.885	.995	.932	1.063
	Dis. duration	.064	.045	2.049	1	.152	1.066	.977	1.165
	Alcohol	.242	.820	.087	1	.768	1.274	.255	6.362
	Constant	1.103	2.184	.255	1	.614	3.012		

Variable(s) entered on step 1: USFR, Age, Dis. duration, Alcohol.

Table 5-56 Variables in the equation of a logistic regression between SSFR and the self-reported vagina dryness in pSS group.

Variables		B	S.E.	Wald	df	Sig.	Exp (B)	95% CI for EXP(B)	
								Lower	Upper
Step 1	SSFR	-.450	.537	.702	1	.402	.637	.222	1.828
	Age	-.015	.033	.212	1	.645	.985	.924	1.050
	Alcohol	.078	.853	.008	1	.928	1.081	.203	5.752
	Dis. duration	.059	.044	1.820	1	.177	1.061	.973	1.157
	Constant	2.239	2.135	1.100	1	.294	9.382		

Variable(s) entered on step 1: SSFR, Age, Alcohol, Dis. duration.

Table 5-57 Variables in the equation of a logistic regression between CODS and the self-reported vagina dryness in pSS group.

Variables		B	S.E.	Wald	df	Sig.	Exp (B)	95% CI for EXP(B)	
								Lower	Upper
Step 1	CODS	.079	.203	.154	1	.695	1.083	.728	1.610
	Age	-.012	.032	.133	1	.715	.988	.929	1.052
	Alcohol	.202	.836	.058	1	.809	1.224	.238	6.305
	Dis. duration	.061	.045	1.860	1	.173	1.063	.973	1.162
	Constant	1.155	1.837	.395	1	.530	3.174		

Variable(s) entered on step 1: CODS, Age, Alcohol, Disease duration.

5.4.7 Objective 14: To investigate the impact of the self-reported vaginal dryness on the sexual function in pSS patients

Pain during sexual activity appears to be associated with vagina dryness (n=26/28) in the sexually active patients (β=-0.2, 95% CI=-6.2 – 1.8), although this correlation was not statistically significant. Fatigue correlated with the FSFI global, sexual desire, arousal, orgasm and satisfaction, however, its effect was not statistically significant. Disease duration appears to associate with lubrication (β=0.3, 95% CI=0-0) and satisfaction (β=0.2, 95% CI=0-0) of the sexual activity, but this association was not statistically significant (Tables 5-58 to 5-64).

Table 5-58 Coefficients' table of the relation between vaginal dryness and the sexual function in the sexually active pSS patients

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	27.424	12.626		2.172	.041	1.167	53.681
Vagina dryness	.223	8.070	.006	.028	.978	-16.560	17.006
Age	-.108	.135	-.165	-.799	.433	-.388	.172
Alcohol	4.056	3.236	.263	1.253	.224	-2.674	10.786
Fatigue	-7.209	6.035	-.247	-1.195	.246	-19.761	5.342
Disease duration	.076	.089	.175	.851	.404	-.110	.261

R^2=0.18

Dependent Variable: Global FSFI for sexually active patients

Table 5-59 Coefficients' table of the relation between vaginal dryness and the sexual desire in the sexually active pSS patients.

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	4.423	1.720		2.571	.018	.846	8.001
Vagina dryness	-.672	1.100	-.126	-.611	.548	-2.959	1.615
Age	-.008	.018	-.096	-.455	.654	-.047	.030
Alcohol	.260	.441	.126	.590	.561	-.657	1.177
Fatigue	-1.191	.822	-.304	-1.448	.162	-2.901	.519
Disease duration	.000	.012	.004	.018	.986	-.025	.025

R^2=0.15

Dependent Variable: D1 (Desire) for the sexually active patients

Table 5-60 Coefficients' table of the relation between vaginal dryness and arousal in the sexually active pSS patients.

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
Constant)	4.443	2.557		1.737	.097	-.875	9.761
Vagina dryness	.348	1.635	.043	.213	.833	-3.051	3.747
Age	-.016	.027	-.119	-.577	.570	-.072	.041
Alcohol	.809	.655	.259	1.234	.231	-.554	2.172
Fatigue	-1.666	1.222	-.281	-1.363	.187	-4.208	.876
Disease duration	.012	.018	.136	.660	.516	-.026	.050

R^2=0.18

Dependent Variable: D2 (Arousal) for the sexually active patients

Table 5-61 Coefficients' table of the relation between vaginal dryness and lubrication in the sexually active pSS patients.

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	3.501	2.461		1.423	.170	-1.617	8.619
Vaginal dryness	.406	1.573	.053	.258	.799	-2.865	3.678
Age	-.032	.026	-.252	-1.214	.238	-.086	.023
Alcohol	.821	.631	.274	1.301	.207	-.491	2.133
Fatigue	-.119	1.176	-.021	-.101	.921	-2.565	2.328
Disease duration	.028	.017	.328	1.587	.127	-.009	.064

R^2=0.17

Dependent Variable: D3 (Lubrication) for the sexually active patients

Table 5-62 Coefficients' table of the relationship between vaginal dryness and orgasm in the sexually active pSS patients.

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	3.041	2.910		1.045	.308	-3.012	9.093
Vaginal dryness	1.374	1.860	.157	.738	.468	-2.495	5.243
Age	.006	.031	.044	.204	.840	-.058	.071
Alcohol	.469	.746	.138	.629	.536	-1.082	2.021
Fatigue	-1.442	1.391	-.224	-1.036	.312	-4.335	1.452
Disease duration	.000	.021	.001	.007	.995	-.043	.043

R^2=0.1

Dependent Variable: D4 (Orgasm) for the sexually active patients

Table 5-63 Coefficients' table of the relationship between vaginal dryness and satisfaction in the sexually active pSS patients.

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	3.544	2.486		1.425	.169	-1.627	8.714
Vaginal dryness	1.357	1.589	.164	.854	.403	-1.948	4.662
Age	-.011	.027	-.080	-.406	.689	-.066	.044
Alcohol	.945	.637	.295	1.482	.153	-.381	2.270
Fatigue	-1.794	1.189	-.296	-1.509	.146	-4.265	.678
Disease duration	.027	.018	.295	1.510	.146	-.010	.063

R^2=0.26

Dependent Variable: D5 (Satisfaction) for the sexually active patients

Table 5-64 Coefficients' table of the relationship between vaginal dryness and pain in the sexually active pSS patients.

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	7.555	3.047		2.480	.022	1.220	13.891
Vaginal dryness	-2.163	1.947	-.219	-1.111	.279	-6.213	1.886
Age	-.046	.032	-.283	-1.405	.175	-.113	.022
Alcohol	1.064	.781	.279	1.362	.188	-.560	2.688
Fatigue	-.799	1.456	-.110	-.549	.589	-3.827	2.230
Disease duration	.019	.022	.177	.885	.386	-.026	.064

R^2=0.22

Dependent Variable: D6 (Pain) for the sexually active patients

5.5 OTHER RESULTS

1. The correlation between the subjective and objective assessments in the pSS group.

A. Correlation between smell function measured by UPSIT and the self-assessment of smell measured by VAS in the pSS group

A positive significant correlation was found between smell and VAS smell in the patients group (r=0.7, p=0.00).

B. Correlation between gustatory function measured by TST and the self-assessment of taste measured by VAS in the pSS group

- **Total score**
  No significant correlation was found between the gustatory function and VAS taste in the patients group (r=0.1).

- **Sweet**
  No significant correlation was found between the gustatory function of tasting sweet and VAS sweet in the patients group (r=0.1).

- **Sour**
  No significant correlation was found between the gustatory function of tasting sour and VAS sour (r=0.1).

- **Salt**
  No significant correlation was found between the gustatory function of tasting salt and the VAS salt (r=0.1).

- **Bitter**
  No significant correlation was found between the gustatory function of tasting bitter and VAS bitter (r=0.2).

C. Correlation between oral dryness tests and the self-perception of oral dryness measured by Xerostomia Inventory in the pSS group

- **Unstimulated salivary flow rate and Xerostomia Inventory**

A significant negative correlation was found between USFR and XI (r=-0.4) (Figure 5-7).

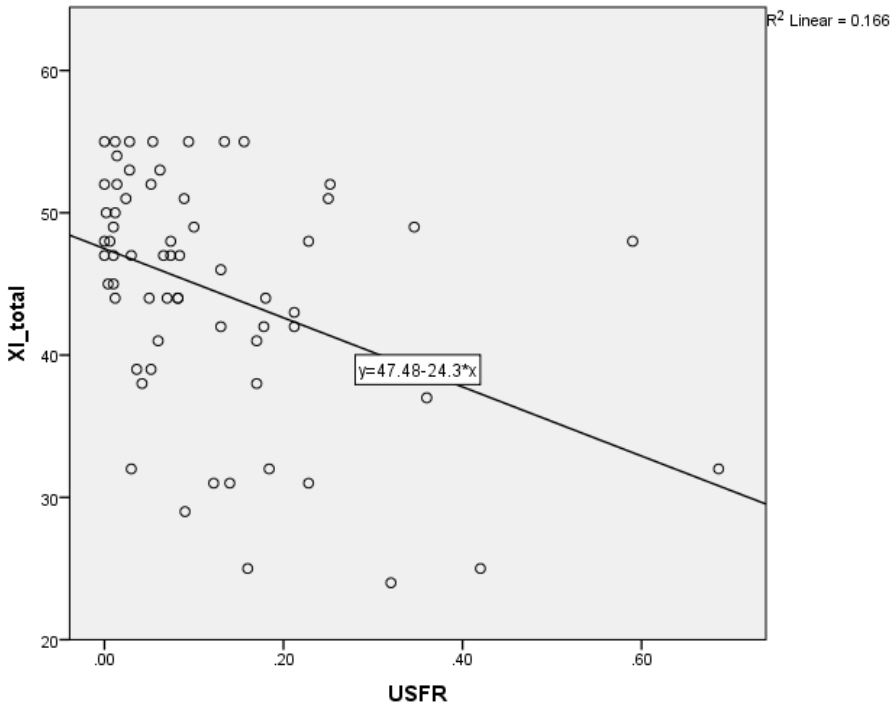

Figure 5-7 Correlation between USFR and XI in the pSS group

- **Stimulated salivary flow rate and Xerostomia Inventory**

A significant negative correlation was found between SSFR and XI (r=-0.2) (Figure 5-8).

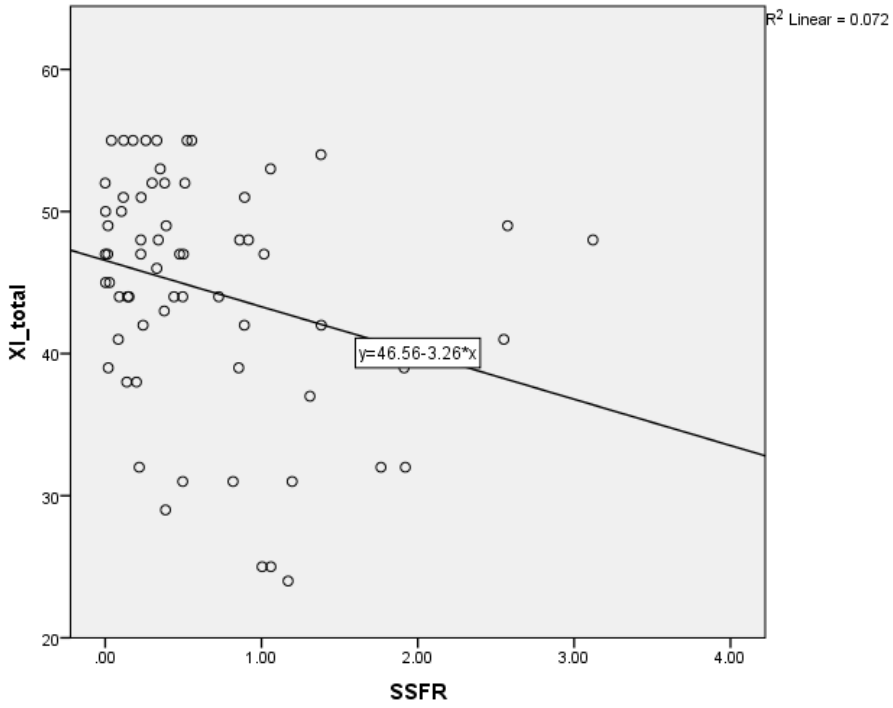

Figure 5-8 Correlation between SSFR and XI in the pSS group

- **Clinical oral dryness score (CODS) and XI**

A significant positive correlation was found between CODS and XI (r=0.3) (Figure 5-9).

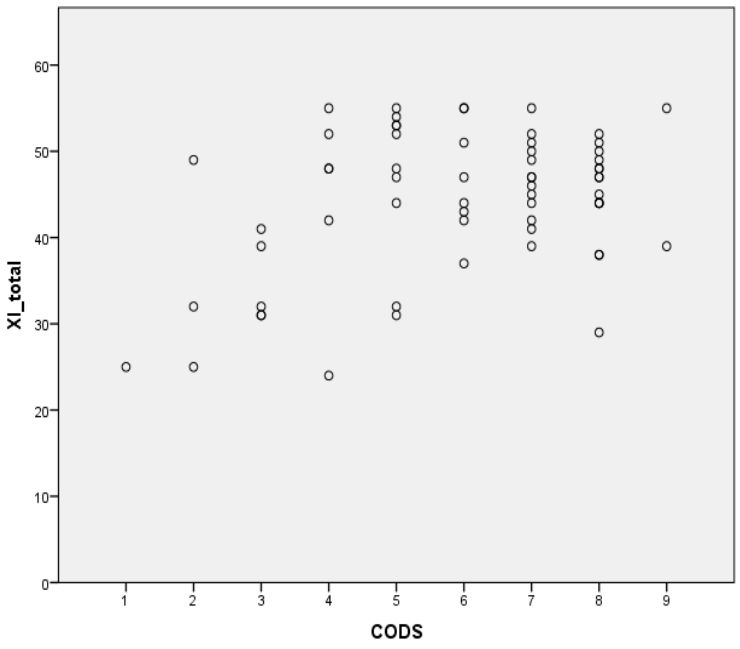

Figure 5-9 Correlation between USFR and XI in the pSS group

D. Correlation of the self-assessment of the nasal dryness measured by XI and the smell function in the pSS group

No significant correlation was found between the self-assessment of the nasal dryness and the smell function (r=-0.02) in the patients group (Figure 5-10).

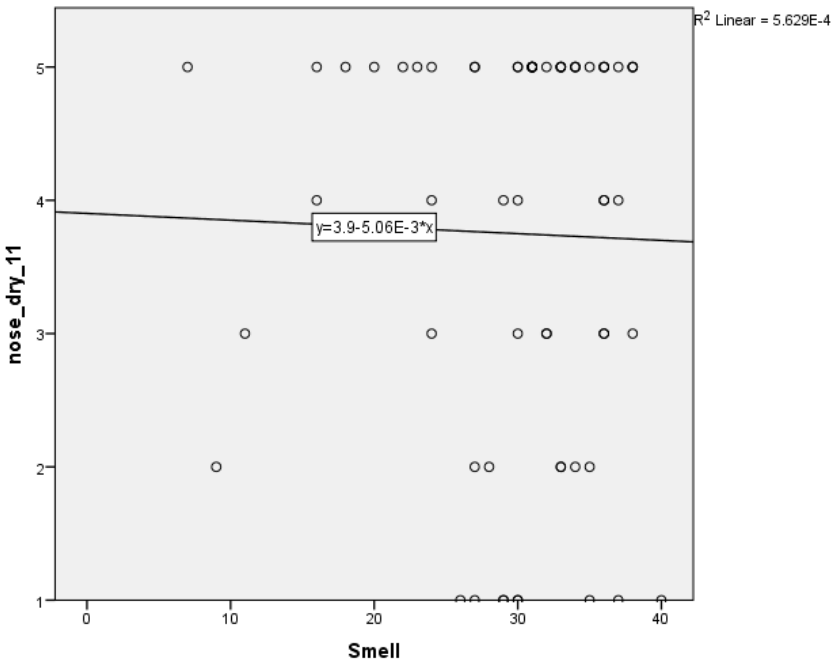

Figure 5-10 Correlation between the self-assessment of the nasal dryness and the smell function in the pSS patients

2. The taste map

A: Comparison of the four basic tastes between the right and left laterals of the tongue in the total population of the study

The results showed no statistical significant difference in the tasting ability of the four taste categories (Sweet, sour, salt and bitter) between the right and the left laterals of the anterior two thirds of the tongue.

B: Comparison of the four taste categories between the tip and laterals of the tongue in the total population of the study

- **Sweet and sour**

The results showed no statistical significant difference in the tasting ability between the tip and the laterals of the tongue (Right and left laterals) in tasting sweet and sour.

- **Salt**

A statistical significant difference was found between the tip and the laterals in tasting salt, the highest mean was for the tip (Mean score of the tip=2.8, mean score of the lateral right=2.3, 95% CI=0.1–0.7, mean score of the lateral left=2.2, 95% CI=0.2–0.8).

- **Bitter**

There was no statistical significant difference between the tip and the right lateral (Mean score of the right lateral=2.3, 95% CI=-0.1–0.5). Significant difference was found between tip of the tongue and the left lateral in tasting bitter. The highest mean score being for the tip (Mean score of the tip=2.5, mean score of the left lateral=2.1, 95% CI=0–0.7).

3. Effect of medicines on mucosal dryness, smell and gustation in the patients group

A: Impact on oral dryness

Topical medicines group (β=0.4, 95% CI=0.3–2.2) was a good predictor of the oral dryness that was tested by CODS. A group of “other drugs” had an effect on the oral dryness that was measured by CODS, however, this variable has not been considered as a predicting factor as it consists of a number of drugs with different effects on the body (Table 5-65).

Table 5-65 Coefficients table of the regression analysis between oral dryness and the medicines taken by pSS patients

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	6.150	.459		13.383	.000	5.223	7.076
Hydroxychloroquine	-.585	.507	-.149	-1.154	.255	-1.608	.437
Pilocarpin	1.760	.998	.239	1.764	.085	-.252	3.771
Supplements	-.351	.588	-.088	-.598	.553	-1.536	.834
Antidepressant	-1.349	.844	-.233	-1.599	.117	-3.051	.352
immunosuppressant	.126	.567	.032	.223	.825	-1.016	1.269
Anticoagulants	1.760	1.366	.188	1.288	.204	-.995	4.516
Antihistamine	-.345	1.157	-.042	-.299	.767	-2.678	1.987
Antihyperthyroid	.260	.660	.053	.394	.696	-1.072	1.592
Antihypothyroid	1.832	1.173	.224	1.561	.126	-.534	4.198
Antibiotics	-.318	1.039	-.039	-.306	.761	-2.414	1.778
Angiotensin	.223	.526	.053	.423	.674	-.839	1.284
Pain relief	-.807	.543	-.194	-1.486	.145	-1.902	.288
Antistomach acid	.552	.697	.109	.792	.433	-.854	1.957
Antihypoglycaemic	.148	.584	.030	.253	.802	-1.030	1.325
Inhalers	-2.085	1.466	-.223	-1.422	.162	-5.040	.871
P. biliary cirrhosis drugs	1.095	1.177	.117	.931	.357	-1.278	3.468
Overactive bladder drugs	-2.348	1.588	-.251	-1.478	.147	-5.550	.855
Topical	1.289	.485	.420	2.657	.011	.311	2.267
Gabapentin	-.230	.980	-.034	-.235	.816	-2.207	1.747
Other drugs	-1.098	.534	-.291	-2.056	.046	-2.174	-.021

R^2=0.45

Dependent Variable: CODS

B: Impact on nasal dryness

The nasal dryness that was assessed subjectively by item 11 of the Xerostomia Inventory. It was found that Hydroxychloroquine (β=0.4, 95% CI=0-2.1) and supplements (β=-0.3, 95% CI=0- -2) had affected the nasal dryness significantly (Table 5-66).

Table 5-66 Coefficients table of the regression analysis between nasal dryness and the medicines taken by pSS patients

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	3.606	.400		9.014	.000	2.799	4.413
Hydroxychloroquine	1.269	.441	.420	2.874	.006	.379	2.159
Pilocarpin	-.005	.868	-.001	-.006	.995	-1.757	1.746
Supplements	-1.005	.512	-.329	-1.965	.056	-2.037	.026
Antidepressant	.262	.735	.059	.357	.723	-1.219	1.744
Immunosuppressant	-.171	.493	-.057	-.347	.730	-1.166	.824
Anticoagulants	1.914	1.189	.266	1.609	.115	-.485	4.313
Antihistamine	-.445	1.007	-.071	-.442	.661	-2.475	1.586
Antihyperthyroid	-.257	.575	-.068	-.447	.657	-1.417	.902
Antihypothyroid	-.583	1.021	-.093	-.571	.571	-2.643	1.477
Antibiotics	-.288	.905	-.046	-.319	.752	-2.113	1.537
Angiotensin	.064	.458	.020	.139	.890	-.860	.988
Pain relief	-.103	.473	-.032	-.219	.828	-1.057	.850
Antistomach acid	-.319	.607	-.082	-.526	.601	-1.543	.904
Antihypoglycaemic	-.570	.508	-.153	-1.122	.268	-1.595	.455
Inhalers	-1.896	1.276	-.263	-1.486	.145	-4.469	.678
P. biliary cirrhosis drugs	-.228	1.024	-.032	-.222	.825	-2.293	1.838
Overactive bladder drugs	.999	1.382	.139	.723	.474	-1.789	3.787
Topical	-.007	.422	-.003	-.016	.988	-.858	.845
Gabapentin	-.408	.853	-.078	-.478	.635	-2.129	1.313
Other drugs	.286	.465	.098	.615	.542	-.651	1.223

R^2=0.29

Dependent Variable: nasal dryness

C: Impact on smell

Topical medicines group (β=-0.4, 95% CI=-8.8 - -0.7) was a good predictor of the smell function in pSS group, where a negative correlation was found between topical medicines and the smell function (Table 5-67).

Table 5-67 Coefficients table of the regression analysis between smell function and the medicines taken in pSS patients.

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	30.641	1.855		16.515	.000	26.902	34.380
Hydroxychloroquine	2.128	2.047	.151	1.039	.304	-1.999	6.254
Pilocarpin	4.142	4.028	.157	1.028	.309	-3.976	12.260
Supplements	-.190	2.373	-.013	-.080	.936	-4.972	4.591
Antidepressant	1.029	3.407	.050	.302	.764	-5.837	7.895
Immunosuppressant	-2.706	2.288	-.193	-1.183	.243	-7.317	1.905
Anticoagulants	.646	5.517	.019	.117	.907	-10.472	11.764
Antihistamine	1.415	4.670	.048	.303	.763	-7.997	10.827
Antihyperthyroid	-3.057	2.667	-.174	-1.147	.258	-8.431	2.317
Antiypothyroid	-1.120	4.737	-.038	-.236	.814	-10.668	8.427
Antibiotics	1.031	4.196	.035	.246	.807	-7.427	9.488
Angiotensin	.134	2.125	.009	.063	.950	-4.148	4.417
Pain relief	.425	2.193	.028	.194	.847	-3.995	4.844
Antistomach acid	.225	2.814	.012	.080	.937	-5.447	5.896
Antihypoglycaemic	-.724	2.357	-.042	-.307	.760	-5.475	4.027
Inhalers	-2.661	5.918	-.079	-.450	.655	-14.589	9.266
P. biliary cirrhosis drugs	-1.053	4.751	-.031	-.222	.826	-10.627	8.521
Overactive bladder drugs	2.528	6.412	.075	.394	.695	-10.394	15.450
Topical	-4.679	1.959	-.425	-2.389	.021	-8.626	-.731
Gabapentin	-.535	3.958	-.022	-.135	.893	-8.511	7.441
Other drugs	.845	2.156	.062	.392	.697	-3.500	5.189

R^2=0.28

Dependent Variable: Smell

D: Impact on taste

Pain relief was a good predictor in this model (β=0.3, 95% CI=0.1-3.8) where a positive association was found between this group of medicines and the taste function. Gabapentin (β=-0.2, 95% CI=-6.4 – 0.3) and inhalers (β=-0.2. 95% CI=-8.8-1.2) seem to correlate with tasting ability, however, the correlation was not significant (Table 5-68).

Table 5-68 Coefficients table of the regression analysis between taste function and the medicines taken in pSS patients.

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	8.328	.784		10.61	.000	6.745	9.911
Hydroxychloroquine	.832	.866	.136	.961	.342	-.915	2.579
Pilocarpin	1.677	1.703	.147	.985	.330	-1.760	5.114
Supplements	-.781	1.003	-.127	-.779	.440	-2.806	1.243
Antidepressant	-.256	1.441	-.028	-.178	.860	-3.163	2.651
Immunosuppressant	.255	.967	.042	.264	.793	-1.697	2.207
Anticoagulants	-2.731	2.333	-.188	-1.171	.248	-7.438	1.977
Antihistamine	-1.784	1.975	-.141	-.903	.372	-5.769	2.202
Antihyperthyroid	.002	1.128	.000	.002	.999	-2.273	2.277
Antihypothyroid	-.976	2.003	-.077	-.487	.629	-5.018	3.067
Antibiotics	-.777	1.774	-.061	-.438	.664	-4.358	2.804
Angiotensin	-.339	.898	-.052	-.377	.708	-2.152	1.475
Pain relief	2.012	.927	.311	2.169	.036	.140	3.883
Stomach acid drugs	-.319	1.190	-.041	-.268	.790	-2.720	2.083
Hypoglycaemic	-.810	.997	-.107	-.812	.421	-2.822	1.202
Inhalers	-3.807	2.502	-.262	-1.522	.136	-8.858	1.243
Primary bil cirrhosis drugs	-2.643	2.009	-.182	-1.316	.195	-6.697	1.411
Overactive bladder drugs	.465	2.711	.032	.172	.865	-5.006	5.936
Topical	-.266	.828	-.056	-.321	.750	-1.937	1.406
Gabapentin	-3.031	1.673	-.288	-1.811	.077	-6.408	.346
Other drugs	1.910	.912	.326	2.096	.042	.071	3.750

R^2=0.35

Dependent Variable: Gustatory function

4. Open-ended questions

Hundred percent of our pSS group answered the open-ended questions on their visit day. Analysis showed that the top two reported symptoms of burden were the oral dryness (n=28/65) and fatigue (n=20/65). One patient reported the frequency of using the toilet because of the higher intake of water due to constant feeling of oral dryness. The same patient also reported having painful intercourse due to vaginal dryness, but that the oral dryness was the worst one symptom that affected her life quality. Another patient reported that “social anxiety” and “inability to plan ahead” were the most two problems with her condition that affected her life quality (Table 5-69).

Overall, three patients thought that oral dryness was the worst symptom among other symptoms of pSS they have, four patients rated eyes dryness as the worst among other symptoms and two patients described fatigue as the worst over other symptoms that affected their life quality.

Table 5-69 Ranking of the symptoms affecting the quality of life as reported by pSS patients

Symptoms	N (%)
Oral dryness	n=28/65, 43%
Fatigue	n=20/65, 30.7%
Eyes dryness	n=18/65, 27.6%
Non-specified “dryness”	n=10/65, 15.3%
Joint pain	n=5/65, 7.6%
Vagina dryness	n=1/65, 1.5%
Smell dysfunction	n=1/65, 1.5%
Ears dryness	n=1/65, 1.5%
Burning mouth sensation	n=1/65, 1.5%
Painful salivary glands	n=2/65, 3%
Neuropathy	n=1/65, 1.5%
Anxiety and inability to plan ahead	n=1/65, 1.5%
Frequency to use the toilet	n=1/65, 1.5%
No symptoms	n=1/65, 1.5%

5. Self-reported neuropathy symptoms

Sixty four pSS patients out of 65 (98.4%) responded to the following questions that evaluated the rate of the neuropathy symptoms (Table 5-70):

- Have you lost feeling in your hands and/or feet?
- Do you have tingling in your hands and/or feet (pins and needles)?
- Do you have numbness in your hands and/or feet?
- Have you suffered from clumsiness?

Table 5-70 Neuropathy symptoms reported by pSS patients

Neuropathy symptoms	N (%)
Lost feeling	n=26/64, 40.5%
Tingling	n=40/64, 62.5%
Numbness	n=30/64, 46.8%
Clumsiness	n=35/64, 54.6%

CAHPTER 6: DISCUSSION

A. Key results

This study was designed to assess the functions of the smell, taste and sexuality in a group of pSS patients, with special focus on assessing the association of the impairment of these functions with the severity of mucosal dryness, and the consequences this may have on quality of life and mental health well-being. Our results demonstrated that pSS patients were affected and that their smell, taste, sexual function, quality of life and mental health well-being were significantly impaired. The dryness of mucosal surfaces was not the key factor in deteriorating the smell, taste and sexual functions as it was alleged before. Patients' life quality and mental health status were compromised by the SD.

B. Strengths and limitations

- **Strengths**
  1. The study was conducted at Barts Health Trust, the largest trust and a major service provider in the UK.
  2. The literature review was structured according to the conceptual model of health related quality of life by Wilson and Cleary (1995).
  3. The study report was structured according to STROBE statement checklist for combined studies (Case-control and cross-sectional studies) (Fernandez, 2005).
  4. The power of the study (90%) and the sample size (Patients n=65, healthy volunteers n=62) was large enough to come out to a conclusion.
  5. The clinical criteria for diagnosing pSS patients was based on the recommended American European Consensus Group Criteria, which ensured identifying a pure group of patients.
  6. The clinical tests used for the assessment of the smell and taste are validated and reliable.
  7. Screening the functions of the smell, taste and sexual activity was performed regardless of the severity of the disease.
  8. The range of the questionnaires used ensured collecting the necessary information from participants.
  9. Data were collected by one researcher, which ensured avoiding performance bias.

- **Limitations**

1. Patients and healthy volunteers were not age matched, which may have resulted in an overestimation of the significance of the results. However, when the data was analysed according to age groups, the results were similar to that when the study group data was analysed collectively.
2. The nasal and vaginal mucosa were not assessed clinically for dryness. The researcher for practical reasons did not perform these assessments. Testing the nasal dryness would have involved using a nasal douche, which can be uncomfortable for the patient and associated with complications. To examine for vaginal dryness, suitable private clinical setting and training of the operator would have been necessary. Therefore, patients were asked to self-report the dryness of the nose and vagina as an alternative.
3. Healthy volunteers were invited to take part in the study by advertising in the hospital's waiting rooms, in schools and at the British Sjögren's Syndrome Association (BSSA) website. All interested volunteers that met the criteria were recruited. The mean age of this group was 43 years, which was less than the patients group (mean 50 years).
4. The power calculation was based on the mean difference of the primary outcomes only. Hence, unpowered regression analysis for the patients' group to investigate the secondary objectives was done.
5. The UPSIT used to test the smell test, requires a pencil to scratch each box in the booklet to release a smell, a technique recommended in the manufacturer's instruction. However, an observed limitation is that a lead layer from the pencil may incur covering the embedded microencapsulated odours. This might have affected the final score.
6. The TST used for the taste, was reported by a number of participants to have exacerbated the dryness due to applying paper strips on the tongue. Although this was uncomfortable for patients, it is unlikely that it affected the results. The other limitation of using this test was the scoring procedure, where a number of

participants could not identify the full scale of the full range of concentrations of a particular taste. Nevertheless these individuals could correctly tick nine tastants on the scoring sheet, and therefore were scored as "normal" as per the test's validated cut-off point. There is a need for a different scoring system and/or different cut-off point of the test to enable researchers or clinicians to assess individual's ability to identify the basic tastes accurately.

7. The EGM was used to assess the neurosensory threshold of taste, which is the only quantitative device available to date for the assessment of the neural function of the taste sensation performed by chorda tympani nerve. A limitation of the EGM is that the presence of saliva on the tongue may increase the conductivity of the generated current to the nerve. Our data showed no evidence that the presence of saliva had an effect on the results, as a group of pSS patients with normal salivary flow, had impaired nerve function reading, indicating that the abundance of saliva does not necessary have an input on the device performance. However, further studies with this regards are needed.
8. A limitation of the FSFI questionnaire reported by a number of our participants, who observed that the four weeks' time limit period in assessing the women's sexual activity is not realistic. Some participants commented that their sexual life changed with losing their partners rather than due to health reasons or declined desire. It should be acknowledged that the FSFI is a brief questionnaire for the assessment of sexual function in women. It was not designed as a diagnostic tool, or to assess the sexual experience, knowledge, attitudes or interpersonal functioning in women. For more detailed studies, a more comprehensive questionnaire to assess sexual function over longer period of time should be used.
9. Impact of choice of methods: Wilson and Cleary (1995) model is the most widely cited conceptual framework of the HRQoL that integrates both biological and psychological aspects of health outcomes (Ojelabi et al., 2017). The model provides theoretical approach to conceptualising HRQoL as a multidimensional construct and is useful to guide the development of new theories. Therefore, it was decided to

apply Wilson and Cleary approach in the study. Lack of use of other models is noted as a limitation in the study.

10. There is a potentially selection bias for patients entering the study, as patients are more likely to have problems with dryness if they are seen at the Dental Hospital, and/or if they have expressed interest in the study.

C. Interpretation of the findings

1. Smell

In this study, we found that 41.5% of pSS patients exhibited disturbance in smell function compared to that of the healthy volunteers (24.1%), which is an indication of the impact of the syndrome on these patients. Interestingly, the majority of pSS patients reported no change in their smell function or acuity, which shows that these patients were coping and not aware of the problem before being clinically tested.

Henkin et al. (1972) and Kamel et al. (2009) suggested a correlation of the deterioration of the smell function in pSS patients due to the nasal mucosa dryness, in particular, to the reduction in the nasal mucin secretion. However, our research contradicted the aforementioned studies, and revealed that the smell dysfunction in the pSS group was not impacted by the dryness of the mucosal linings. Additionally, a correlation between the smell function and oral dryness could not be established in our pSS group. Moreover, smell impairment was not correlated with the severity of the nasal dryness that was subjectively reported by patients. These findings support a previous study by Rasmussen et al. (1986) which demonstrated no correlation between smell thresholds and the severity of the dryness of the nasal mucosa in pSS patients.

Nevertheless, the sample size of the present study was planned to explore the mean difference between patients and healthy volunteers. Therefore, in order to explore the impact of the dryness of the nasal mucosa on the smell function accurately, a study with sample size that is specifically designed to detect the effect of dryness is required.

The prevalence of the neuropathy, which is known to be part of pSS symptoms, was reported by 81.2% of our pSS population. The reported symptoms ranged from “Lost feeling” to “Tingling”, “Numbness” or “Clumsiness”. We, therefore, suggest a possible

correlation between the neuropathy and the smell impairment in pSS patients. Our results supported findings by Welge-Lussen et al. (2004) who found that the integrity of the neurological function of olfaction was important for smell acuity. Our study agreed with Heckmann et al. (2009), who found that a large number of polyneuropathic patients recorded smell disturbances. However, assessing the nerve function of the smell sensation was beyond the remit of the present study, and there is a need for more studies with this regards.

In an attempt to find a correlation between the medicines taken by pSS patients and the impairment of smell function, we found that the topical medicines (Eye drops, Eye gels, Viscotears –liquid gel-, Skin creams and Telmesteine) were the most affecting medicines (β=-0.4, 95% CI=-8.6 - -0.7) on the smell function. This can possibly indicate that patients with severe symptoms of pSS would suffer from smell dysfunction and tend to use more from topical medicines, rather than the influence of the topical medicine itself on smell acuity. We found no association between antihypertensive drugs and the smell function as it was previously reported (Deems et al., 1991, Doty et al., 2003). Due to the rarity of pSS patients, it was difficult to exclude patients on medications, which would otherwise limit the pool of subjects required for research investigation. When confidence intervals were reported, the interpretation was aided by the knowledge of range of possible results rather than a single p-value. Bonferroni correction may have been considered in the future.

Moreover, age was not correlated with smell in our pSS group, which contradicts a previous statement of the negative correlation between age and smell in pSS patients (Kamel et al., 2009). However, in our healthy volunteers group, there was significant negative correlation between age and smell, which is an anticipated normal regression of the smell function with age (Doty and Kamath, 2014, Thesen and Murphy, 2001, Doty et al., 1984). The lack of association between the smell and age in our pSS group indicated the presence of other factors that abolished the impact of age on olfaction, which in our study can be referred to the neuropathy.

Additionally, smoking was found to have no important association with the smell function in the patients and volunteers groups. This finding supports Kamel et al. (2009) and

contradicts Frye et al. (1990) and Vennemann et al. (2008), who demonstrated a correlation between heavy smoking and smell deficit. Interestingly, our data showed that the highest score of the smell test (39/40) was recorded by a heavy smoker healthy volunteer, who reported smoking a total of 20 cigarettes per day. The subject reported that the smell acuity has not been changed, which can be referred to the continuous renewing process of the nasoepithelium due to the exposure to the smoke particles. Disease duration had no significant influence on smell function in the patients group. We are not aware of a study that has investigated the association of the disease duration with the smell function before in pSS patients, therefore, studies for comparison are not applicable.

In the early stages of the study, it was decided to use the phenyl ethyl alcohol detection threshold test (Smell Threshold Test). But after consulting Professor Chris Hawkes (adviser) and Professor Richard Doty, we decided to use the University of Pennsylvania Identification Test (UPSIT-40) was chosen for the following reasons:

1. The test was validated and widely used for research purposes compared with the former test.
2. The test is reliable and highly correlated with the Smell Threshold Test. It is worth to note that the threshold, discrimination and identification abilities of smell are correlated with each other, and that when one of these abilities affected, the other is affected as well (Hummel T et al., 1997).
3. Unlike Sniffin Sticks and the Smell Threshold Tests, UPSIT is hygienic. It is also straightforward to achieve, cheaper, can be self-administered and it employs familiar odours.

Professor Chris Hawkes had also advised to moisten the nasal cavity before testing the smell in the patients group. Professor Antje Welge-Lüssen, University of Basel, Germany who was contacted with this regards, also supported this suggestion. However, after consulting the supervisors of the present study, we found that the need to moisten the nasal cavity was negated by the presence of the healthy volunteers group, which provides information of the smell function without being affected by the nasal dryness. Also by using the nasal douche, the study will be complicated and participants will be overburdened with

further procedures, which may raise potential ethical issue, and above all the study will go out of the target.

In the present study, our sample was representative of our database population, but it does not represent a prevalence of the smell and taste in all pSS patients. However, our results showed that patients with a confirmed diagnosis of pSS were more likely to have impaired smell function compared with healthy volunteers, which agree with Kamel et al. (2009).

2. Taste

The present study shows high degree of impairment in the taste function in pSS patients compared with healthy volunteers. Anecdotally, patients with pSS have been observed developing taste deterioration. However, it has not been established yet whether it is related to the syndrome manifestations or not.

Our findings agreed with Henkin et al. (1972), Weifenbach et al. (1995), Gomez et al. (2004), Negoro et al. (2004) and Kamel et al. (2009) who reported that taste function was significantly deteriorated in SS patients compared to controls. We proved taste disorder in 54% of pSS group (n=34 of 63) vs 8.3% in the healthy volunteers group (n=5 of 60). This rate differs from the last stated by Kamel et al (Kamel et al., 2009) who reported 71% hypogeusic SS patients (n=28, 25 females/ 3 males) vs 13% of their controls group (n=37, 35 females/ 2 males). The difference in the taste dysfunction rate between studies can be referred to the difference in the sample size recruited. Additionally, the results of Kamel et al's study may not be applied to the female population of SS patients, as there was 11% males recruited in the pSS group.

In our study, the number of patients who were aware of the loss of their taste acuity 21.9% (n=14 of 64) was approximately half of the number of patients who recorded taste dysfunction objectively. This suggests that patients were coping with the slowly growing problems of taste.

Our systematic search in five medical databases from inception to June 2015 (Al-Ezzi et al., 2016), showed five studies in which taste threshold was assessed in SS patients, and therefore comparable to our study (Henkin et al., 1972, Weifenbach et al., 1995, Gomez et

al., 2004, Negoro et al., 2004, Kamel et al., 2009). Henkin et al's research is a pioneering study in the field of assessing the smell and taste in pSS patients. However, most of its methodology relied on the clinical experience of the researchers at the time, which nowadays are guided by validated criteria and scales. However, due to the lack of the available resources for comparisons, this study was cited in the review.

It is important to note that the study by Kamel et al. (2009) was the only one that met our inclusion criteria in the systematic review and meta-analysis, although there was no information about the severity of oral dryness. The other four studies have investigated the correlation between the oral dryness and taste function; however, patients' sampling was not based on the recommended criteria (AECG) (Vitali et al., 2002) for diagnosing SS patients. The Systematic Review showed that the data available in the literature was limited and heterogeneous.

A systematic review differs from traditional literature review in several ways. The traditional reviews are generally descriptive, without systematic search of the literature, and hence focused on studies chosen based on their availability or author's selection. Therefore, the literature review although informative, can have a tendency of selection bias, and can also be confusing when similar studies have diverging results and conclusions. Systematic reviews (SR), as the name implies, involve detailed and comprehensive search strategy, planned by a team of at least three people usually, with the intention of reducing bias by identifying, appraising and synthesizing all relevant studies according to a peer reviewed protocol. The topic in the SR is focused on a single question that is usually PICO based, which gives the SR a narrow but specific focused scope that helps to answer a research question (Uman, 2011). Therefore, we started with literature review as a broad approach and once decided on the subject we want to address, we conducted a comprehensive focused systematic review.

The regional assessment of the gustatory function on three tested places of the anterior 2/3 of the tongue (Tip, right and left) revealed that tasting ability of the laterals was worse than the tip in the pSS group. Whilst in the healthy volunteers, the three tested sites of the tongue did not differ significantly between each other. These findings indicate impairment in interpreting or transmitting of the taste stimulations to the higher brain centres. Our results agreed with others who found that the function of the laterals of the tongue was

better only at higher threshold of taste than other sites of the tongue in patients with burning mouth syndrome and Parkinson's disease respectively (Just et al., 2010, Doty et al., 2015). In our study, the function of the tip of the tongue was more sensitive in identifying the four basic tastes than the laterals of the tongue. This is the first study to report regional taste assessment of the tongue in pSS patients.

A comparison of each tastant of the four basic tastes was conducted on the tip of the tongue to represent the whole mouth testing ability, as was indicated by the TST manual. We proved that the tip was more sensitive and better in reflecting tasting ability of the four basic tastes than the laterals of the tongue. The ability to taste sweet in the patients group was statistically significantly impaired compared to the healthy volunteers. Our results contradicted previous studies in which no difference between pSS patients and controls in tasting sweet was reported, and that the ability to taste sweet was the least affected in pSS patients (Gomez et al., 2004, Kamel et al., 2009). We found that the ability to taste sweet in the pSS group was minimally affected only when compared to other tastants in the patients group. Our findings were in agreement with others who believed that the quality of tasting sweet was independent of other tastants, and was not affected by saliva depletion or higher brain function (Henkin et al., 1972, Kaneda et al., 2000, Kamel et al., 2009).

The ability to taste sour, salt and bitter did not differ significantly between each other in the patients group, but differed significantly from tasting sweet, indicating that sour, salt and bitter were affected equally. In the present study, these tastes (Sour, salt and bitter) were shown to be more vulnerable in the pSS group, in agreement to previous reports who found that the three tastants were more affected compared to sweet (Gomez et al., 2004, Kamel et al., 2009).

The number of patients who were able to identify the full range of concentrations of each tastant (low to high), varied significantly between patients and healthy volunteers. Identifying the lowest concentration of sweet recorded better frequency than the other three tastants on the three tested places of the tongue in both groups. However, patients were less able to identify the lowest concentration of sweet, as indicated by the half

frequency compared to healthy group in table 5-6. The tip of the tongue in the patients group was more sensitive in identifying the lowest concentrations in the patients group, as we proved above. The lack in studies investigating individuals' ability to identify the lowest concentrations of the basic tastes precluded any comparisons.

In light of anecdotal evidence that certain classes of drugs may be associated with alteration of tasting ability, we sought to establish whether such associations present in the pSS group. We found no association between antihypertensive drugs and taste deterioration in the pSS group as it was previously reported (Deems et al., 1991, Doty et al., 2003). Pain relief medicines (Naproxen, Painkiller, Paracetamol, Aspirin, Codein, Co-codamol, Diclofenac, Fentanyl) that were reported by patients, appeared to be associated with the taste impairment. Apart from pain relief medicines, no important correlations were found between drugs used to treat asthma, depression and sleeping problems and taste deterioration as it was reported by Casaburi et al. (2002), Godara et al. (2011) and Suliburska et al. (2012). Our binary data were not showing the dosage and timing of the medicines taken by patients, making the analysis of limited value. Nevertheless, this preliminary assessment of the effect of the medicines on the tasting ability sheds a light on the importance of conducting a study with adequate information regarding the impact of the medicines taken on the tasting ability in pSS patients. The "other drugs" category although analysed, its results were not interpreted in the Discussion section as it contains miscellaneous drugs and the analysis was found to be of limited value. This was explained in the results section page 155.

Participants in the current project were recruited from the largest Trust in the UK, which attracts patients from different places in the country, including the rural areas. However, the environmental impact is not a factor that can be adjusted statistically, unless using specific instruments to assess certain environmental effect, which is beyond the scope of the current study.

Taste was evaluated by testing the gustatory function and the neurosensory threshold of taste. The gustatory function is represented by the function of the taste buds, and the

neurosensory threshold of taste is represented by testing the threshold of the chorda tympani nerve, which innervates the taste buds in the anterior 2/3 of the tongue. Measuring taste function by these two methods provided comprehensive assessment that helped to draw conclusion for the etiology of the taste dysfunction in the pSS group.

Burghart Medical Technologies was contacted to seek their advice about the best taste test. The company suggested using GU002 gustometer, which is a computer-controlled machine that presents programmed concentrations of different tastants inside the patient's mouth. The machine is precise and reliable in assessing the taste threshold and it was used in a number of studies. However, the space requirement for the machine and economic cost precluded its use in the study. Therefore, we opted to assess the gustatory function by the Taste Strips Test (TST), Burghart Messtechnik, Germany, over other tests. TST exhibits regional tongue assessment, which is not offered by other tests. Additionally, it is easy to conduct with a long shelf life and it provides clinical assessment in approximately ten minutes time for a single region, which is clinically favourable. Provided that the test-retest reliability (0.68) of the TST is comparable with other well established test of the three-drop-technique (Mueller et al., 2003) that supports its reliability. The TST was also used in two studies that assessed the sense of taste and had proved its practicality in groups of SS patients (Negoro et al., 2004, Kamel et al., 2009).

3. The taste map

In this comparison, tasting ability was assessed by identifying any concentration of the taste strips of each tastant in the total population of the study. Our results showed that the laterals of the tongue functioned equally in tasting the four tastants in the total population of the study. There was no statistical difference between both laterals in tasting the sweet, sour, salt and bitter.

In a comparison between the tip and the laterals, there was no statistical difference between the three sites of the tongue in tasting sweet and sour, indicating that the sweet and sour can be identified equally at these places. These findings contradicted the oft-repeated popular belief, which limited tasting sweet to the tip of the tongue, while tasting

sour on the posterior laterals of the tongue. Our study presents evidence of an equal tasting ability of the four fundamental tastes on all the regions of the tongue.

In terms of tasting salt, there was statistical difference between the tip and both laterals, where the tip recorded the highest mean scores, indicating that the tip was the most sensitive among the three places in tasting salt. Our findings contradicted the oft-quoted concept of the tongue map in that tasting salt can only be felt on the anterior laterals of the tongue.

Tasting bitter was of same quality on the tip and the right lateral, but was at its lowest level on the left lateral. The tip was the most sensitive among the three tested places of the tongue. These findings also contradicted the previous statement in that tasting bitter was confined to the posterior laterals of the tongue.

The tip was the most sensitive place of the tongue in tasting the four basic tastes, therefore, we recommend testing the tip for the clinical and research studies as it reflects the whole mouth tasting ability, and can taste the four fundamental tastes better than the laterals.

4. The neurosensory threshold of taste

Our results showed that the total average of the neurosensory threshold of taste was significantly higher in the patients' group compared with the healthy volunteers, indicating that the neurological impairment was prevalent in pSS patients and associated with the syndrome. The neurosensory function of taste reflects the sensitivity of the chorda tympani nerve, which is responsible for the taste sensation in the anterior 2/3 of the tongue. Therefore, high neurosensory threshold reflects a deficit in the function of chorda tympani.

We reported 31.7% dysfunction rate of the neurosensory threshold in our pSS group (mean score=5.7, SD=±8.4, n=20/63) which was three times higher than that of the healthy population who scored 9.8% dysfunction (mean score=-0.3, SD=±6.6, n=6/61). Our results were consistent with others who reported neurological taste disorders in 27% (Mean score =4.9, SD=±11.1, n=31) in a group of both primary and secondary SS (Negoro et al., 2004).

However, authors of the study did not use reliable criteria for diagnosing SS patients, and patients with sicca symptoms might have been included in the study.

The scores of pSS group ranged within the positive scale (range=3.7–7.4) compared with the scores of the healthy population group which ranged well within the negative scale (range=-0.8 - -0.1), indicating that the healthy volunteers required minimal amount of the current generated by EGM to stimulate the sensation of the tongue.

In a comparison of the regional testing of the tongue (tip, right and left of the anterior 2/3 of tongue) between patients and healthy volunteers, the current study presents evidence of significant regional variations of the neurological threshold of taste in the anterior 2/3 of the tongue. We found that the tip functioned significantly better than the laterals of the tongue, and that the laterals recorded same level of dysfunction with no significant difference in the pSS group. In the healthy volunteers group, we proved that the three tested regions had same performance with no significant difference between each other. Our findings of the healthy volunteers group contradicted others who found in a small study of non-smoking healthy subjects (n=16), that the tip of the tongue was more sensitive than the laterals (Shawn L. Miller, 2002). To our knowledge, there is no study of the regional testing of the neurosensory taste threshold in pSS patients.

Several studies suggested that peripheral neuropathy was involved in the pathogenesis of SS and was known to be part of the syndrome (Svein I. Mellgren et al., 1989 , Koike and Sobue, 2013, Indart et al., 2017). Our findings of the gustatory function that was assessed by TST, revealed that the laterals of the tongue worked worse than the tip. This implies that the impaired gustatory function in the laterals of the tongue was precipitated by the significant neurosensory deterioration of the laterals in pSS group.

The neurosensory threshold of taste was assessed by the electrogustometer (EGM), which is a validated and well-established battery operated clinical device (Miller et al., 2002, Berling et al., 2011), that measures nerve thresholds in a range of -6 to 34 decibel (dB). The machine presents faint electrical currents to the tongue (See Methodology 3.12.2.B) to

assess the neurosensory threshold of taste. Since it was developed in the 1950s, it has been used in a number of studies (Krarup, 1958, Fons, 1970, Kikuchi et al., 1988, Stillman et al., 2003). The EGM is a portable small size device, with no preparation or storage requirements needed, therefore it is generally practical. It is also pain free on use, and does not require rinsing or expectoration between trials.

Shorter durations of 0.5 or 1 seconds were insufficient to produce taste sensation for some of our participants. Therefore, a duration of 1.5 second was chosen as it was detected by all participants in the current study.

To avoid reporting the sensation by the trigeminal nerve, it was explained to the participants to ignore tingling and that only a taste or change of taste should be reported. Testing by this machine was conducted on the anterior two thirds of the tongue, where the sensory innervation is supplied by the chorda tympani nerve (Ian Shaw et al., 2010). This device has no risk of harm (Tomita and Ikeda, 2002), and it has been in use in the Neurology department at the Royal London Hospital, for the regional mapping of the taste sensation. The device was approved by the Physics department at Barts Health Trust, The Royal London Hospital, to be used in this research.

5. Salivary flow rate

The present study provides evidence of sever oral dryness in our pSS group. Saliva was collected by means of USFR and SSFR. These methods are easily conducted and affordable by clinicians and patients, widely used in clinical studies, provided that the saliva collected by these methods reflect natural oral environment. As expected, oral dryness was statistically significantly higher in the pSS group than that in the healthy volunteers'.

It has been observed that the USFR was influenced by a number of factors, the main ones being hydration, body posture, olfactory stimulation, seasons and light exposure (Navazesh, 1993). Shannon (1972) compared USFR under different body postures in his study group, and concluded that standing position had higher values of USFR than in laying position, in comparison with sitting posture. Therefore, it was necessary to unify the

collection posture for all participants in the present study, and it was decided to consider the upright sitting position as the position of choice. Additionally, subjects were advised to refrain from eating, drinking and smoking 1-2 hours prior to the test term. It was suggested to set a certain time of the day and/or time of the year to collect USFR to avoid bias (Navazesh, 1993). However, due to the rarity of pSS, it was difficult to manage collecting saliva in a certain season and at a particular time of the day.

Despite of its objectivity, USFR test is prone to individuals' willing to spit, therefore this test is also subjective which affects its reliability. Hence, it was decided to measure the stimulated SSFR as well as USFR, in order to be able to understand the impact of pSS on patients' salivation.

It was suggested to use Lashley Cup method in the current project, for the local saliva collection from the Parotid gland as a substitution for the SSFR. However, the procedure of saliva collection by this technique is troublesome for participants and complicated if compared with the aforementioned methods. Additionally, Lashley cup method provides localized saliva collection, while SSFR allows testing whole saliva, which reflects natural oral environment.

6. Lack of association between taste and oral dryness

In the multivariate regression model, we found no association between the oral dryness and the patients' gustation as it was previously reported (Henkin et al., 1972, Negoro et al., 2004, Kamel et al., 2009). Our findings supported previous studies, which demonstrated that normal salivation was not necessary for maintaining normal taste function (Weifenbach et al., 1995, Gomez et al., 2004). Another small study (n=8) by Weiffenbach et al. (1986) tested the correlation of the taste threshold with the severity of oral dryness in patients with xerostomia. The same study further supported the lack of association between normal salivary gland function and normal taste perception.

The number of variables included in the regression analysis in the current project was considered sufficient according to (Austin and Steyerberg, 2015) Austin and Steyerberg

(2015) who recommended a minimum of two cases per variable, where in our study, the number of cases per variable ranged from three to 13.

When assessing the effect of oral dryness on the ability to taste each of the four basic tastants, we found that oral dryness was not a good predictor for tasting sweet or sour, but only tasting bitter was affected by the oral dryness in the patients' group. These findings supported others who suggested a possible impact of these two tastants by the time of the syndrome's evolution or by the severity of oral dryness (Gomez et al., 2004). Oral homeostasis depends largely on the proteins composition in saliva, and hence, individuals with reduced amount of saliva showed reduced amounts of salivary proteins on the anterior tongue (Pramanik et al., 2010). Therefore, a correlation between tasting bitter and oral dryness supports the theory of the association between proteolysis and the interpretation of the bitter taste (Dsamou et al., 2012).

We also found that the oral dryness did not affect the neurosensory thresholds of taste measured by EGM, in agreement with others where a correlation between SFR and the neurosensory function of taste in a group of primary and secondary SS patients could not be established (Negoro et al., 2004). This lack of association indicates that oral dryness has no impact on the nerve endings of the chorda tympani in the pSS group, and that the low performance of the chorda tympani during taste function can be referred to the neuropathy associated with the syndrome. These findings supported Negoro et al. (2004), who found that a group of patients with Sicca Syndrome (non SS) did not show association between oral dryness and taste impairment. This is an indication of the impact of the neuropathy, which is known to be part of SS, and the deterioration of the taste function.

We sought to investigate the effect of the severity of oral dryness on the gustatory function of taste in the total population of the study (n=127). A significant association was observed between the oral dryness that was measured by USFR and CODS, with the gustatory function of taste, indicating that oral dryness is deteriorating the taste function. Age, in this association, had a significant moderating role on the relationship between the oral dryness and taste. This was anticipated since that age was not controlled, which is a limitation in

the study. It is worth noting that when the regression analysis was run with the total population of the study, a significant impact of the oral was observed on the deterioration of the taste function, whilst when the regression was run on the pSS group only, there was lack of association between the oral dryness and the taste. This lack of association supports our previous suggestion of the possibility of association between the deterioration of taste and the neuropathy.

A moderator is a qualitative (e.g., sex, race class) or quantitative (e.g., level of reward) variable that affects the direction and/or the strength of the association between a predictor and a dependent variable(Reuben M. Baron and Kenny, 1986) (Baron and Kenny, 1986). Whereas a mediator explains how external physical events take on internal significance. When a moderator variable specifies when certain effects will hold, mediators indicate how and why such effects occur (ibid).

We hypothesised that the gustatory function is moderated by age and mouthwash when the USFR is an independent variable. Since age and mouthwash have had significant effect on the gustatory function in the total population. Therefore, appendix 28, page 339 illustrated the change in the standardised coefficient of beta when USFR was the predictor, and age and mouthwash were added alternately to the model. The coefficient was changed by β=0.252 and β=0.003 when age followed by mouthwash was added respectively to the model, indicating that age and mouthwash had moderated the model. We did not have adequate power to test for mediation analysis; therefore, we recommend powered sample size to test for mediation in the future.

7. Gustation and neurosensory threshold of taste

Peripheral neuropathy is well documented and one of the frequent manifestations of pSS (Svein I. Mellgren et al., 1989 , Goransson et al., 2006). Our results of the multivariate regression analysis demonstrated that high neurosensory thresholds of taste were associated with the gustatory impairment that was measured by TST in pSS group. Therefore, the present study suggests a possible contribution of the neuropathy to the

aetiology of the taste dysfunction in pSS patients. This is a novel finding of the present study that sheds light on the possible aetiology of the taste impairment in pSS patients. This finding was confirmed when the regression analysis was run with the total population of the study, and a significant impact of the oral dryness was observed on the deterioration of the taste function. Whilst when the regression was run on the pSS group only, there was lack of association between the oral dryness and the taste. This lack of association confirms our previous finding of the possibility of association between the deterioration of taste and the neuropathy.

Small fibre neuropathy is a recognised complication of SS. The burning sensation of the tongue/loss of taste in the general population has been shown related to small fibre neuropathy. However, the aetiology of burning tongue/loss of taste has not been established in pSS. Therefore, we investigated whether taste loss in pSS patients is related to neuropathy of the tongue. Our results showed that compared with healthy controls, pSS patients had higher neurosensory threshold readings (indicating neuropathy), and this correlated with taste dysfunction. Our results indicates that neuropathy should be considered as a possible contributor to taste dysfunction in SS

Our open-ended questions that evaluated the rate of the neuropathy symptoms, revealed that all of the pSS subjects who responded to these questions (n=64/65) experienced peripheral neuropathy, which supports our assumption of the neuropathy effect on the taste dysfunction. The symptoms ranged from “Lost feeling”, “Tingling”, and “Numbness” to “Clumsiness” in hands and/or feet. All pSS patients reported one or more manifestations of neuropathy. The information we obtained by employing the routinely asked questions in the Neurology Department at the Royal London Hospital, shed a light on the need to explore in greater depth the impact of pSS on nerve function.

Five of our pSS patients were able to taste the taste strips, but were unable to identify the category of taste, which can be referred to the impaired function of the nerve endings in the taste buds, and that these nerve endings were unable to transmit the taste stimuli to the brain centres for interpretation.

In this study, we found that age was a common confounder that interfered with the tasting ability of the four taste categories in pSS group, in agreement with a recent large study (n=1000) of general population, where taste was found to decline significantly with age (Doty et al., 2017). Previous studies on healthy subjects arrived to a conclusion in line to ours with regards to the correlation of age with taste impairment (Mojet et al., 2005, Suchecka et al., 2012). Our findings contradict others who reported no association between taste and age in SS patients (Gomez et al., 2004, Kamel et al., 2009). However, even if age had a strong contribution to the taste perception in the pSS group, our results presented evidence of significant impairment of the taste in our pSS group compared to the healthy volunteers when age was adjusted.

Mouthwash use was the only variable that had an impact on the neurosensory tasting ability. This association suggested a possible damage to the nerve endings by the frequent use of mouthwash. Of our notes during the study, one of the healthy volunteers had an extremely impaired taste although no health problems were reported. The patient was found to have several fixed bridges and therefore she tended to use alcoholic mouthwash twice daily to maintain a good oral hygiene. We instructed the patient to reduce the rinsing administration to once before bedtime, and to refrain from rinsing completely three days prior to the re-testing day. When the patient was re-tested, her taste score was significantly improved and was as normal as other healthy subjects in the study were. We therefore speculate that alcoholic mouthwash can exert adverse but reversible effect on tasting ability.

In the current study, a group of pSS patients who demonstrated normal salivary flow rate, scored high with the Electrogustometer, indicating impaired function of the nerve. This is suggestive that there is limited association between salivary flow rate and the conductivity of the electric current on the chorda tympani function. Experts have also shown in an unpublished study (personal communication with Professor Hawkes, Neurology Department Barts Health, UK, and Professor Doty, University of Pennsylvania, USA) that drying the tongue did not seem to affect the results of electrogustometer. This was confirmed when the regression analysis was run on the total population of the study, when

a significant impact of the oral dryness was observed on the deterioration of the gustatory function, while when the regression was run on the pSS group only, there was lack of association between the oral dryness and gustation. However, further research is needed to confirm our findings. Other variables such as smoking and appliances (e.g. dentures, night guards or orthodontic appliances) were also found to associate with the impaired tasting ability in pSS patients. A group of "Other medicines" (Tidilan, Carbocistene, Epilim, Cough suppressant syrup, GTN spray, Atravastine, Migraleve, Alendronic acid, Hormone replacement therapy, Contraception, Lymecycline, Naltrexone, Pregabalin and antianxiety) was not taken into account in interpreting the results as it contained miscellaneous kinds of drugs that had different impacts on patients' health status.

8. Correlation between smell and taste

The evidence in the literature is conflicting on whether a correlation between smell and taste exists. Our study revealed significant positive correlation between smell and taste in our healthy volunteers group (n=62) and in the total study population (n=127), but no correlation was found between smell and taste when data was analysed in the patients group only. The lack of the association between the smell and taste in the patients group can be attributed to the presence of underlined factors impeded the correlation of both variables in this group, which in our study can be referred to the neuropathy.

When the whole study population was analysed with a total of 127 subjects, a correlation between the smell and taste was presented (r=0.2). However, only 40% of the variance was explained in the regression model, which did not strongly support the statement of the smell and taste being correlated. Our results supported others who reported no meaningful influence of the smell loss on taste function in patients with chemosensory disturbance (Stinton et al., 2010, Fasunla et al., 2012, Ros et al., 2012), and contradicted previous findings of a correlation between the smell and taste (Dzaman et al., 2005, Kamel et al., 2009).

9. Sexual function

The present study demonstrated that the prevalence of the SD in the sexually active pSS women, was double of that in the healthy volunteers. We found high proportion of patients were not sexually active (57%, n=37/65) which was higher than the previously reported (28.2%) in a study of 46 pSS females (van Nimwegen et al., 2015). This high proportion of the sexually inactive patients indicates that pSS patients were affected by the syndrome. Furthermore, using a cut-off score of 26.5, a total of 23/28 patients (82.1%) and 14/42 healthy volunteers (33.3%) were considered to have impaired sexual function. This proportion is comparable to a previous report where 20/24 (83.3%) patients, and 9/24 (37.5%) healthy volunteers reported SD (Priori et al., 2015).

The score of zero of an individual domain indicates that the subject reported having no sexual activity during the past four weeks. Any values above zero, indicates sexual functionality. The results showed obvious impairment of sexual function in the pSS group compared with the healthy volunteers.

We found that all FSFI domains (Desire, arousal, lubrication, orgasm, satisfaction, pain and total FASI) have been affected significantly in women with pSS, and showed more sexual impairment compared with healthy volunteers. We further found that the inability to lubricate and the feel of pain were the most prominent symptoms that pSS patients suffer from during the sexual function, with the greatest mean difference of 2.1 and 1.9 respectively between patients and healthy volunteers. Our findings supported others who reported that lubrication and pain were of the most affected domains in pSS patients (van Nimwegen et al., 2015, Priori et al., 2015).

Vaginal dryness is frequently reported by pSS patients, and the present study confirmed that, and was consistent with others who reported that dry vagina was a common symptom in pSS patients (Marchesoni et al., 1995, Mulherin et al., 1997, Bongi et al., 2013). Large proportion (92.8%, n=26/28) of our sexually active patients have had dry vagina. Likewise, 75.6% (n = 28/37) of the sexually inactive patients have also reported vagina dryness. Therefore, it appears that dry vagina was not a major factor affecting sexual activity, as the

sexually active and inactive patients reported having the symptom. This perhaps is an indication for the lack of association between vagina dryness and sexual activity.

Vaginal dryness was subjectively assessed by asking patients whether or not they suffer from the symptom. This approach, albeit of being less complicated for patients than referring them to gynaecologist for a clinical assessment, we found it was not a sensitive measure to assess the severity of vaginal dryness (Appendix 24).

In the subgroup analysis of the FSFI stratified according to the sexually active patients using multiple regression model, we found that the self-reported vagina dryness did not play key role in compromising the global FSFI score. These results agreed with others who concluded that the sexual function and the frequency of intercourse in pSS was not correlated with the dry vagina (Skopouli et al., 1994, Marchesoni et al., 1995, Valtysdottir et al., 2003).

We found that fatigue has interfered with the sexual function and the patients' senses of desire, arousal, orgasm and satisfaction. This finding is compatible with the results of a previous large survey (n=615) of the sexual function in women with chronic fatigue syndrome, where sexual dysfunction was found greater in patients with intense fatigue ($p<0.05$) including SS (n=510) (Blazquez et al., 2015a). The results of our open-ended questions that asked about the main one symptom that the patients think was affecting their QoL, have confirmed the above findings. We found that fatigue was the second most frequently reported symptom to compromise patients' QoL.

The open-ended questions highlighted aspects that were not covered by the routine clinical tests and the questionnaires used in the study. One of our patients was diagnosed with an epilepsy alongside pSS, and was prescribed a number of medicines to control both conditions. The patient's main complaint was the failure to pursue a successful sexual relationship, referring the reason to the fatigue. The patient believed that fatigue was worsened by the variety of medicines taken as she described. Same patient reported that due to the fatigue, she had no energy to interact sexually with her partner and therefore she constantly tended to avoid having sexual relationship. The patient further reported that

the SD was risking her marital life and that she was "not far from getting divorced" because of the constant fatigue she suffered from. Two more patients had similar views in that SS has affected their sexual life, and that it was one of the reasons that led to the termination of their relationships with their partners. We therefore suggest evaluating patients' sexual problems through semi-structured interviews with predetermined topics, to explore in greater depth the issues raised which will help develop referral pathway for affected patients.

We report that the sexual performance was painful with increased vaginal dryness, as it was shown in the regression analysis. Our findings supported others who referred their congruent results to the patient's fear of pain due to insufficient lubrication during intercourse (Blazquez et al., 2015a). The results of our open-ended questions supported this finding and showed that one of our patients referred her SD to the lack of desire because of the fear of pain during intercourse, in agreement with Blazquez et al. (2015).

In a large (n=302) Systemic Lupus Erythematosus cohort, 30% (n=85) of the subjects had accompanied SS with vaginal dryness, and reported SD. However, their FSFI scores were not significantly different from those without SS (Tseng et al., 2011), which indicates that vaginal dryness was not the a major factor of the sexual problems.

Some studies attributed the reason of the SD to the Sjögren's Syndrome-related vasculitis, trauma or inflammation, rather than to the commonly encountered vaginal dryness (Skopouli et al., 1994, Mulherin et al., 1997, Graziottin A and Giraldi A, 2006, Tseng et al., 2011). Vaginal lubrication that usually occurs during normal intercourse was referred to a form of transudate from the blood vessels due to the increased blood flow on vaginal wall, and not because of the vaginal glands secretions. Therefore, the reduction in the vaginal glands secretion in pSS group may not contribute to the failure of having a successful relationship.

Interestingly, our open-ended questions revealed that vaginal dryness (1.5%, n = 1/65) was not reported as the most one symptom that affected patients' QoL. In fact only one patient

reported dry vagina as the worst symptom of the syndrome. Two more patients reported painful intercourse despite of using lubricants. Three other patients thought that their vaginal dryness was “not too bad”. All other patients who declared having impaired sexual function, did not refer the reason to “vaginal dryness” but described fatigue (30%, n=20/65) or non-specified dryness (15.3%, n = 10/65) instead. This may possibly suggest that the SD can be referred to the physical pain represented by fatigue and/or joint stiffness rather than vaginal dryness. Additionally, due to the sensitivity of the subject, patients could have found it hard to describe their vaginal problems as their main complaint of the syndrome, and substituted the term with non-specified “dryness”.

Our study supported others in showing that the SD and vaginal dryness were extremely frequent in the SS patients (Marchesoni et al., 1995, Priori et al., 2015). However, in the multivariate regression model, we found no association between the self-reported vaginal dryness and the sexual activity in pSS patients. Our findings were compatible with others where no association was found between decreased vaginal lubrication and dyspareunia in a sample of 21 pSS patients diagnosed by the European criteria (Valtysdottir et al., 2003). This is not surprising as dyspareunia was also reported in premenopausal pSS patients with healthy vaginal mucosa in a study of 51 SS patients. Therefore, we support others in that the sexual life of pSS patients is driven by the severity of fatigue rather than vaginal dryness (Goodwin, 1997, Frikha et al., 2011, Blazquez et al., 2015a, van Nimwegen et al., 2015).

Alcohol was found to be associated with the global score of the sexual function, arousal, lubrication, satisfaction and pain. This relationship between sexual function and alcohol intake may be a cause and effect relationship. It was admitted that the regression analyses was unpowered in the study as the power calculation was conducted to detect the mean difference between the patients and the healthy volunteers. Therefore, it is anticipated that a relationship between the variables may become more obvious when the sample size of the sexually active patients is increased.

In the present study, we were unable to match the age between groups, which counts one of the limitations of the study. A more detailed matching would have required selection

according to several variables including age. However, we adjusted for these variables in the multivariate regression model.

However, despite of the general belief of the decline in the sexual activity with increasing age, we found that age was not a strong predictor of the FSFI global in the pSS group. Our results showed that age was only associated with the impairment of lubrication and worsened the feeling of pain in pSS patients. This correlation can be linked to the hormonal changes that affect the mental health status and hence raising the fear from pain that was resulted by the increase in vaginal problems. Our findings supported previous studies where age was found to have negative correlation with the sexual function in pSS patients (van Nimwegen et al., 2015, Isik et al., 2016). However, even if the age was negatively correlated with some aspects of the sexual activity in our study, a subgroup analysis of 20-50 years old pSS patients (n=7/9), scored significantly lower FSFI global, compared with age-matched healthy volunteers (n=13/39). Indicating that age was not a major contributor for the decline in sexuality, and that the impact of the disease cannot be denied when age is adjusted.

The number of the sexually active patients (n=28) was significantly lower than that of the healthy volunteers (n=42) which itself an indication of the impact of the disease on sexuality rather than the aging effect. The reasons that the patients were not sexually active, may differ from the reasons of the SD, and therefore may not be related to age. Our findings supported others who reported that dyspareunia was not limited to the old age and it was found in 40% of premenopausal pSS patients (Skopouli et al., 1994). The study was focused on finding out how the patients' group is affected by the syndrome, and it was not feasible to run the regression analyses for the control group and compare the results. Moreover, if the regression analyses was run for the pooled population of the study, there will be high amount of variation in the outcome variable compared to the pSS group association alone, and hence, the p-value cannot be relied on in interpreting the results, as it violates the assumption of homogenous variance.

The duration of having the syndrome that was reported by pSS group, was found to affect lubrication and satisfaction of the sexual performance. This finding contradicted previous studies where no association between SD and disease duration was reported (Skopouli et al., 1994, Marchesoni et al., 1995, Priori et al., 2015). The difference in the methodology and the criteria that was applied in diagnosing pSS patients between these studies and ours, can explain the diversity of the results. All p-values were reported for transparency regardless of significance.

When performing logistic regression, a correlation was established between oral dryness and vaginal dryness. To find out whether mucosal dryness of one site can be indicative of dryness of other mucosal surfaces, we analysed the relationship between the oral and vaginal dryness in our study group. The results did not show significant correlation. It is acknowledge that one of the measures is an objective assessment tool and the other is subjective, which further undermines the reliability of this analysis. However, powered regression analysis is needed to confirm these findings. To our knowledge, this is the first time that this relationship has been reported.

10. Quality of life

Quality of life assessment has received increasing attention in evaluating the impact of chronic diseases, in contemporary public health research and practice. In the present study, the QoL was drastically affected and that pSS patients were compromised physically, psychologically, socially and even environmentally in comparison to healthy volunteers, being more affected physically than other domains. Our findings were consistent with previous studies which assessed the QoL of pSS patients using WHOQoL-BRÉF (Bowman et al., 2004a, Inal et al., 2010), and found that all domains were affected in pSS patients except for “Environment” which was comparable between patients and controls. The pilot study gave us idea of the feasibility to use questionnaires to avoid data loss in the main study.

We present interesting evidence that SD has significantly compromised patients’ social life quality. This was manifested by self-reporting of dissatisfaction with personal relationships, social support and sexual activity. This is a novel finding that highlights the importance of

sexual satisfaction for the perception of living a full active social life. However, the clinical management of pSS in most UK clinics at present does not include routine formal assessment of the sexual activity. The introduction of an assessment package including relevant questionnaire or an appropriate referral pathway for patients with SD would improve the quality of the clinical service provision for these patients and may improve their QoL.

There was significant difference in the outcomes between the patients and healthy volunteers groups in the t-test analysis, the patients' group only was approached for objective eight. Since that the patients' group is approached on clinic, we sought to investigate the variables that contribute in predicting the affected outcomes.

The taste impairment was found to compromise the social life quality of pSS patients, although the contribution of the taste dysfunction was not as significant as that of the sexual impairment. Anecdotally, dry mouth patients often complain that the loss of taste has significantly affected their social life, as it interferes with sharing meals with their families or friends. To our knowledge, this aspect has not been documented before and therefore the availability of studies for comparison was not applicable.

We found that the SD was a common debilitating factor that interfered with the QoL of patients in the four domains despite of the not significant contribution in three domains (Physical, psychological and environmental). However, SD had the highest coefficient, which indicates that it contributes to the QoL compared to the other variables. Our findings were consistent with others who reported that the SD contributed to the impaired QoL of pSS patients (Bongi et al., 2013, van Nimwegen et al., 2015, Priori et al., 2015).

The questions that assessed the environmental domain were asking whether individuals feel safe, healthy, having access to health services and the related information, having enough money and opportunity for leisure, satisfied with their living conditions and transport. However, the fact that the SD in the present study had impaired patients' environmental QoL, indicates that these patients did not get sufficient support to help them cope with the sexual impairment they suffer from.

We concluded that the smell dysfunction did not compromise the QoL of patients, which indicates that smell problems were not identified as a health issue by pSS patients, and it is a condition that can be coped with. Our findings contradicted others who suggested that the impairment of smell and taste contributed to the reduced QoL of pSS patients (Kamel et al., 2009).

Alcohol intake was found associated with the environmental domain of the patients' life quality. This association makes sense as patients who were unsatisfied with their environment, tended to increase the amount of alcohol intake.

11. Oral health related quality of life

The oral health related quality of life is considered as a relevant end-point criterion in evaluating the effects of a disease on individual's oral health over time. The oral health related QoL was highly compromised in pSS patients compared to the healthy volunteers. Our results were consistent with other previous who reported oral distress in pSS patients compared to controls (McMillan et al., 2004, Stewart et al., 2008, Enger et al., 2011). The minimal important difference (MID) in the OHIP-14 score between the patients and healthy volunteers groups (Mean difference=13.7) was higher than the five scale units that was estimated by Locker et al. (2004). This shows that patients with pSS demonstrated magnificent deterioration in their oral health life quality. The oral health related quality of life was not associated with the taste impairment in pSS patients. To our knowledge this is the first study to investigate the impact of taste impairment in pSS patients on oral health quality of life, and hence, no studies are available for comparison.

The impact of the oral dryness on the oral health QoL has been well documented and the clinically relevant variables to the oral health QoL were included in the regression model. Since USFR, SSFR and CODS are different tests for assessing the same outcome (oral dryness), they were not included in one regression to avoid the collinearity. Therefore, for the oral dryness assessing tests to be included in the regression analysis, the regression has to be run three times for each OHIP domain as well as the total OHIP, which will mean an additional 24 regression tests (three tests for each of the seven domains and one for the

total OHIP). Calculating numerous correlation increases the risk of type 1 error, and compromises the clarity of the rationale of the Results and the Discussion.

The prevalence, extent and severity of oral health problems were significantly higher in the pSS group compared to the healthy volunteers. However, patients with increased oral health problems did not necessarily equate to the oral dryness, especially that 23% of patients had intraoral appliances including night guards, partial or complete dentures, which may contribute to their oral health problems.

We found that the most affected domain of OHIP-14 was the "Functional limitation" in the pSS patients compared to the healthy volunteers. In the regression analysis, we found that age and the use of mouthwash had contributed significantly to the compromised functional aspect of patients' oral health.

Age and alcohol intake were common variables associated with oral distress and the physical disability of the patients' oral health. These findings contradicted others who found no correlation between ageing and oral health quality (Rodakowska et al., 2014, Bortoluzzi et al., 2015). For alcohol, the association with oral health problems may indicate that patients with reduced oral health related QoL tend to take more alcohol than healthy people. However, the regression analysis does not reveal causality and therefore more research is needed with this regards. To our knowledge, there has been no previous demonstration that these correlations were reported in this group of pSS patients.

12. Mental health well-being

It is well documented that pSS is a chronic debilitating condition that affects patients' health physically and mentally (Valtysdottir et al., 2003, Champey et al., 2006). Therefore, it was important to assess the mood status of pSS patients, as it can be detrimental to the patients' well-being. We found that the mental health status of pSS patients was significantly impaired in comparison to the healthy volunteers, which supported the suggestion that pSS was a chronic debilitating condition and affects patients' health physically and mentally (Valtysdottir et al., 2003, Champey et al., 2006). The pSS patients were more anxious and four times more depressed than the healthy volunteers. Our

results were in line with others who found that the mental health well-being was significantly affected in pSS patients (Stevenson et al., 2004, Inal et al., 2010, Bongi et al., 2013, Lendrem et al., 2014, Ugurlu et al., 2014). The present study showed that anxiety symptoms in pSS patients were higher but not significantly different from that of the healthy volunteers. Unlike anxiety, depression was significantly higher in our pSS group than that in the healthy volunteers. These findings supported others who reported that depression symptoms were more pronounced than anxiety in pSS patients when assessed by HADS (Stevenson et al., 2004, Lendrem et al., 2014, van Nimwegen et al., 2015, Vita et al., 2015). Only one study with relatively small sample size (n=24) reported that anxiety symptoms were significantly higher than depression symptoms in pSS patients compared to controls (Priori et al., 2015). Whilst other studies that used AECG criteria in diagnosing pSS patients reported that anxiety and depression symptoms were equally present in pSS patients (Inal et al., 2010, Bongi et al., 2013).

When performing the multivariate regression analysis to investigate the predictors of the mental health status in pSS patients, we found that the sexual function and ageing contributed to the anxiety symptoms although not significantly. As for anxiety, depression was affected by the impaired sexual function in pSS patients. Our results supported others who referred the compromised mental well-being in pSS patients to the impaired sexual life in pSS patients (Bongi et al., 2013, Ugurlu et al., 2014, van Nimwegen et al., 2015, Priori et al., 2015). The impairment of the smell and taste as well as the disease duration had no important contribution to the anxiety or depression symptoms in the pSS patients.

From the above discussion, our findings of the QoL revealed that neither smell nor taste dysfunction had affected the generic QoL or mental health well-being in pSS patients. The SD had contributed to the compromised QoL and mental health status in the pSS group, however, a study with powered regression analysis is needed to confirm these findings.

13. Subjective and objective measures

Patients were aware of the smell change developed in the course of pSS, and that the self-assessment of the smell function that was rated on VAS, was consistent with the results of the clinical assessment tested by UPSIT. Whilst for taste, patients' self-assessment was not

reflective of their taste function that was tested in the clinic, indicating that patients can cope with the slow impairment of the taste during the course of the syndrome.

The self-assessment of oral dryness measured by XI was reflective of the clinical tests of oral dryness. Therefore, administering XI may save patients the burden of the clinical tests. We found significant correlation between oral dryness that was assessed by the XI and each of the USFR and CODS. Therefore, we suggest administering XI for patients who cannot afford the clinical oral dryness tests.

It was beyond the scope of our study to measure the severity of the nasal dryness, however, item 11 of the XI assesses the self-perception of the internal nasal dryness. We found no correlation between the subjective assessment of the nasal dryness and the smell function assessed clinically by UPSIT. With this regard, more studies are needed to investigate the influence of the severity of nasal dryness on the acuity of the smell in pSS patients.

14. Effect of medicines on mucosal dryness

The impact of medicines was tested against oral dryness that was assessed by the CODS. CODS was chosen over the SFR tests in this analysis, as it reflects the severity of oral dryness assessed by the clinician rather than being controlled by the patients' willing to spitting out. Oral dryness was found to be strongly predicted by the topical medicines (Eye drops, Eye gels, Viscotears, Skin creams, Telmesteine), and that pilocarpin, antidepressants, hypothyroidism and inhalers were weaker predictors for oral mucosa dryness. This association did not necessarily indicate the impact of the medicine itself on the oral dryness. It rather showed that patients with severe oral dryness, suffered from dryness elsewhere in the body and they tend to use topical medicines more than other drugs.

Nasal dryness was strongly affected by hydroxychloroquin and supplements (Ferrous fumarate liquid, ferrous sulphate, folic acid, folate, Vitamin B, Vitamin D, Calcichew, Buckwheat oil and Omega7).

To this end, the predictors in the above associations do not necessarily indicate causative factors. Therefore, these relationships may suggest indirect association between the

mucosal dryness encountered by these patients and the severity of the syndrome. To our knowledge, this is the first time that these correlations are reported.

15. Comparing functions between two age groups

In the current study, the age group was not specified due to the rarity of the syndrome, which is a limitation of the study and may overestimate the results. However, when data were subdivided into two age groups based on menstrual age of under and over 50 years of age (Dalal and Agarwal, 2015), a significant difference was observed in a number of the tested functions between patients and healthy volunteers. Even when the significance level was not reached, the patients' mean score was lower than that of the healthy volunteers, which is an indication of the impact of the pSS on these functions. These analyses were inserted lately in the thesis in an attempt to control for age, which has been found the main confounder in the study. One obvious limitation of obtaining unmatched age of participants per group has been observed, which affects the homogeneity of variance assumption and hence the validity of the analysis.

In the first group, aged 20-50 years, functions of the taste (gustatory and neurosensory threshold), sexuality, general and oral life quality as well as the mental health status were significantly less in pSS patients (n=16) than that of healthy volunteers (n=47). Only the smell function did not reach the significance level, although the mean score in the patients' group was less than that in the healthy volunteers.

In the second age group of 51 years and over, patients also recorded statistical differences compared with healthy volunteers in the functions of gustatory, sexuality, general and oral life quality (except the social domain of the WHOQoL-BRÉF) and mental health status. The smell, neurosensory threshold and the social domain of the WHOQoL-BRÉF were not statistically different between patients and healthy volunteers; although patients' mean scores were less than that of the healthy volunteers.

Anyfanti et al. (2013) evaluated 557 patients with rheumatic diseases, and found that old age was a good predictor for SD. They also reported that old age affected the physical and psychological status of rheumatic patients. Other studies stated a negative impact of age on the smell function but no/or weak association with taste in pSS patients (Kamel et al.,

2009, Rusthen et al., 2017). However, even if the age has a negative impact on these functions, our results showed that pSS patients of pre and postmenstrual age had lower scores in all of the tested functions compared to the healthy volunteers group. Our results present evidence of a prominent negative impact on pSS patients' life quality after age has been adjusted. As the reviewed studies differ in the methodology and the outcome measure they have used, it would be misleading to compare their results directly.

D. Conclusion

This study presents evidence of the negative impact of pSS on the patients' senses of the smell, taste and sexuality. The smell and taste were not affected by the dryness of the mucosal linings, and they were not correlated with each other in the patients' group. Our study suggests a possible neurological aetiology for the impairment of taste in pSS patients. The patients' OHRQoL was compromised in pSS patients but this was not due to compromised smell or taste. Sexual function deterioration was not associated with the severity of self-reported vaginal dryness, but rather with fatigue. We present evidence that sexual dysfunction significantly compromises patients' social life quality. This important finding highlights the significance of sexual satisfaction for the perception of living a full active social life. SD had a negative effect on QoL and the mental health status of pSS patients in all aspects, but mostly affected the quality of social life.

1. Recommendations for clinical practice

- Sexual history should be taken from pSS patients as part of the clinical management as part of the patients would benefit from appropriate referral.
- Assessing the smell and taste for pSS patients would inform a referral pathway.
- CODS or XI can be used as an alternative to the SFR assessment.
- Tasting the tip of the tongue is adequate for the taste assessment.

2. Recommendations for research

- A qualitative and an in-depth investigation of the sexual health problem would provide an insight into the patients' perception and the coping mechanisms with the problem and its impact on the QoL. This will contribute to the understanding of the possible causes of SD in pSS patients.
- Study the impact of the neuropathy on the gustatory function in pSS patients.
- Investigate the severity of nasal dryness and its impact on the smell function in pSS patients.
- Evaluate the severity of vaginal dryness and its impact on the sexual function in pSS patients.
- Compare the sexual function in patients with different autoimmune diseases that are complicated by SS to assess the impact of SS on sexual life.

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APPENDICES

Appendix *1*

American-European Consensus Sjögren's Classification Criteria (Vitali et al., 2002)

I. Ocular Symptoms (at least one)

- Dry eyes >3 months.
- Foreign body sensation in the eyes.
- Use of artificial tears >3x per day.

II. Oral Symptoms (at least one)

- Dry mouth >3 months.
- Recurrent or persistently swollen salivary glands.
- Need liquids to swallow dry foods.

III. Ocular Signs (at least one)

- Schirmer's test, (without anaesthesia) ≤5 mm/5 minutes
- Positive vital dye staining (van Bijsterveld ≥4)

IV. Histopathology Lip biopsy showing focal lymphocytic sialoadenitis (focus score ≥1 per 4 mm^2)[2]

V. Oral Signs (at least one)

- Unstimulated whole salivary flow (≤1.5 mL in 15 minutes).
- Abnormal parotid sialography.
- Abnormal salivary scintigraphy.

VI. Autoantibodies (at least one)

- Anti-SSA (Ro) or Anti-SSB (La)

For a primary Sjögren's diagnosis:

a. Any 4 of the 6 criteria, must include either item IV (Histopathology) or VI (Autoantibodies).

b. Any 3 of the 4 objective criteria (III, IV, V, VI).

For a secondary Sjögren's diagnosis:

In patients with another well-defined major connective tissue disease, the presence of one symptom (I or II) plus 2 of the 3 objective criteria (III, IV and V) is indicative of secondary SS.

Exclusion Criteria

- Past head and neck radiation treatment
- Hepatitis C infection
- Acquired immunodeficiency syndrome (AIDS)
- Pre-existing lymphoma
- Sarcoidosis
- Graft versus host disease
- Current use of anticholinergic drugs

Appendix 2

Excluded studies with reasons

First author	Year	Title of Study	Reason for exclusion
Midilli R	2013	Nasal and paranasal involvement in primary Sjögren's syndrome	European criteria
Al-Hashimi I	2001	Frequency and predictive value of the clinical manifestations in Sjögren's syndrome	European criteria
Weiffenbach JM	1986	Taste and salivary function	Clinical experience in diagnosing pSS
Weiffenbach JM	1993	Odor identification ability among patients withSjögren’s syndrome	Clinical experience in diagnosing pSS
Weiffenbach JM	1995	Taste performance in Sjögren's syndrome	Clinical experience in diagnosing pSS
Rasmussen N	1986	Smell and nasal findings in patients with primary Sjögren's syndrome	No reliable diagnostic criteria used
Falkoff RJ	1986	Nasal manifestations of systemic immunologic disorders	Review
Su Nan	2015	Does Sjögren's syndrome affect odor identification abilities?	Letter
Rohrauer A	2006	Improvement of a Sjögren-syndrome associated anosmia with acupuncture	Case report
Cho MA	2010	Salivary flow rate and clinical characteristics of patients with xerostomia according to its aetiology	No data of taste dysfunction
Negoro A	2004	Taste function in Sjögren's syndrome patients with special reference to clinical tests	European criteria
Gomez FE	2004	Detection and recognition thresholds to the 4 basic tastes in Mexican patients with primary Sjögren 's syndrome	European criteria
Weber JC	1996	[Changes in taste and smell caused by hydroxychloroquine]	Letter
Rovni A	1978	Sialometric and gustometric investigations in some parotid gland diseases	Clinical experience in diagnosing pSS
Henkin RI	1972	Abnormalities of taste and smell in Sjögren's syndrome	Clinical experience in diagnosing pSS
Aoki H	2007	Effect of oral moisture on taste sensation	Unreliable classification criteria
Carson JA	1976	Disease-medication relationships in altered taste sensitivity	No data of pSS
Heckmann JG	2009	Smell and taste disorders in polyneuropathy: a prospective study of chemosensory disorders	No data of pSS

Epstein JB	2015	Oral symptoms and oral function in people with Sjögren's syndrome	Letter
Sellier S	2006	Dyspareunia and Sjögren's Syndrome	European criteria
Haga HJ	2005	Reproduction and gynaecological manifestations in women with primary Sjögren's Syndrome: a case-control study.	Not examined sexual dysfunction
Valtysdottir ST	2003	Mental wellbeing and quality of sexual life in women with primary Sjögren's Syndrome are related to circulating dehydroepiandrosterone sulphate.	European and Copenhagen criteria
Mulherin DM	1997	Sjögren's Syndrome in women presenting with chronic dyspareunia.	European criteria
Tayal SC	1996	Dyspareunia in undiagnosed Sjögren's Syndrome.	Case report
Marchesoni D	1995	Gynaecological aspects of primary Sjögren's Syndrome.	European criteria
Skopouli FN	1994	Obstetric and gynaecological profile in patients with primary Sjögren's Syndrome.	Clinical experience in diagnosing pSS
Lehrer S	1994	Gynaecologic manifestations of Sjögren's Syndrome.	No data of sexual dysfunction
Capriello P	1988	Sjögren's Syndrome: clinical, cytological, histological and coloscopic aspects in women.	Cytological and histological examination only, not about sexual dysfunction
Kageyama K	1981	Past histories of patients with Sjögren's syndrome the high incidence of gynaecological diseases in patients with Sjögren's syndrome evaluated from their past histories (author's transl).	Unclear diagnostic criteria
Blazquez A	2015	The effect of fatigue and fibromyalgia on sexual dysfunction in women with chronic fatigue syndrome.	Unclear whether primary or secondary SS has been diagnosed. No clear data.
Hackett KL	2012	Impaired functional status in primary Sjögren's syndrome.	No data of sexual dysfunction
Araujo DB	2010	Sexual function in rheumatic diseases	Review
Specker C	2005	Gynaecological and obstetrical problems in Sjögren's syndrome.	Review
Saad SC	1999	Vaginal lubrication in women with scleroderma and Sjögren's syndrome.	About secondary SS
Sheeran T	1992	Chronic dyspareunia Sjögren's syndrome- another clinical presentation.	Unreliable diagnostic criteria used
El Miedany Y	2012	Sexual dysfunction in rheumatoid arthritis patients: Arthritis and beyond.	No data of pSS
Tseng JC	2011	The Impact of Systemic Lupus Erythematosus on Women's Sexual Functioning.	No data of pSS

Curry SL	1994	The impact of systemic lupus erythematosus on women's sexual functioning.	No data of pSS
Priori R	2013	Outcome of pregnancy in Italian patients with primary Sjögren's syndrome	Not examined sexual dysfunction
Anyfanti P	2013	The impact of frequently encountered cardiovascular risk factors on sexual dysfunction in rheumatic disorders.	Unclear diagnostic criteria
Anyfanti P	2014	Association Between Mental Health Disorders and Sexual Dysfunction in Patients Suffering from Rheumatic Diseases	No pSS group
Ricaud L	1979	Acquired atresia of the vagina (Sjögren's Syndrome).	Case report
Tristano A	2009	The impact of rheumatic diseases on sexual function	Review
Picone O	2006	Sjögren's syndrome in obstetrics and gynaecology: Literature review	Review
Anderson E	2009	Sexual Dysfunction among Women with Connective Tissue Disease	No data on pSS patients
Mecacci F	2007	The impact of autoimmune disorders and adverse pregnancy outcome.	Review
Cirpan T	2007	Comparison of human papillomavirus testing and cervical cytology with coloscopic examination and biopsy in cervical cancer screening in a cohort of patients withSjögren's syndrome	Not clear which diagnostic criteria has been used
Johnson M	1997	Obstetric complications and rheumatic disease	Review

Appendix 3

MODIFIED NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability. A maximum of three starts can be given for Outcome.

Selection

1) Is the case definition adequate?
   a) Yes, with independent validation ✸
   b) Yes, e.g. record linkage or based on self-reports
   c) No description
2) Representativeness of the cases
   a) Consecutive or obviously representative series of cases ✸
   b) Potential for selection biases or not stated
3) Selection of Controls
   a) Community controls ✸
   b) Hospital controls
   c) No description
4) Definition of Controls
   a) No history of disease (endpoint) ✸
   b) No description of source
5) Sample size:
   a) Justified and satisfactory. ✸
   b) Not justified.
6) Demonstration that outcome of interest was not present at start of study
   a) Yes ✸
   b) No

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
   a) Study controls for _____ (Select the most important factor) ✸

b) Study controls for any additional factor (This criteria could be modified to indicate specific _____ control for a second important factor) ✸

Exposure

1) Ascertainment of exposure

a) Secure record (e.g. surgical records) ✸

b) Structured interview where blind to case/control status ✸

c) Interview not blinded to case/control status

d) Written self-report or medical record only

e) No description

2) Same method of ascertainment for cases and controls

a) Yes ✸

b) No

3) Non-Response rate

a) Same rate for both groups ✸

b) Non respondents described

c) Rate different and no designation

Outcome

1) Assessment of the outcome:

a) Independent blind assessment. ✸

b) Record linkage. ✸

c) Self report✸

d) No description.

2) Statistical test:

a) The statistical test used to analyse the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value) ✸

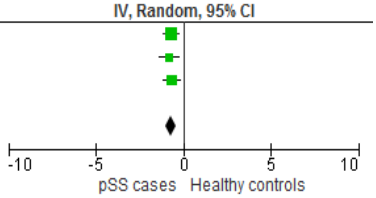
b) The statistical test is not appropriate, not described or incomplete.

Appendix 4

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]**

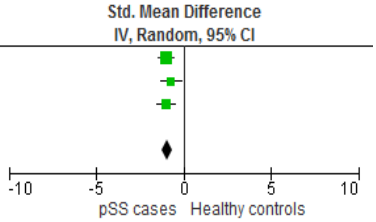
Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 2 (P = 0.92); I² = 0%
Test for overall effect: Z = 4.93 (P < 0.00001)



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]**

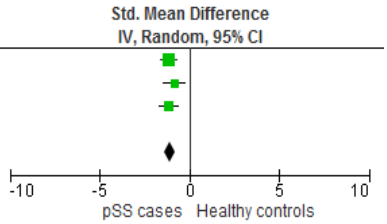
Heterogeneity: Tau² = 0.00; Chi² = 0.73, df = 2 (P = 0.69); I² = 0%
Test for overall effect: Z = 6.25 (P < 0.00001)



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]**

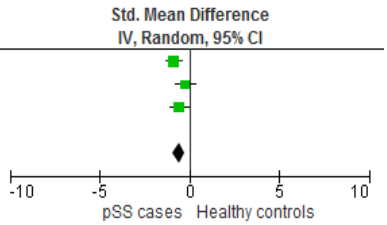
Heterogeneity: Tau² = 0.00; Chi² = 0.76, df = 2 (P = 0.68); I² = 0%
Test for overall effect: Z = 7.06 (P < 0.00001)



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]**

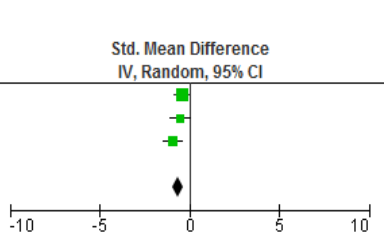
Heterogeneity: Tau² = 0.04; Chi² = 3.25, df = 2 (P = 0.20); I² = 38%
Test for overall effect: Z = 3.19 (P = 0.001)



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]**

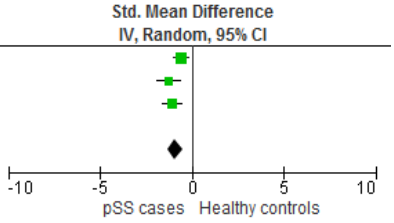
Heterogeneity: Tau² = 0.01; Chi² = 2.24, df = 2 (P = 0.33); I² = 11%
Test for overall effect: Z = 3.92 (P < 0.0001)



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]**

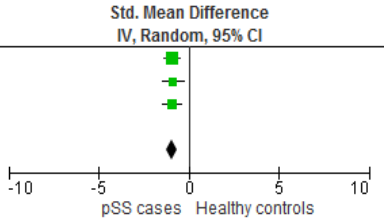
Heterogeneity: Tau² = 0.06; Chi² = 3.83, df = 2 (P = 0.15); I² = 48%
Test for overall effect: Z = 4.36 (P < 0.0001)



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]**

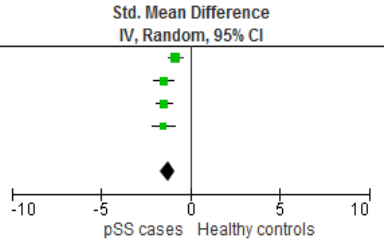
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 2 (P = 0.96); I² = 0%
Test for overall effect: Z = 6.22 (P < 0.00001)



H

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bongi et al., 2013	42.33	8.75	62	48.9	6.82	50	30.9%	-0.82 [-1.21, -0.43]
Kamel et al., 2009	37.71	10.69	28	51.95	8.57	37	22.9%	-1.48 [-2.03, -0.92]
Nimwegen et al., 2015	37.92	11.65	46	52.55	7.64	43	26.8%	-1.46 [-1.93, -0.99]
Priori et al., 2015	43.6	24.59	24	75.4	15.69	24	19.4%	-1.52 [-2.16, -0.87]
Total (95% CI)			**160**			**154**	**100.0%**	**-1.28 [-1.65, -0.90]**

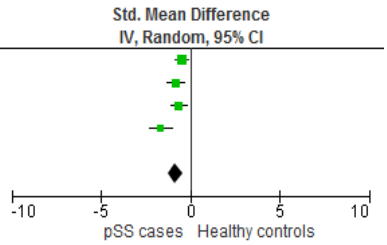
Heterogeneity: Tau² = 0.08; Chi² = 6.69, df = 3 (P = 0.08); I² = 55%
Test for overall effect: Z = 6.65 (P < 0.00001)



I

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bongi et al., 2013	39.32	9.82	62	44.16	11.21	50	28.7%	-0.46 [-0.84, -0.08]
Kamel et al., 2009	44.56	10.48	28	52.05	7.79	37	24.3%	-0.82 [-1.33, -0.31]
Nimwegen et al., 2015	44.52	10.72	46	50.71	8.38	43	27.1%	-0.64 [-1.06, -0.21]
Priori et al., 2015	41.2	20.8	24	72.4	15.7	24	19.8%	-1.67 [-2.33, -1.00]
Total (95% CI)			**160**			**154**	**100.0%**	**-0.83 [-1.27, -0.40]**

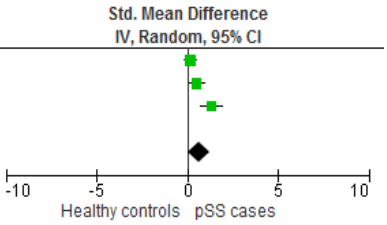
Heterogeneity: Tau² = 0.14; Chi² = 9.90, df = 3 (P = 0.02); I² = 70%
Test for overall effect: Z = 3.74 (P = 0.0002)



J

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bongi et al., 2013	7.54	4.55	62	6.86	4.29	50	36.3%	0.15 [-0.22, 0.53]
Nimwegen et al., 2015	5.98	4.28	46	4.07	3.11	43	34.9%	0.50 [0.08, 0.93]
Priori et al., 2015	12	4.89	24	6.5	3.09	24	28.7%	1.32 [0.69, 1.95]
Total (95% CI)			**132**			**117**	**100.0%**	**0.61 [0.02, 1.20]**

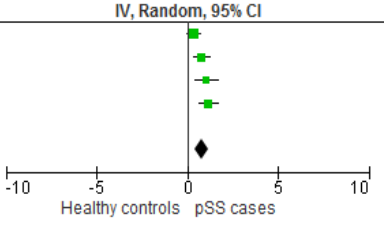
Heterogeneity: Tau² = 0.22; Chi² = 9.85, df = 2 (P = 0.007); I² = 80%
Test for overall effect: Z = 2.02 (P = 0.04)



K

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bongi et al., 2013	7.06	3.75	62	5.7	3.57	50	30.2%	0.37 [-0.01, 0.74]
Nimwegen et al., 2015	4.5	3.61	46	2.16	2.16	43	27.3%	0.77 [0.34, 1.21]
Priori et al., 2015	8.8	3.89	24	5.3	2.48	24	19.8%	1.06 [0.45, 1.66]
Ugurlu et al., 2014	16.5	7.27	32	8.62	6.46	32	22.8%	1.13 [0.60, 1.66]
Total (95% CI)			**164**			**149**	**100.0%**	**0.79 [0.43, 1.15]**

Heterogeneity: Tau² = 0.08; Chi² = 6.92, df = 3 (P = 0.07); I² = 57%
Test for overall effect: Z = 4.28 (P < 0.0001)



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).

Appendix 5

Queen Mary University of London

Barts Health NHS NHS Trust

Title of project: The effect of primary Sjögren's Syndrome on the senses of smell and taste, and sexuality in female patients in the UK: Impact on quality of life
Chief Investigator (CI): Dr Minan Al-Ezzi
Principal Investigator (PI): Professor Anwar Tappuni **IRAS Project ID:** 186276

Dear

Invitation to take part in research at Barts Health Trust

As a health care provider, I am involved in treating my patients and promoting research in order to understand and find better ways to manage clinical problems. I am writing to tell you about a study being conducted at Barts Health Trust, which is sponsored by Queen Mary University of London. I am supervising my PhD student Minan Al-Ezzi on a project aims to find out the impact of primary Sjgören's Syndrome (pSS) on the senses of smell and taste and on the sexual activity in female patients in the UK.

I am contacting you to let you know about the research in case you are interested to learn more. It is important to know that this letter is not to tell you to join this study. Taking part in this research is your decision. Your participation is voluntary and confidential, and will not be connected to your name in any reports of the data. Whether or not you participate in this study, will have no effect on your relationship with Barts Health Trust as a patient. However, if you decide to take part, your participation will help inform clinicians the quality of life of patients affected by Sjögren's syndrome.

If you would like to take part in the study, please check box 1 on the enclosed Response Form and return it in the provided pre-paid envelope. Once we get your response, you will be contacted to book an appointment for one visit, scheduled at your convenience, to test your smell and taste and to fill in questionnaires.

If you do not wish to take part in this research, and do not wish to be contacted again about this study, please check box 2 on the enclosed Response Form, and return it in the provided pre-paid envelope.

For more information, you can contact the research team on:

Dr Minan Al-Ezzi	**Tel:** 020 7377 7830	**email:** m.al-ezzi@qmul.ac.uk
Professor Anwar Tappuni	**Tel:** 020 7882 8655	**email:** a.r.tappuni@qmul.ac.uk

If we do not receive your reply in the next two weeks, you may be contacted again by a member of the research team.

Thank you for your consideration.

Sincerely,
Professor Anwar Tappuni

Include: Information sheet, Leaflet, Response form. V4 12.01.2016

Appendix 6

Queen Mary University of London

Barts Health NHS NHS Trust

Response Form

Title of project: The effect of primary Sjögren's Syndrome on the senses of smell and taste, and sexuality in female patients in the UK: Impact on quality of life

Chief Investigator (CI): Dr Minan Al-Ezzi

Principal Investigator (PI): Professor Anwar Tappuni **IRAS Project ID:** 186276

Please complete the following form and return in the pre-paid envelope provided

1. ☐ I am interested to take part in the study. I will be happy to be contacted to book an appointment, using the following information:

Name: _____

Telephone(s): _____

Best time and day to call: _____

Email: _____@_____

2. ☐ I am **NOT** interested in this study.

Appendix 7

Queen Mary University of London

Barts Health NHS NHS Trust

Patients information sheet

Title of Project: The effect of primary Sjögren's Syndrome on the senses of smell and taste, and sexuality in female patients in the UK: Impact on quality of life

Chief Investigator (CI): Dr Minan Al-Ezzi
Principal Investigator (PI): Professor Anwar Tappuni **IRAS Project ID:** 186276

One copy for patient; one copy for researcher and one copy to be kept in the hospital notes

1. Invitation

You are being invited to take part in a research study. Before you decide whether to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

2. What is the purpose of the study?

The study has been designed to investigate the impact of Primary Sjögren's Syndrome (pSS) on the quality of life of female patients in the UK. This condition causes dryness and can affect multiple body systems. One of our goals, is to find out whether smell, taste and sexual activity are affected in patients with pSS and whether this is impacting on their quality of life. This study will provide important information from patients' point of view and will help inform clinicians who are dealing with this group of patients.

3. Where will the study be undertaken?

If you decide to take part, you will be invited to attend Clinic 6 on the 2nd floor of the Institute of Dentistry in Whitechapel, Quen Mary University of London :
Turner Street, E1 2AD

4. Why have I been chosen?

The reason you have been chosen is because you have been diagnosed with pSS. Your participation will help us compare your health status with that of another group who do not have pSS.

5. Do I have to take part?

It is enirely up to you to decide wheteher or not to take part. Your participation is optional and if you decide not to participate or if you choose to withdraw from the study at any time, you do not have to give a reason, and the standards of healthcare you receive will not be affected in any way. We will describe the project and go through this information sheet, which we will then give to you. If you decide to take part after you have the opportunity to consider the information, we will ask you to sign a consent form to show that you have agreed to take part. You are free to withdraw at any time, without giving any reason.

Queen Mary University of London

Barts Health NHS NHS Trust

Patients information sheet

Title of Project: The effect of primary Sjögren's Syndrome on the senses of smell and taste, and sexuality in female patients in the UK: Impact on quality of life

Chief Investigator (CI): Dr Minan Al-Ezzi
Principal Investigator (PI): Professor Anwar Tappuni **IRAS Project ID:** 186276

6. What will happen if I agree to participate in this research?
If you decide to take part in the study, you will be invited to attend our clinic for one visit scheduled at your convenience. During the study visit, you will be required to fill out five questionnaires to assess your general and oral health related quality of life, mental health well-being, the senses of smell and taste and sexual activity. You do not have to answer all the questions but the more you answer the more beneficial your participation will be. As some of the questions are personal, you will be offered a private room to complete the questionnaires. You do not have to write your name on the questionnaires as they will be coded and anonymised. Answering all the questions will take 10-20 minutes of your time.

We will estimate the dryness of your mouth by asking you to spit in a container for five minutes. The smell will be tested by asking you to smell several cards with different odours. The taste will be investigated by applying strips with different tastes on your tongue. We will also use a battery-operated device with a metal disk applied on your tongue which will produce a very slight current that lasts for 1.5 seconds for each stimulus to check your tongue's ability to taste. This will incur a slight tingling sensation but there will be no pain or soreness. These tests will collectively take just over 48 min of your time. The information you will provide, will be compared with other information we will get from the non-pSS group. We will also store your personal identifiable information as we may need to contact you in the future to ask you whether you want to participate in a follow up research. We will need to get access to your medical records to collect information and get access to tests' results in order to help us relate our findings with your medical condition.

7. How long will the visit take?
You will need to attend our clinic for one visit scheduled at your conveniences. We estimate that the visit will take just over one hour.

8. What are the risks of taking part in this study?
There are no anticipated risks to you when taking part in this study. The tests we are using have been used in the past in a number of studies and there are no reported side effects associated with them. However, we realised that you might find the questionnaire that assesses your sexual function intrusive and distressing, as it includes questions about your sexual satisfaction with your partner. In the event that you feel distressed after answering these questions or you need further support then please contact your GP, who has been informed of your participation in this study and has been asked to provide support should you need.

Queen Mary University of London

Barts Health NHS NHS Trust

Patients information sheet

Title of Project: The effect of primary Sjögren's Syndrome on the senses of smell and taste, and sexuality in female patients in the UK: Impact on quality of life

Chief Investigator (CI): Dr Minan Al-Ezzi
Principal Investigator (PI): Professor Anwar Tappuni **IRAS Project ID:** 186276

In testing the innervation of your tongue, you may find that the current we will apply on your tongue is uncomfortable and unusual, however, the sensation is similar to tingling and lasts for 1.5 seconds only. This equipment is in regular use in neurology department in the UK, and has been used in several studies and on hundreds of participants without any reported complications. If you have any concerns about any aspect of the study, you should ask the research team who will do their best to answer your questions. Additionally, if you have any problem during the study procedures, you should report it to the research team at the earliest possible opportunity (see contact details in point 14).

9. What are the possible benefits from this study?
There would be limited clinical benefit directly to you. However, you will have the chance to test your smell and taste and whether they are affected. The information you will provide, will help us identify the problems and difficulties faced by pSS patients, and will help inform clinicians to improve management with pSS patients in the future. The results of these studies are likely to be published in scientific journals and presented at national and international conferences and patients' forum but will not identify you.

10. Who will have access to my information?
Only members of the study's team will have access to the information you provide, and you will not be identified from your responses in any publication or presentation resulting from this research. The information we will get from you will be treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998.

11. What happens to the information I am providing?
The information you will provide will have a code number and will be kept confidentially and securely. These codes will be used to pseudo-anonymise the data we will get from participants of the study. Only research team members will have access to your data. Your personal details will not be identified in publications at any occasion, but will help us to draw a final conclusion. Your data will only be used for research directly related to this project, and will not be used for other research.

12. What will happen to my data after the study is over or if I withdraw from participation?
As a rule, the data we will get from you will be stored securely, until it is destroyed after about 6-12 months of completing the study. Your personal information will only be kept at Barts Health NHS Trust and will be protected by the NHS privacy policies. Only anonymised data will be transferred to Queen Mary University of London computers. The people conducting

Queen Mary University of London

Barts Health NHS NHS Trust

Patients information sheet

Title of Project: The effect of primary Sjögren's Syndrome on the senses of smell and taste, and sexuality in female patients in the UK: Impact on quality of life

Chief Investigator (CI): Dr Minan Al-Ezzi
Principal Investigator (PI): Professor Anwar Tappuni **IRAS Project ID:** 186276

the study will abide by the Data Protection Act 1998, and the rights you have under this Act. For more information please have a look on the web at
http://www.gmc-uk.org/guidance/ethical_guidance/confidentiality.asp

If you decide, at any time, to withdraw from the study, we will keep the data collected up to the time you leave the study.

13. Who has reviewed the study?
The study is sponsored by Queen Mary University of London and is funded by the Iraqi Government Ministry of Higher Education & Scientific Research as part of the Chief Investigator's PhD fulfilment. The study has been reviewed by London Bridge Research Ethics Committee and Barts Health NHS Trust R&D Department.

14. What happens if there is a problem?
Queen Mary University of London has agreed that if you are harmed as a result of your participation in the study, you will be compensated, provided that, on the balance of probabilities, an injury was caused as a direct result of the intervention or procedures you received during the course of the study. These special compensation arrangements apply where an injury is caused to you that would not have occurred if you were not in the trial. These arrangements do not affect your right to pursue a claim through legal action.

15. Expenses and Payments
Taking part in this project is voluntary so you will not receive any payment. However, we will offer you a £10 market vouchers as a thank you.

Please contact Patient Advisory Liaison Service (PALS) if you have any concerns regarding the care you have received, or as an initial point of contact if you have a complaint. Please telephone 020 7377 6335, minicom 020 7943 1350, or email pals@bartsandthelondon.nhs.uk. You can also visit PALS by asking at any hospital reception. If you have any questions or concerns about the manner in which the study was conducted please contact the researcher responsible for the study in the first instance on the following details:

Queen Mary University of London

Barts Health NHS NHS Trust

Patients information sheet

Title of Project: The effect of primary Sjögren's Syndrome on the senses of smell and taste, and sexuality in female patients in the UK: Impact on quality of life

Chief Investigator (CI): Dr Minan Al-Ezzi
Principal Investigator (PI): Professor Anwar Tappuni **IRAS Project ID:** 186276

CI: Dr Minan Al-Ezzi **Tel:** 020 7377 7830 **email:** m.al-ezzi@qmul.ac.uk
PI: Dr Anwar Tappuni **Tel:** 020 7882 8655 **email:** a.r.tappuni@qmul.ac.uk

If you feel that these procedures are inappropriate, please contact the following:
The Secretary at the Queen Mary Ethics of Research Committee, Room W117, Queen's Building, Mile End Campus, Mile End Road, London or email: research-ethics@qmul.ac.uk

Appendix 8

Queen Mary University of London

Barts Health NHS NHS Trust

Healthy Volunteers information sheet

Title of Project: The effect of primary Sjögren's Syndrome on the senses of smell and taste, and sexuality in female patients in the UK: Impact on quality of life

Chief Investigator (CI): Dr Minan Al-Ezzi
Principal Investigator (PI): Professor Anwar Tappuni **IRAS Project ID:** 186276

One copy for patient; one copy for researcher and one copy to be kept in the hospital notes

1. Invitation

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

2. What is the purpose of the study?

The study has been designed to investigate the impact of Primary Sjögren's Syndrome (pSS) on the quality of life of female patients in the UK. This condition causes dryness and can affect multiple body systems. One of our goals is to find out whether smell, taste and sexual activity are affected in patients with pSS and whether this is impacting on their quality of life. This study will provide important information from the patients' point of view and will help inform clinicians who are dealing with this group of patients.

3. Where will the study be undertaken?

If you decide to take part, you will be invited to attend Clinic 6 on the 2nd floor of the Institute of Dentistry in Whitechapel, Quen Mary University of London :
Turner Street, E1 2AD.

4. Why have I been chosen?

You have been asked to take part in this study because you are generally healthy and do not suffer from pSS. Your participation will provide useful information to help us compare your health status, with that of pSS participants who have also agreed to take part. However, your participation is completely voluntary and refusing to take part will not affect your rights in any way.

5. Do I have to take part?

It is enirely up to you to decide wheteher or not to take part. Your participation is voluntary and if you decide not to participate or if you choose to withdraw from the study at any time, you do not have to give a reason, and the standards of healthcare you receive will not be affected in any way. We will describe the project and go through this information sheet, which we will then give to you. If you decide to take part after you have the opportunity to consider the information, we will ask you to sign a consent form to show that you have agreed to take part. You are free to withdraw at any time, without giving any reason.

Queen Mary University of London

Barts Health NHS NHS Trust

Healthy Volunteers information sheet

Title of Project: The effect of primary Sjögren's Syndrome on the senses of smell and taste, and sexuality in female patients in the UK: Impact on quality of life

Chief Investigator (CI): Dr Minan Al-Ezzi
Principal Investigator (PI): Professor Anwar Tappuni **IRAS Project ID:** 186276

6. What will happen if I agree to participate in this research?

If you decide to take part in the study, you will be invited to attend our clinic for one visit scheduled at your convenience. During the study visit, you will be required to fill out five questionnaires to assess your general and oral health related quality of life, mental health well-being, the senses of smell and taste and sexual activity. You do not have to answer all the questions but the more you answer the more beneficial your participation will be. As some of the questions are personal, you will be offered a private room to complete the questionnaires. You do not have to write your name on the questionnaires as they will be coded and anonymised. Answering all the questions will take 10-20 minutes of your time.

We will estimate the dryness of your mouth by asking you to spit in a container for five minutes. The smell will be tested by asking you to smell several cards with different odours. The taste will be investigated by applying strips with different tastes on your tongue. We will also use a battery-operated device with a metal disk applied on your tongue which will produce a very slight current that lasts for 1.5 seconds for each stimulus to check your tongue's ability to taste. This will incur a slight tingling sensation but there will be no pain or soreness. These tests will collectively take about 50 minutes of your time. The information you will provide, will be compared with other information we will get from the pSS patients group.

7. How long will the visit take?

You will need to attend our clinic for one visit scheduled at your conveniences. We estimate that the visit will take just over one hour.

8. What are the risks of taking part in this study?

There are no anticipated risks to you when taking part in this study. The tests we are using have been used in the past in a number of studies and there are no reported side effects associated with them. However, we realised that you might find the questionnaire that assesses your sexual function intrusive and distressing, as it includes questions about your sexual satisfaction with your partner. In the event that you feel distressed after answering these questions or you need further support then please contact your GP, who has been informed of your participation in this study and has been asked to provide support should you need.

In testing the innervation of your tongue, you may find that the current we will apply on your tongue is uncomfortable and unusual, however, the sensation is similar to tingling and lasts for 1.5 seconds only. This equipment is in regular use in neurology department in the UK, and

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Healthy Volunteers information sheet

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has been used in several studies and on hundreds of participants without any reported complications. If you have any concerns about any aspect of the study, you should ask the research team who will do their best to answer your questions. Additionally, if you have any problem during the study procedures, you should report it to the research team at the earliest possible opportunity (see contact details in point 14).

9. What are the possible benefits from this study?
You will have the benefit of testing your senses of smell and taste. Otherwise, there is no direct benefit to you. The information you provide will help us identify the problems and difficulties faced by pSS patients, and will help inform clinicians to improve management with pSS patients in the future. The results of these studies are likely to be published in scientific journals and presented at national and international conferences and patients' forum but will not identify you.

10. Who will have access to my information?
Only members of the study's team will have access to the information you provide, and you will not be identified from your responses in any publication or presentation resulting from this research. The information we will get from you will be treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998.

11. What happens to the information I am providing?
The information you will provide will have a code number and will be kept confidentially and securely. These codes will be used to pseudo-anonymise the data we will get from participants of the study. Only research team members will have access to your data. Your personal details will not be identified in publications at any occasion, but will help us to draw a final conclusion. Your data will only be used for research directly related to this project, and will not be used for other research.

12. What will happen to my data after the study is over or if I withdraw from participation?
As a rule, the data we will get from you will be stored securely, until it is destroyed after about 6-12 months of completing the study. Your personal information will be kept at Barts Health and will be protected by the NHS privacy policies. Only anonymised data will be transferred to Queen Mary university of London computers. The people conducting the study will abide by the Data Protection Act 1998, and the rights you have under this Act. For more information please have a look on the web at
http://www.gmc- uk.org/guidance/ethical_guidance/confidentiality.asp

Queen Mary University of London

Barts Health NHS NHS Trust

Healthy Volunteers information sheet

Title of Project: The effect of primary Sjögren's Syndrome on the senses of smell and taste, and sexuality in female patients in the UK: Impact on quality of life

Chief Investigator (CI): Dr Minan Al-Ezzi
Principal Investigator (PI): Professor Anwar Tappuni **IRAS Project ID:** 186276

If you decide at any time to withdraw from the study, we will keep the data collected up to the time of your withdrawal from the study but collect no further information.

13. Who has reviewed the study?
The study is sponsored by Queen Mary University of London and is funded by the Iraqi Government Ministry of Higher Education & Scientific Research as part of the Chief Investigator's PhD fulfilment. The study has been reviewed by London Bridge Research Ethics Committee and Barts Health NHS Trust R&D Department.

14. What happens if there is a problem?
Queen Mary University of London has agreed that if you are harmed as a result of your participation in the study, you will be compensated, provided that, on the balance of probabilities, an injury was caused as a direct result of the intervention or procedures you received during the course of the study. These special compensation arrangements apply where an injury is caused to you that would not have occurred if you were not in the trial. These arrangements do not affect your right to pursue a claim through legal action.

15. Expenses and Payments
Taking part in this project is voluntary so you will not receive any payment. However, we will offer a £10 market vouchers as a thank you.

Please contact Patient Advisory Liaison Service (PALS) if you have any concerns regarding the care you have received, or as an initial point of contact if you have a complaint. Please telephone 020 7377 6335, minicom 020 7943 1350, or email pals@bartsandthelondon.nhs.uk. You can also visit PALS by asking at any hospital reception. If you have any questions or concerns about the manner in which the study was conducted please contact the researcher responsible for the study in the first instance on the following details:

CI: Dr Minan Al-Ezzi **Tel:** 020 7377 7830 **email:** m.al-ezzi@qmul.ac.uk
PI: Professor Anwar Tappuni **Tel:** 020 7882 8655 **email:** a.r.tappuni@qmul.ac.uk

If you feel that these procedures are inappropriate, please contact the following:
The Secretary at the Queen Mary Ethics of Research Committee, Room W117, Queen's Building, Mile End Campus, Mile End Road, London or email: research-ethics@qmul.ac.uk

Appendix 9

Queen Mary University of London

Barts Health NHS NHS Trust

Patients Consent Form

Title of Project: The Effect of primary Sjögren's Syndrome on the Senses of Smell and Taste and Sexuality in Female Patients in the UK: Impact on quality of life

Chief Investigator: Dr Minan Al-Ezzi

Principal Investigator (PI): Professor Anwar Tappuni **IRAS Project ID:** 186276

One copy for patient; one copy for researcher; one copy to be kept in the hospital notes

	Please initial box to Indicate agreement
I confirm that I have read and understood the information sheet version 08, dated 13.01.2016 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	
I give permission for the research team members to access my medical and dental records.	
I agree that my GP is informed of my participation in the study.	
I consent for my identifiable information to be stored in order to facilitate contacting me for related future projects.	
I agree to take part in the above study.	

Name of Patient	Date	Signature
Name of Person taking consent (If different from Investigator)	Date	Signature
Investigator	Date	Signature

Appendix 10

Queen Mary University of London

Barts Health NHS NHS Trust

Healthy Volunteers Consent Form

Title of Project: The Effect of primary Sjögren's Syndrome on the Senses of Smell and Taste and Sexuality in Female Patients in the UK: Impact on quality of life

Chief Investigator (CI): Dr Minan Al-Ezzi
Principal Investigator (PI): Professor Anwar Tappuni **IRAS Project ID:** 186276

One copy for patient; one copy for researcher; one copy to be kept in the hospital notes

Please initial box to indicate agreement

I confirm that I have read and understood the information sheet version 4, dated 13.01.2016 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
I agree that my GP is informed of my participation in the study.	
I agree to take part in the above study.	

Name of Participant	Date	Signature
Name of Person taking consent (If different from Investigator)	Date	Signature
Investigator	Date	Signature

Appendix 11

WHO/MSA/MNH/PSF/97.6
English only
Distr.: Limited

WHOQOL-BREF

PROGRAMME ON MENTAL HEALTH
WORLD HEALTH ORGANIZATION
GENEVA

For office use only

	Equations for computing domain scores	Raw score	Transformed scores*	
			4-20	0-100
Domain 1	(6-Q3) + (6-Q4) + Q10 + Q15 + Q16 + Q17 + Q18 ☐ + ☐ + ☐ + ☐ + ☐ + ☐ + ☐	=		
Domain 2	Q5 + Q6 + Q7 + Q11 + Q19 + (6-Q26) ☐ + ☐ + ☐ + ☐ + ☐ + ☐	=		
Domain 3	Q20 + Q21 + Q22 ☐ + ☐ + ☐	=		
Domain 4	Q8 + Q9 + Q12 + Q13 + Q14 + Q23 + Q24 + Q25 ☐ + ☐ + ☐ + ☐ + ☐ + ☐ + ☐ + ☐	=		

* Please see Table 4 on page 10 of the manual, for converting raw scores to transformed scores.

MSA/MNH/PSF/97.6
Page 2

I.D. number

ABOUT YOU

Before you begin we would like to ask you to answer a few general questions about yourself: by circling the correct answer or by filling in the space provided.

What is your **gender**? Male Female

What is you **date of birth**? _____ / _____ / _____
Day / Month / Year

What is the highest **education** you received?
None at all
Primary school
Secondary school
Tertiary

What is your **marital status**?
Single Separated
Married Divorced
Living as married Widowed

Are you currently **ill**? Yes No

If something is wrong with your health what do you think it is?_____illness/ problem

Instructions

This assessment asks how you feel about your quality of life, health, or other areas of your life. **Please answer all the questions.** If you are unsure about which response to give to a question, **please choose the one** that appears most appropriate. This can often be your first response.

Please keep in mind your standards, hopes, pleasures and concerns. We ask that you think about your life **in the last two weeks.** For example, thinking about the last two weeks, a question might ask:

		Not at all	Not much	Moderately	A great deal	Completely
	Do you get the kind of support from others that you need?	1	2	3	4	5

You should circle the number that best fits how much support you got from others over the last two weeks. So you would circle the number 4 if you got a great deal of support from others as follows.

		Not at all	Not much	Moderately	A great deal	Completely
	Do you get the kind of support from others that you need?	1	2	3	4	5

You would circle number 1 if you did not get any of the support that you needed from others in the last two weeks.

Please read each question, assess your feelings, and circle the number on the scale for each question that gives the best answer for you.

		Very poor	Poor	Neither poor nor good	Good	Very good
1(G1)	How would you rate your quality of life?	1	2	3	4	5

		Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
2 (G4)	How satisfied are you with your health?	1	2	3	4	5

The following questions ask about **how much** you have experienced certain things in the last two weeks.

		Not at all	A little	A moderate amount	Very much	An extreme amount
3 (F1.4)	To what extent do you feel that physical pain prevents you from doing what you need to do?	1	2	3	4	5
4(F11.3)	How much do you need any medical treatment to function in your daily life?	1	2	3	4	5
5(F4.1)	How much do you enjoy life?	1	2	3	4	5
6(F24.2)	To what extent do you feel your life to be meaningful?	1	2	3	4	5

		Not at all	A little	A moderate amount	Very much	Extremely
7(F5.3)	How well are you able to concentrate?	1	2	3	4	5
8 (F16.1)	How safe do you feel in your daily life?	1	2	3	4	5
9 (F22.1)	How healthy is your physical environment?	1	2	3	4	5

The following questions ask about **how completely** you experience or were able to do certain things in the last two weeks.

		Not at all	A little	Moderately	Mostly	Completely
10 (F2.1)	Do you have enough energy for everyday life?	1	2	3	4	5
11 (F7.1)	Are you able to accept your bodily appearance?	1	2	3	4	5
12 (F18.1)	Have you enough money to meet your needs?	1	2	3	4	5
13 (F20.1)	How available to you is the information that you need in your day-to-day life?	1	2	3	4	5
14 (F21.1)	To what extent do you have the opportunity for leisure activities?	1	2	3	4	5

		Very poor	Poor	Neither	Good	Very good

				poor nor good		
15 (F9.1)	How well are you able to get around?	1	2	3	4	5

The following questions ask you to say how **good or satisfied** you have felt about various aspects of your life over the last two weeks.

		Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
16 (F3.3)	How satisfied are you with your sleep?	1	2	3	4	5
17 (F10.3)	How satisfied are you with your ability to perform your daily living activities?	1	2	3	4	5
18(F12.4)	How satisfied are you with your capacity for work?	1	2	3	4	5
19 (F6.3)	How satisfied are you with yourself?	1	2	3	4	5
20(F13.3)	How satisfied are you with your personal relationships?	1	2	3	4	5
21(F15.3)	How satisfied are you with your sex life?	1	2	3	4	5
22(F14.4)	How satisfied are you with the support you get from your friends?	1	2	3	4	5
23(F17.3)	How satisfied are you with the conditions of your living place?	1	2	3	4	5
24(F19.3)	How satisfied are you with your access to health services?	1	2	3	4	5
25(F23.3)	How satisfied are you with your transport?	1	2	3	4	5

The following question refers to **how often** you have felt or experienced certain things in the last two weeks.

		Never	Seldom	Quite often	Very often	Always
26 (F8.1)	How often do you have negative feelings such as blue mood, despair, anxiety, depression?	1	2	3	4	5

Did someone help you to fill out this form?.....

How long did it take to fill this form out?.....

Do you have any comments about the assessment?

.....

.....

THANK YOU FOR YOUR HELP

Appendix 12

Participant's Initials: Participant's Code:

The Effect of primary Sjögren's Syndrome on the Senses of Smell and Taste, and on Sexuality in Female Patients in the UK: Impact on quality of life

(OHIP-14)

The following 14 questions will assess the health status of your mouth:

1. Have you had trouble *pronouncing any words* because of problems with your teeth, mouth or dentures?
□Never □Hardly ever □Occasionally □Fairly often □Very often

2. Have you felt that your *sense of taste* has worsened because of problems with your teeth, mouth or dentures?
□Never □Hardly ever □Occasionally □Fairly often □Very often

3. Have you had *painful aching* in your mouth?
□Never □Hardly ever □Occasionally □Fairly often □Very often

4. Have you found it *uncomfortable to eat any foods* because of problems with your teeth, mouth or dentures?
□Never □Hardly ever □Occasionally □Fairly often □Very often

5. Have you been *self-conscious* because of your teeth, mouth or dentures?
□Never □Hardly ever □Occasionally □Fairly often □Very often

6. Have you *felt tense* because of problems with your teeth, mouth or dentures?
□Never □Hardly ever □Occasionally □Fairly often □Very often

7. Has your *diet been unsatisfactory* because of problems with your teeth, mouth or dentures?
□Never □Hardly ever □Occasionally □Fairly often □Very often

8. Have you had to *interrupt meals* because of problems with your teeth, mouth or dentures?
□Never □Hardly ever □Occasionally □Fairly often □Very often

V4 The Effect of Primary Sjögren's Syndrome 26.10.2015

Participant's Initials: Participant's Code:

9. Have you found it *difficult to relax* because of problems with your teeth, mouth or dentures?
□Never □Hardly ever □Occasionally □Fairly often □Very often

10. Have you been a bit *embarrassed because* of problems with your teeth, mouth or dentures?
□Never □Hardly ever □Occasionally □Fairly often □Very often

11. Have you been a bit *irritable with other people* because of problems with your teeth, mouth or dentures?
□Never □Hardly ever □Occasionally □Fairly often □Very often

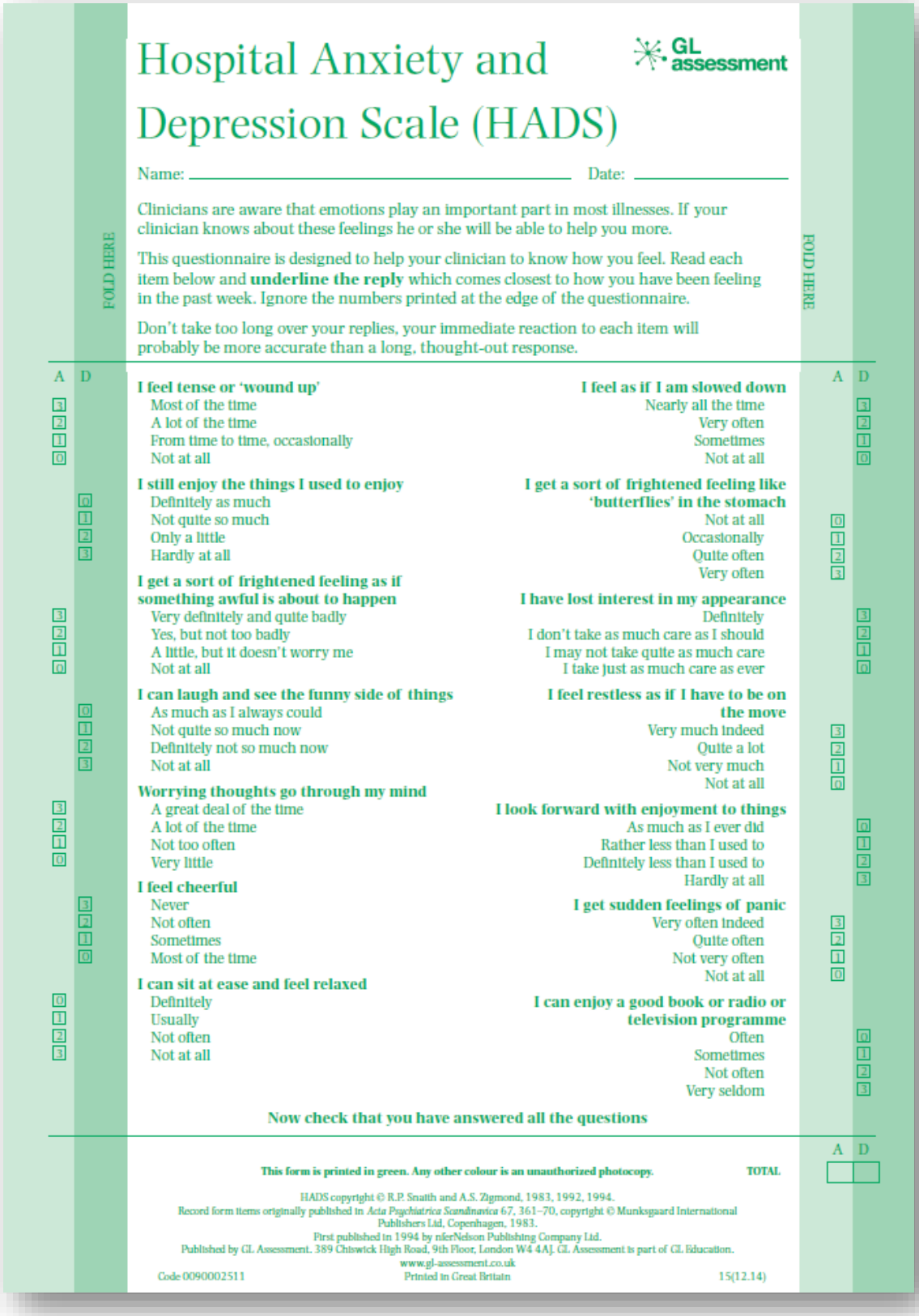
12. Have you had *difficulty doing your usual jobs* because of problems with your teeth, mouth or dentures?
□Never □Hardly ever □Occasionally □Fairly often □Very often

13. Have you felt that life in general was *less satisfying* because of problems with your teeth, mouth or dentures?
□Never □Hardly ever □Occasionally □Fairly often □Very often

14. Have you been *totally unable to function* because of problems with your teeth, mouth or dentures?
□Never □Hardly ever □Occasionally □Fairly often □Very often

Total Score:

Appendix 13



Hospital Anxiety and Depression Scale (HADS)

GL assessment

Name: _____ Date: _____

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and **underline the reply** which comes closest to how you have been feeling in the past week. Ignore the numbers printed at the edge of the questionnaire.

Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

FOLD HERE

FOLD HERE

A	D		A	D
		I feel tense or 'wound up'		
3		Most of the time		3
2		A lot of the time		2
1		From time to time, occasionally		1
0		Not at all		0
		I still enjoy the things I used to enjoy		
	0	Definitely as much		
	1	Not quite so much		
	2	Only a little		
	3	Hardly at all		
		I get a sort of frightened feeling as if something awful is about to happen		
3		Very definitely and quite badly		3
2		Yes, but not too badly		2
1		A little, but it doesn't worry me		1
0		Not at all		0
		I can laugh and see the funny side of things		
	0	As much as I always could		
	1	Not quite so much now		
	2	Definitely not so much now		
	3	Not at all		
		Worrying thoughts go through my mind		
3		A great deal of the time		
2		A lot of the time		
1		Not too often		
0		Very little		
		I feel cheerful		
	3	Never		
	2	Not often		
	1	Sometimes		
	0	Most of the time		
		I can sit at ease and feel relaxed		
0		Definitely		
1		Usually		
2		Not often		
3		Not at all		
		I feel as if I am slowed down		
		Nearly all the time		3
		Very often		2
		Sometimes		1
		Not at all		0
		I get a sort of frightened feeling like 'butterflies' in the stomach		
		Not at all	0	
		Occasionally	1	
		Quite often	2	
		Very often	3	
		I have lost interest in my appearance		
		Definitely		3
		I don't take as much care as I should		2
		I may not take quite as much care		1
		I take just as much care as ever		0
		I feel restless as if I have to be on the move		
		Very much indeed	3	
		Quite a lot	2	
		Not very much	1	
		Not at all	0	
		I look forward with enjoyment to things		
		As much as I ever did		0
		Rather less than I used to		1
		Definitely less than I used to		2
		Hardly at all		3
		I get sudden feelings of panic		
		Very often indeed	3	
		Quite often	2	
		Not very often	1	
		Not at all	0	
		I can enjoy a good book or radio or television programme		
		Often		0
		Sometimes		1
		Not often		2
		Very seldom		3

Now check that you have answered all the questions

A	D

TOTAL

This form is printed in green. Any other colour is an unauthorized photocopy.

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www.gl-assessment.co.uk
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Appendix 14

Female Sexual Function Index (FSFI) ©

Subject Identifier _____ Date _____

INSTRUCTIONS: These questions ask about your sexual feelings and responses during the past 4 weeks. Please answer the following questions as honestly and clearly as possible. Your responses will be kept completely confidential. In answering these questions the following definitions apply:

Sexual activity can include caressing, foreplay, masturbation and vaginal intercourse.

Sexual intercourse is defined as penile penetration (entry) of the vagina.

Sexual stimulation includes situations like foreplay with a partner, self-stimulation (masturbation), or sexual fantasy.

CHECK ONLY ONE BOX PER QUESTION.

Sexual desire or interest is a feeling that includes wanting to have a sexual experience, feeling receptive to a partner's sexual initiation, and thinking or fantasizing about having sex.

1. Over the past 4 weeks, how **often** did you feel sexual desire or interest?

   - ☐ Almost always or always
   - ☐ Most times (more than half the time)
   - ☐ Sometimes (about half the time)
   - ☐ A few times (less than half the time)
   - ☐ Almost never or never

2. Over the past 4 weeks, how would you rate your **level** (degree) of sexual desire or interest?

   - ☐ Very high
   - ☐ High
   - ☐ Moderate
   - ☐ Low
   - ☐ Very low or none at all

Page 1 (of 5)

Sexual arousal is a feeling that includes both physical and mental aspects of sexual excitement. It may include feelings of warmth or tingling in the genitals, lubrication (wetness), or muscle contractions.

3. Over the past 4 weeks, how **often** did you feel sexually aroused ("turned on") during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

4. Over the past 4 weeks, how would you rate your **level** of sexual arousal ("turn on") during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Very high
- ☐ High
- ☐ Moderate
- ☐ Low
- ☐ Very low or none at all

5. Over the past 4 weeks, how **confident** were you about becoming sexually aroused during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Very high confidence
- ☐ High confidence
- ☐ Moderate confidence
- ☐ Low confidence
- ☐ Very low or no confidence

6. Over the past 4 weeks, how **often** have you been satisfied with your arousal (excitement) during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

7. Over the past 4 weeks, how **often** did you become lubricated ("wet") during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

8. Over the past 4 weeks, how **difficult** was it to become lubricated ("wet") during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Extremely difficult or impossible
- ☐ Very difficult
- ☐ Difficult
- ☐ Slightly difficult
- ☐ Not difficult

9. Over the past 4 weeks, how often did you **maintain** your lubrication ("wetness") until completion of sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

10. Over the past 4 weeks, how **difficult** was it to maintain your lubrication ("wetness") until completion of sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Extremely difficult or impossible
- ☐ Very difficult
- ☐ Difficult
- ☐ Slightly difficult
- ☐ Not difficult

11. Over the past 4 weeks, when you had sexual stimulation or intercourse, how **often** did you reach orgasm (climax)?

- ☐ No sexual activity
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

12. Over the past 4 weeks, when you had sexual stimulation or intercourse, how **difficult** was it for you to reach orgasm (climax)?

- ☐ No sexual activity
- ☐ Extremely difficult or impossible
- ☐ Very difficult
- ☐ Difficult
- ☐ Slightly difficult
- ☐ Not difficult

13. Over the past 4 weeks, how **satisfied** were you with your ability to reach orgasm (climax) during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

14. Over the past 4 weeks, how **satisfied** have you been with the amount of emotional closeness during sexual activity between you and your partner?

- ☐ No sexual activity
- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

15. Over the past 4 weeks, how **satisfied** have you been with your sexual relationship with your partner?

- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

16. Over the past 4 weeks, how **satisfied** have you been with your overall sexual life?

- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

17. Over the past 4 weeks, how **often** did you experience discomfort or pain during vaginal penetration?

- ☐ Did not attempt intercourse
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

18. Over the past 4 weeks, how **often** did you experience discomfort or pain following vaginal penetration?

- ☐ Did not attempt intercourse
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

19. Over the past 4 weeks, how would you rate your **level** (degree) of discomfort or pain during or following vaginal penetration?

- ☐ Did not attempt intercourse
- ☐ Very high
- ☐ High
- ☐ Moderate
- ☐ Low
- ☐ Very low or none at all

Thank you for completing this questionnaire

Appendix 15

Participant's code:

The Effect of primary Sjögren's Syndrome on the Senses of Smell and Taste, and Sexuality in Female Patients in the UK: Impact on quality of life

VAS

Please indicate your state of smell and taste by selecting a point on the lines below:

1. How do you rate your sense of smell?

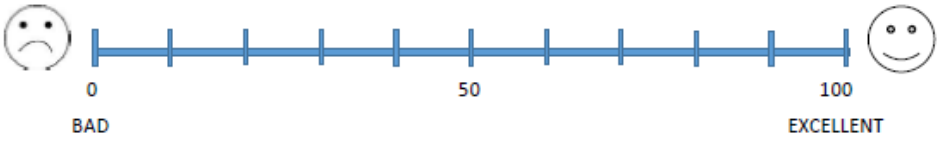
2. How do you rate your general oral health?

3. How do you rate your sense of taste in general?

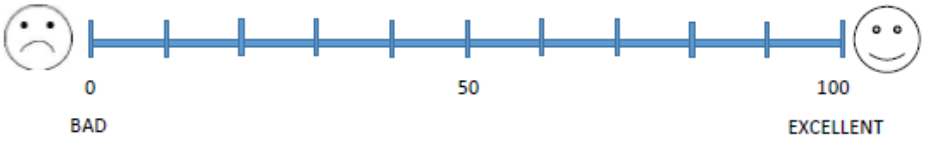
4. How do you rate your ability to taste sweet?

Participant's code:

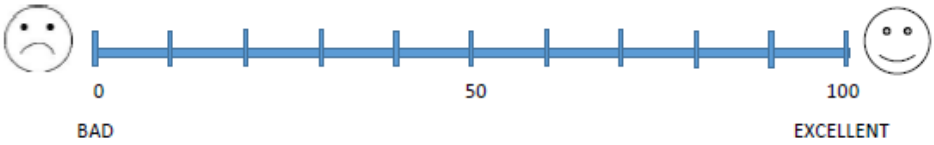
5. How do you rate your ability to taste sour?



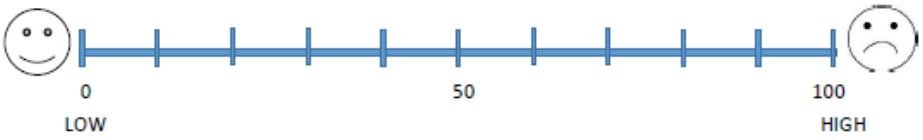
6. How do you rate your ability to taste salt?



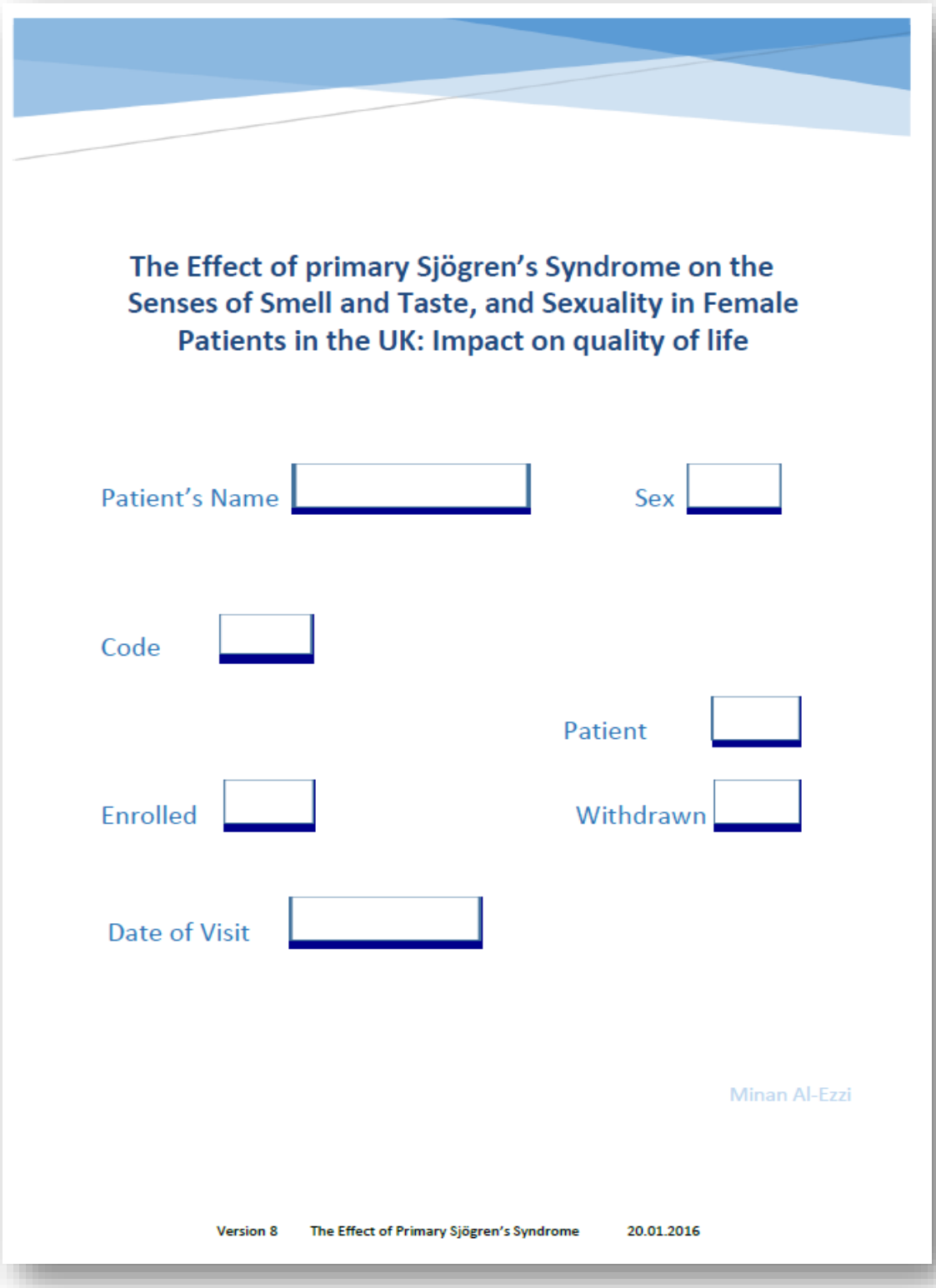
7. How do you rate your ability to taste bitter?



8. How do you rate the severity of fatigue you currently suffer from?



Appendix 16



The Effect of primary Sjögren's Syndrome on the Senses of Smell and Taste, and Sexuality in Female Patients in the UK: Impact on quality of life

Patient's Name _____ Sex _____

Code _____

Patient _____

Enrolled _____ Withdrawn _____

Date of Visit _____

Minan Al-Ezzi

Version 8 The Effect of Primary Sjögren's Syndrome 20.01.2016

The Effect of primary Sjögren's Syndrome on the Senses of Smell and Taste, and Sexuality in Female Patients in the UK: Impact on quality of life ID: 186276

Subject's Initials: Subject's Number:

Study Group

Inclusion Criteria: Subjects will be included in the study if ALL of the following boxes are ticked

1. Female patients aged 18 years and older.	
2. Confirmed diagnosis of SS (Appendix 1) for a minimum of three months confirmed in accordance to the revised Euro-American SS definition.	
3. Patients with the capacity to provide informed consent as defined by the Mental Capacity Act2005.	
4. Patients who are able to understand verbal explanations and written information in English with the support of a research assistant, if needed.	

Exclusion Criteria: Subjects will be excluded from the study if ANY of the following boxes were ticked

1. Past head, neck and/or lower abdomen radiation treatment.	
2. Past chemotherapy treatment.	
3. History of having salivary gland disease or swelling.	
4. Pregnancy or breast feeding.	
5. Patients with the presence of confounding signs and symptoms due to other systemic diseases such as asthma, sinusitis, nasal polyps, flu, and cold.	
6. Patients with other autoimmune diseases or secondary SS.	
7. The presence of-neurologic conditions that might affect their smell and/or taste sensation such as Parkinson's disease and Alzheimer's disease.	
8. The presence of oral conditions that are deemed to interfere with smell and taste. Such as Candidiasis and lichen planus.	
9. Uncontrolled diabetic patients.	
10. Staff, colleagues and dental students at Barts and the London School of Medicine and Dentistry will be excluded.	
11. Significant dental problems.	
12. Individuals who withhold consent.	

The Effect of primary Sjögren's Syndrome on the Senses of Smell and Taste, and Sexuality in Female Patients in the UK: Impact on quality of life ID: 186276

Subject's Initials: Subject's Number:

Demographics

D.O.B				
Sex				
Address				
Occupation				
Religion				
House hold income/Month	500 - 1000 £	1000 - 2000 £	More than 2000£	
Have a partner	Yes	No		
Education	Not at all	Primary school	Secondary school	Tertiary

Ethnicity

White

English	Welsh	Scottish	Northern Irish	British
Irish				
Gypsy or Irish Traveller				
Any other White background, please describe				

Mixed / Multiple ethnic groups

White and Black Caribbean	
White and Black African	
White and Asian	
Any other Mixed/ Multiple ethnic background, please describe	

Asian / Asian British

Indians	
Pakistani	
Bangladeshi	
Chinese	
Any other Asian background, please describe	

Black / African / Caribbean / Black British

African	
Caribbean	
Any other Black / African / Caribbean background, please describe	

Subject's Initials: Subject's Number:

Other ethnic group

Arabs	
Any other ethnic group, please describe	

Smoking, tobacco chewing and alcohol drinking status

Type	Yes	No	Units per day	Units per week
Smoking				
Pann chewing				
Alcohol				

Mouth Wash

Mouth Wash	Yes	No	Times a day/a week

Any appliance (denture, orthodontic …) currently used or exists in your mouth?

Yes	No	Type	
Times a day	Times a week	Times a month	Occasionally

The Effect of primary Sjögren's Syndrome on the Senses of Smell and Taste, and Sexuality in Female Patients in the UK: Impact on quality of life ID: 186276

Subject's Initials: Subject's Number:

Medical History

Medical History	Yes	No	
Heart disease			
Stomatitis			
Thyroid problems			
Liver diseases			
Diabetes mellitus			
HIV			
Others			
Any surgeries conducted			
Medications			

Clinical Investigations

Date:

Tests	Positive	Negative
Ro		
La		
ANA		1:60
ENA		
CRP		<5mg/l
Hb	g/dl	12-15 g/dl Female
WCC	$x10^9/l$	11-20 $x10^9/l$

The Effect of primary Sjögren's Syndrome on the Senses of Smell and Taste, and Sexuality in Female Patients in the UK: Impact on quality of life ID: 186276

Subject's Initials: Subject's Number:

Neutrophils	$x10^9/l$	2-7.5 $x10^9/l$
Lymphocytes	$x10^9/l$	3.5 x $10^9/l$
CD4 count	$x10^6/l$	
CD8 count	$x10^6/l$	
TSH	µIU/mL	0.3-5 µIU/mL
Vit. D	ng/mL	<20 ng/ml = deficiency 20-30 ng/ml =insufficiency
ESR	mm/hr	18 to 50 years: 1-20 mm/hour Over 50 years: 1-30 mm/hour

Ultrasound for salivary glands (data collected from database)

1.Date		
Results	+ve	-ve
2. Date		
Results	+ve	-ve

The Effect of primary Sjögren's Syndrome on the Senses of Smell and Taste, and Sexuality in Female Patients in the UK: Impact on quality of life ID: 186276

Subject's Initials: Subject's Number:

Lip biopsy (data collected from database):

1. Date		
Results	+ve for pSS	-ve for pSS
2. Date		
Results	+ve for pSS	-ve for pSS

Fatigue

Do you feel fatigue?	Yes	No	
Medications used to relief fatigue	Yes	No	
Do you suffer from dry skin?	Yes	No	
Have you ever been diagnosed with anxiety and/or depression?	Yes	No	
Have you been treated for it?	Yes	No	
Medications	Yes	No	

The Effect of primary Sjögren's Syndrome on the Senses of Smell and Taste, and Sexuality in Female Patients in the UK: Impact on quality of life ID: 186276

Subject's Initials: Subject's Number:

Neuropathy assessment

1. Have you lost feeling in your hands and/or feet?	YES	When?	No
2. Have you got tingling in your hands and/or feet? (pins & needls)	Yes	When?	No
3. Have you got numbness in your hands and/or feet?	Yes	When?	No
4. Have you suffered from clumsiness?	Yes	When?	No

Extra oral examination

Facial symmetry	Normal	Abnormal
TMJ	Normal	Abnormal
lips	Normal	Abnormal
Upper cervical lymph nodes	Normal	Abnormal
Submandibular triangle	Normal	Abnormal
Right salivary glands	Normal	Abnormal
Left salivary glands	Normal	Abnormal
Pain and/or tenderness on palpation	Yes	No
Others, please specify		

The Effect of primary Sjögren's Syndrome on the Senses of Smell and Taste, and Sexuality in Female Patients in the UK: Impact on quality of life ID: 186276

Subject's Initials: Subject's Number:

Schirmer's Test

Date	Right eye	Left eye			
	m/5min	m/5min	+ve for pSS	-ve for pSS	Border line
	m/5min	m/5min	+ve for pSS	-ve for pSS	Border line

Unstimulated whole salivary flow rate (UWSF) cut off point ≤ 0.1 ml/min

Date		ml/min	Indicative for pSS	Not indicative for pSS
Date		ml/min	Indicative for pSS	Not indicative for pSS

Stimulated whole salivary flow rate (SWSF) cut off point ≤ 0.6 ml/min

Date		ml/min	Indicative for pSS	Not indicative for pSS
Date		ml/min	Indicative for pSS	Not indicative for pSS

The Effect of primary Sjögren's Syndrome on the Senses of Smell and Taste, and Sexuality in Female Patients in the UK: Impact on quality of life ID: 186276

Subject's Initials: Subject's Number:

-What is the one symptom of pSS the most affect your quality of life?

Xerostomia Inventory: Participants will be asked the following questions to assess their oral dryness on a scale of 0 to 11 according to Xerostomia Inventory:

1. Do you sip liquids to help swallow food?	Never	Hardly ever	Occasionally	Fairly often	Very often
2. Does your mouth feel dry when eating a meal?	Never	Hardly ever	Occasionally	Fairly often	Very often
3. Do you get up at night to drink?	Never	Hardly ever	Occasionally	Fairly often	Very often
4. Does your mouth feel dry?	Never	Hardly ever	Occasionally	Fairly often	Very often
5. Do you have difficulty in eating dry food?	Never	Hardly ever	Occasionally	Fairly often	Very often
6. Do you suck sweets or cough lollies to relieve dry mouth?	Never	Hardly ever	Occasionally	Fairly often	Very often
7. Do you have difficulties swallowing certain foods?	Never	Hardly ever	Occasionally	Fairly often	Very often
8. Does the skin of your face feel dry?	Never	Hardly ever	Occasionally	Fairly often	Very often
9. Do your eyes feel dry?	Never	Hardly ever	Occasionally	Fairly often	Very often
10. Do your lips feel dry?	Never	Hardly ever	Occasionally	Fairly often	Very often
11. Does the inside of your nose feel dry?	Never	Hardly ever	Occasionally	Fairly often	Very often

Total score Date

The Effect of primary Sjögren's Syndrome on the Senses of Smell and Taste, and Sexuality in Female Patients in the UK: Impact on quality of life ID: 186276

Subject's Initials: Subject's Number:

Dry mouth score: (Point for each feature)

1. Mirror sticks to buccal mucosa	
2. Mirror sticks to tongue	
3. Saliva frothy/ stringy/ absent	
4. No saliva pooling in the floor of mouth	
5. Tongue shows loss of papillae	
6. Altered/ smooth gingival architecture (especially anterior)	
7. Glassy appearance to oral mucosa (especially palate)	
8. Tongue highly fissured	
9. Cervical caries or restorations (more than two teeth)/ high DMF	
10. Debris on palate (excluded under dentures)	

Total score Date

The Effect of primary Sjögren's Syndrome on the Senses of Smell and Taste, and Sexuality in Female Patients in the UK: Impact on quality of life ID: 186276

Subject's Initials: Subject's Number:

Eligibility

Fitness and eligibility to participate in the study	Supportive	Not Supportive
Providing the information sheet to the participants	Provided	Not Provided
Signing the consent by eligible participants	Signed	Not Signed

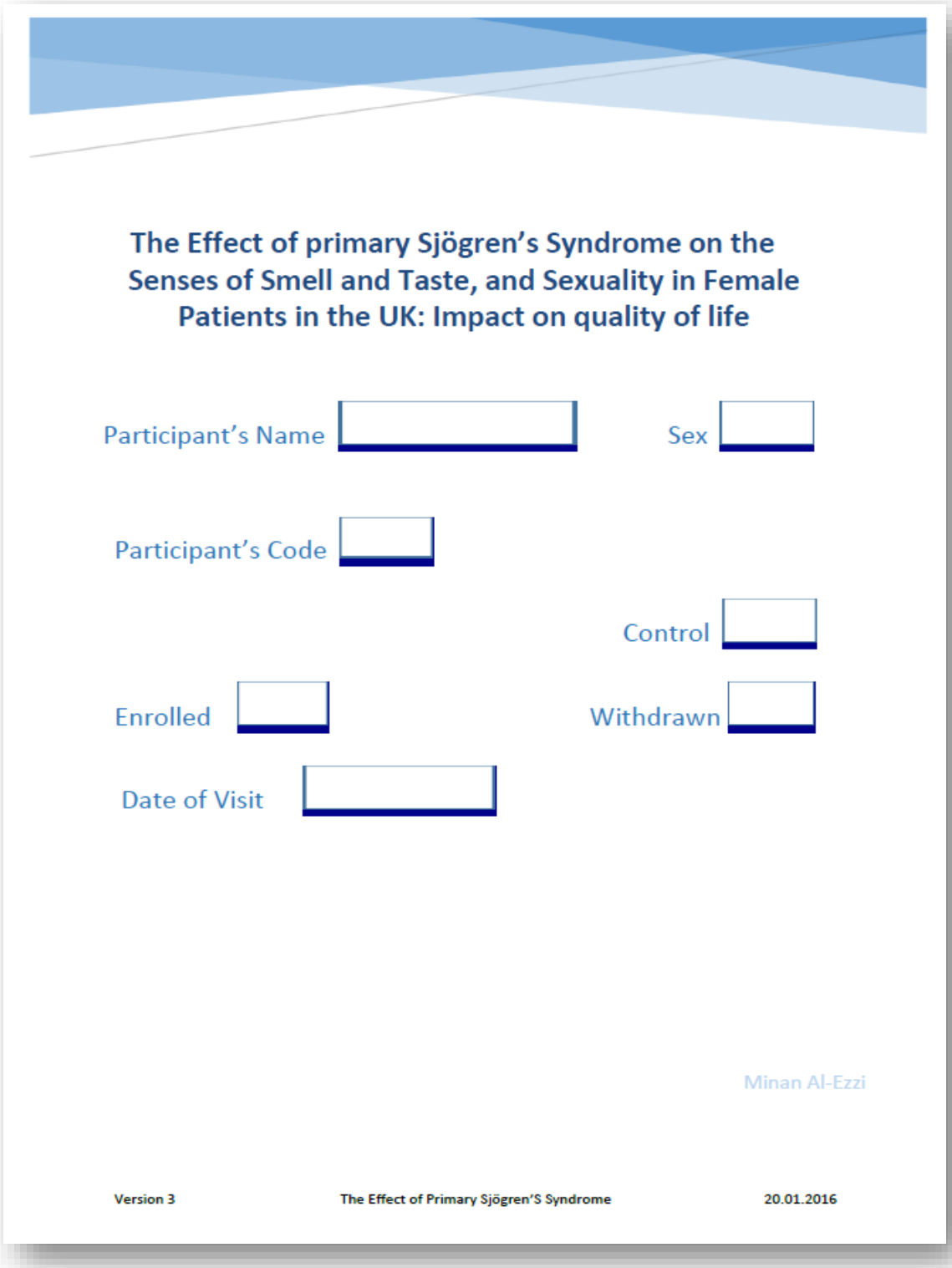
Smell and Taste Evaluation.

-UPSIT final score

-TST results

-EGM results

Appendix 17



The Effect of primary Sjögren's Syndrome on the Senses of Smell and Taste, and Sexuality in Female Patients in the UK: Impact on quality of life

Participant's Name _____ Sex _____

Participant's Code _____

Control _____

Enrolled _____ Withdrawn _____

Date of Visit _____

Minan Al-Ezzi

Version 3 The Effect of Primary Sjögren'S Syndrome 20.01.2016

The Effect of primary Sjögren's Syndrome on the Senses of Smell and Taste, and Sexuality in Female Patients in the UK: Impact on quality of life ID: 186276

Subject's Initials: Subject's Number:

Control Group

Inclusion Criteria: Subjects will be included in the study if ALL of the following boxes were ticked

1. Age matched female patients.	
2. Generally fit and healthy.	
3. Patients with the capacity to provide informed consent as defined by the Mental Capacity Act 2005.	
4. Patients who are able to understand verbal explanations and written information in English with the support of a research assistant, if needed.	

Exclusion Criteria: Subjects will be excluded from the study if ANY of the following boxes were ticked

1. Past head, neck and/or lower abdomen radiation treatment.	
2. Past chemotherapy treatment.	
3. History of having salivary gland disease or swelling.	
4. Pregnancy or breast feeding.	
5. Patients with the presence of confounding signs and symptoms due to other systemic diseases such as asthma, sinusitis, nasal polyps, flu, and cold.	
6. Patients with other autoimmune diseases or secondary SS.	
7. The presence of-neurologic conditions that might affect their smell and/or taste sensation such as Parkinson's disease and Alzheimer's disease.	
8. The presence of oral conditions that are deemed to interfere with smell and taste. Such as Candidiasis and lichen planus.	
9. Uncontrolled diabetic patients.	
10. Staff, colleagues and dental students at Barts and the London School of Medicine and Dentistry will be excluded.	
11. Significant dental problems.	
12. Individuals who withhold consent.	

The Effect of primary Sjögren's Syndrome on the Senses of Smell and Taste, and Sexuality in Female Patients in the UK: Impact on quality of life ID: 186276

Subject's Initials: Subject's Number:

Demographics

D.O.B				
Sex				
Address				
Occupation				
Religion				
House hold income/Month	500 - 1000 £	1000 - 2000 £	More than 2000£	
Have a partner	Yes	No		
Education	Not at all	Primary school	Secondary school	Tertiary

Ethnicity

White

English	Welsh	Scottish	Northern Irish	British
Irish				
Gypsy or Irish Traveller				
Any other White background, please describe				

The Effect of primary Sjögren's Syndrome on the Senses of Smell and Taste, and Sexuality in Female Patients in the UK: Impact on quality of life ID: 186276

Subject's Initials: Subject's Number:

Mixed / Multiple ethnic groups

White and Black Caribbean	
White and Black African	
White and Asian	
Any other Mixed/ Multiple ethnic background, please describe	

Asian / Asian British

Indians	
Pakistani	
Bangladeshi	
Chinese	
Any other Asian background, please describe	

Black / African / Caribbean / Black British

African	
Caribbean	
Any other Black / African / Caribbean background, please describe	

The Effect of primary Sjögren's Syndrome on the Senses of Smell and Taste, and Sexuality in Female Patients in the UK: Impact on quality of life ID: 186276

Subject's Initials: Subject's Number:

Other ethnic group

Arabs	
Any other ethnic group, please describe	

Smoking, tobacco chewing and alcohol drinking status

Type	Yes	No	Units per day	Units per week
Smoking				
Pann chewing				
Alcohol				

Mouth Wash

Mouth Wash	Yes	No	Times a day/a week

Any appliance (denture, orthodontic ...) currently used or exists in your mouth?

Yes	No	Type	
Times a day	Times a week	Times a month	Occasionally

The Effect of primary Sjögren's Syndrome on the Senses of Smell and Taste, and Sexuality in Female Patients in the UK: Impact on quality of life ID: 186276

Subject's Initials: Subject's Number:

Medical History

Medical History	Yes	No	
Heart disease			
Stomatitis			
Thyroid problems			
Liver diseases			
Diabetes mellitus			
HIV			
Others			
Any surgeries conducted			
Medications			

Extra oral examination

Facial symmetry	Normal	Abnormal
TMJ	Normal	Abnormal
lips	Normal	Abnormal
Upper cervical lymph nodes	Normal	Abnormal
Submandibular triangle	Normal	Abnormal
Right salivary glands	Normal	Abnormal
Left salivary glands	Normal	Abnormal
Pain and/or tenderness on palpation	Yes	No
Others, please specify		

The Effect of primary Sjögren's Syndrome on the Senses of Smell and Taste, and Sexuality in Female Patients in the UK: Impact on quality of life ID: 186276

Subject's Initials: Subject's Number:

Unstimulated whole salivary flow rate (UWSF) cut off point ≤ 0.1 ml/min

Date		ml/min	Indicative for pSS	Not indicative for pSS
Date		ml/min	Indicative for pSS	Not indicative for pSS

Stimulated whole salivary flow rate (SWSF) cut off point ≤ 0.6 ml/min

Date		ml/min	Indicative for pSS	Not indicative for pSS
Date		ml/min	Indicative for pSS	Not indicative for pSS

The Effect of primary Sjögren's Syndrome on the Senses of Smell and Taste, and Sexuality in Female Patients in the UK: Impact on quality of life ID: 186276

Subject's Initials: Subject's Number:

Xerostomia Inventory: Participants will be asked the following questions to assess their oral dryness on a scale of 0 to 11 according to Xerostomia Inventory:

1. Do you sip liquids to help swallow food?	Never	Hardly ever	Occasionally	Fairly often	Very often
2. Does your mouth feel dry when eating a meal?	Never	Hardly ever	Occasionally	Fairly often	Very often
3. Do you get up at night to drink?	Never	Hardly ever	Occasionally	Fairly often	Very often
4. Does your mouth feel dry?	Never	Hardly ever	Occasionally	Fairly often	Very often
5. Do you have difficulty in eating dry food?	Never	Hardly ever	Occasionally	Fairly often	Very often
6. Do you suck sweets or cough lollies to relieve dry mouth?	Never	Hardly ever	Occasionally	Fairly often	Very often
7. Do you have difficulties swallowing certain foods?	Never	Hardly ever	Occasionally	Fairly often	Very often
8. Does the skin of your face feel dry?	Never	Hardly ever	Occasionally	Fairly often	Very often
9. Do your eyes feel dry?	Never	Hardly ever	Occasionally	Fairly often	Very often
10. Do your lips feel dry?	Never	Hardly ever	Occasionally	Fairly often	Very often
11. Does the inside of your nose feel dry?	Never	Hardly ever	Occasionally	Fairly often	Very often

Total score Date:

The Effect of primary Sjögren's Syndrome on the Senses of Smell and Taste, and Sexuality in Female Patients in the UK: Impact on quality of life ID: 186276

Subject's Initials: Subject's Number:

Dry mouth score: (Point for each feature)

1. Mirror sticks to buccal mucosa	
2. Mirror sticks to tongue	
3. Saliva frothy/ stringy/ absent	
4. No saliva pooling in the floor of mouth	
5. Tongue shows loss of papillae	
6. Altered/ smooth gingival architecture (especially anterior)	
7. Glassy appearance to oral mucosa (especially palate)	
8. Tongue highly fissured	
9. Cervical caries or restorations (more than two teeth)/ high DMF	
10. Debris on palate (excluded under dentures)	

Total score Date:

Eligibility

Fitness and eligibility to participate in the study	Supportive	Not Supportive
Providing the information sheet to the participants	Provided	Not Provided
Signing the consent by eligible participants	Signed	Not Signed

The Effect of primary Sjögren's Syndrome on the Senses of Smell and Taste, and Sexuality in Female Patients in the UK: Impact on quality of life ID: 186276

Subject's Initials: Subject's Number:

Smell and Taste Evaluation

-UPSIT final score

-TST results

-EGM results

Appendix 18

ELECTROGUSTOMETER TEST Tongue Region Test F B L R First Second

Name _____ Gender _____ Age _____ Date _____

Tester _____ Patient Observations _____

Time _____

34.0																									400
32.0																									320
30.0																									250
28.0																									200
26.0																									160
24.0																									130
22.0																									100
20.0																									80
18.0																									64
16.0																									50
14.0																									40
12.0																									32
10.0																									25
8.0																									20
6.0																									16
4.0																									13
2.0																									10
0.0																									8
-2.0																									6.4
-4.0																									5
-6.0																									4
(db) (next row is # on dial)		E E O	O O E	E E O	E O E	O E O	O E E	E O E	E O O	O E E	E O O	O O E	E E O	O O E	E E O	O O E	E E O	O E E	E O E	E O O	O E O	O O E	E O O	E E O	E O E	**Micro-amps**

Appendix 19

Sjögren's patients volunteers needed for research on smell, taste and sexual function

Are you a female of 18 years or over?

Do you have about an hour to spare, to fill in questionnaires about: your quality of life and sexual activity

and to test your senses of smell and taste?

Get Involved

Version 4

Who we are

We are a group of researchers looking at the senses of smell and taste in patients diagnosed with pSS. One of our goals, is to find out whether the senses of smell and taste and the sexual activity, are affected in patients with pSS and whether this is impacting on patients' quality of life. This study will provide important information from patients' point of view and will help inform clinicians to improve the clinical management of this group of patients.

For more information about the project please contact us on:

Dr Minan Al-Ezzi Tel: 020 7377 7830
E-mail: m.al-ezzi@qmul.ac.uk
Professor Anwar Tappuni
Tel: 020 7882 8655
E-mail: a.r.tappuni@qmul.ac.uk
PALS: pals@bartsandthelondon.nhs.uk

Queen Mary University of London
Barts Health NHS Trust

The Effect of Primary Sjögren's Syndrome

Get Involved

12.01.2016

Support Our Project

Do I have to take part?

It is entirely up to you whether or not to take part. Your participation is voluntary. All the information you provide will be kept securely and confidential and you will not be identified in any of the published data. Your participation will provide us with important information to help understand Sjögren's Syndrome better, and to improve the clinical management of pSS patients.

What will happen if I decide to take part?

If you decide to take part, you will be invited to attend one visit at our clinic, scheduled at your convenience. The visit will take just over one hour of your time. You will be asked to fill out five questionnaires about your quality of life and sexual function. You will have the option not to answer all the questions, but the more you answer the more beneficial it will be for our research.

We will check your smell and taste by simple and validated tests.

This is a great opportunity to help Sjögren's patients in the future

Taking part in this project is voluntary so you will not receive any payment. However, we will offer a £10 market vouchers as a thank you.

For more information, please contact us on:

Dr Minan Al-Ezzi Tel: 020 7377 7830
E-mail: m.al-ezzi@qmul.ac.uk
Professor Anwar Tappuni
Tel: 020 7882 8655
E-mail: a.r.tappuni@qmul.ac.uk
PALS: pals@bartsandthelondon.nhs.uk

Appendix 20

Volunteers needed for research on smell, taste and sexual function

Are you a female of 18 years or over?

Do you have about an hour to spare, to fill in questionnaires about: your quality of life and sexual activity

and to test your senses of smell and taste?

Get Involved

Version 4

Who we are

We are a group of researchers looking at the senses of smell and taste in patients diagnosed with primary Sjögren's Syndrome (pSS). This syndrome is generally characterized by dryness of the nose, mouth and the genital area. We want to find out whether the dryness caused by pSS has an impact on smell, taste and sexual function, and whether this is impacting on patients' quality of life. To do this, we need to compare patients' information with that of healthy controls'. This study will provide important information from patients' point of view, and will help inform clinicians to improve dealing with this group of patients.

Queen Mary University of London

Barts Health NHS Trust

The Effect of Primary Sjögren's Syndrome

Get Involved

12.01.2016

Support Our Project

Do I have to take part?

It is entirely up to you whether or not to take part. Your participation is confidential and voluntary. You will not be identified in any of the published data. Your participation will provide us with important information to help us understand Sjögren's Syndrome better, and to improve the clinical management of pSS patients.

What will happen if I decide to take part?

If you decide to take part, you will be invited to attend one visit at our clinic, scheduled at your convenience. The visit will take just over one hour of your time. You will be asked to fill out five questionnaires about your quality of life and sexual function. You will have the option not to answer all the questions, but the more you answer the more beneficial it will be for our research.

We will check your smell and taste by simple and validated tests.

This is a great opportunity to help Sjögren's patients in the future

Taking part in this project is voluntary so you will not receive any payment. However, we will offer a £10 market vouchers as a thank you.

For more information, please contact us on:

Dr Minan Al-Ezzi **Tel**: 020 7377 7830
E-mail: m.al-ezzi@qmul.ac.uk
Professor Anwar Tappuni
Tel: 020 7882 655
E-mail: a.r.tappuni@qmul.ac.uk
PALS:pals@bartsandthelondon.nhs.uk

Appendix 21

VOLUNTEERS NEEDED

for research on
Smell, Taste and Sexual Function

Are you a female of 18 years or over?

Do you have about an hour to spare, to fill in questionnaires about your quality of life, mental health well-being and sexual activity; and to test your smell and taste?

To get involved

Or for more information, please contact the Chief Investigator

Dr Minan Al-Ezzi

020 7377 7830

m.al-ezzi@qmul.ac.uk

Appendix 22

Queen Mary University of London

Barts Health NHS NHS Trust

Letter to GP

Title of project: The effect of primary Sjögren's Syndrome on the senses of smell and taste, and sexuality in female patients in the UK: Impact on quality of life

Chief Investigator (CI): Dr Minan Al-Ezzi

Principal Investigator (PI): Professor Anwar Tappuni **IRAS Project ID:** 186276

Date:

Dear Doctor

RE: Research study entitled the effect of primary Sjögren Syndrome on the senses of smell and taste, and sexuality in female patients in the UK: Impact on quality of life.

I am writing to inform you that your above named patient has consented to participate in the aforementioned study. This study is being conducted at Barts Health Trust, and is sponsored by Queen Mary University of London. The study is an observational (case-control) research which aims to find out the impact of primary Sjögren's Syndrome on the senses of smell and taste, and on the sexual activity in female patients in the UK. The senses of smell and taste will be tested and the participants are asked to fill out questionnaires about: general and oral health related quality of life, anxiety and depression status and sexual activity. Participants are advised to contact their GP should they need to address any concerns highlighted by the sexual questionnaire. I enclose a copy of the Participants' Information Sheet dated in 13.01.2016 for your reference, however if you have any queries or require further information please contact:

Dr Minan Al-Ezzi **Tel:** 020 7377 7830 **email:** m.al-ezzi@qmul.ac.uk
Professor Anwar Tappuni **Tel:** 020 7882 8655 **email:** a.r.tappuni@qmul.ac.uk

Yours sincerely,
Professor Anwar Tappuni

Included: Participants' Information Sheet V3 18.01.2016

Appendix 23

TasteStrips

burghart MESSTECHNIK

A					
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Seite 5 von 5

Stand: 01. Jun 2014

Appendix 24

Impact on vaginal dryness

Medicines of supplements, anticoagulants, antihistamines and inhalers had an impact on vaginal dryness.

Table 4-68 Variables in the equation of a logistic regression for the prediction of vaginal dryness from medicines taken by pSS patients, n = 65.

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Hydroxychloroquine	18.167	6147.873	.000	1	.998	77573182.913	.000	.
	Pilocarpin	.455	32524.427	.000	1	1.000	1.576	.000	.
	Supplements	35.860	9734.967	.000	1	.997	3748126417157834.500	.000	.
	Antidepressant	17.648	11770.197	.000	1	.999	46179179.648	.000	.
	Immunosuppressant	18.674	19659.278	.000	1	.999	128829074.310	.000	.
	Anticoagulants	34.045	51329.877	.000	1	.999	6101727401300030.500	.000	.
	Antihistamine	-37.236	28161.531	.000	1	.999	.000	.000	.
	Hyperthyroidism	18.994	14805.652	.000	1	.999	177344084.857	.000	.
	Hypothyroidisms	1.612	19653.962	.000	1	1.000	5.014	.000	.
	Antibiotics	15.090	30681.390	.000	1	1.000	3575114.000	.000	.
	Blood pressure	2.477	18770.153	.000	1	1.000	11.910	.000	.
	Pain relief	-1.099	1.633	.453	1	.501	.333	.014	8.182
	Stomach acid	3.221	18827.692	.000	1	1.000	25.041	.000	.
	Hypoglycaemic	-19.027	6445.745	.000	1	.998	.000	.000	.
	Inhalers	-37.915	26959.320	.000	1	.999	.000	.000	.
	Primary_bil	-.329	24535.838	.000	1	1.000	.720	.000	.
	Overactive bladder	15.919	48346.595	.000	1	1.000	8198128.193	.000	.
	Topical	-15.010	25913.686	.000	1	1.000	.000	.000	.
	Gabapentin	16.418	21494.346	.000	1	.999	13495332.961	.000	.
	Other drugs	-2.477	18770.153	.000	1	1.000	.084	.000	.
	Constant	1.099	.816	1.810	1	.178	3.000		

. a. Variable(s) entered on step 1: Hydroxychloroquine, Pilocarpin, Supplements, Antidepressant, Immunosuppressant, Anticoagulants, Antihistamine, Hyperthyroidism, Hypothyroidism, Antibiotics, Blood pressure, Pain relief, Stomach acid, Hypoglycaemic, Inhalers, Primary_bil, Overactive bladder, Topical, Gabapentin, Other drugs

Appendix 25

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	27
Objectives	3	State specific objectives, including any prespecified hypotheses	29
Methods			
Study design	4	Present key elements of study design early in the paper	93
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	97
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	--
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	94
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	--
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	--
		Case-control study—For matched studies, give matching criteria and the number of controls per case.	96
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	100

Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	101
Bias	9	Describe any efforts to address potential sources of bias	113
Study size	10	Explain how the study size was arrived at	114
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	100
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	115
		(*b*) Describe any methods used to examine subgroups and interactions	117
		(*c*) Explain how missing data were addressed	117
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	--
		Case-control study—If applicable, explain how matching of cases and controls was addressed	96
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	none
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	119
		(b) Give reasons for non-participation at each stage	119
		(c) Consider use of a flow diagram	119
Descriptive data	14*	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders	121
		(b) Indicate number of participants with missing data for each variable of interest	119
		(c) *Cohort study*—Summarise follow-up time (e.g., average and total amount)	---

Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	---
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	121
		Cross-sectional study—Report numbers of outcome events or summary measures	---
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	123
		(*b*) Report category boundaries when continuous variables were categorized	140
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Irrelevant
Other analyses	17	Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses	---
Discussion			
Key results	18	Summarise key results with reference to study objectives	194
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	194
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	195
Generalisability	21	Discuss the generalisability (external validity) of the study results	194
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	26

Appendix 26

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Primary Sjögren's syndrome impact on smell, taste, sexuality and quality of life in female patients: A systematic review and meta-analysis

Minan Y. Al-Ezzi, Neha Pathak, Anwar R. Tappuni & Khalid S. Khan

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ORIGINAL ARTICLE

Primary Sjögren's syndrome impact on smell, taste, sexuality and quality of life in female patients: A systematic review and meta-analysis

Minan Y. Al-Ezzi[1], Neha Pathak[2], Anwar R. Tappuni[1], and Khalid S. Khan[2]

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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. Standardized 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.

Keywords

Primary Sjögren's syndrome; Smell; Sexual function; Taste

History

Received 5 August 2016
Accepted 4 October 2016

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 [3,10–12]. 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-centered 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.

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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; (iv) studies that used the American European Consensus Group (AECG) criteria as a standard to categorize 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 were 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, Díaz et al. [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

Standardized 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).

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 [13,14,21]. Three studies [13,14,20] evaluated the impact of sexual dysfunction on mental health well-being by using the Hospital Anxiety and Depression Scale (HADS), and one study [21] assessed the impact of sexual dysfunction on mental health using Beck's Depression Inventory (BDI). Four studies [6,13,14,20] 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 [20] 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.

Smell and taste function

One study [6], 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

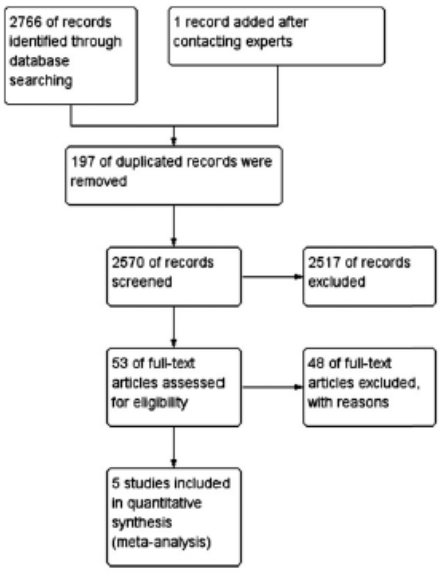

Figure 1. Studies selection process.

DOI: 10.1080/14397595.2016.1249538

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. [6]	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. [20]	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. Uguzhu et al. [21]	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. [14]	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. Prion et al. [13]	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

($p < 0.001$). 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 PSFI in three included studies [13,14,21], 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 PSFI 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 PSFI ($p < 0.00001$, 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 [6,13,14,20] 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) (Figure 2).

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.

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

	Selection						Exposure			Outcome		
Studies	Case definition	Representativeness of cases	Selection of controls	Controls definition	Sample size	Outcome was not at start of study	Comparability	Ascertainment of exposure	Same ascertainment for cases & controls	Non-response rate	Outcome assessment	Statistical analysis	Evidence quality
Kamel et al. [6]	*	–	–	–	–	*	**	*	*	–	*	*	High
Bougi et al. [20]	*	–	–	*	*	*	*	–	–	–	*	*	Moderate
Ugurlu et al. [21]	*	–	–	*	–	–	**	–	*	–	*	*	Moderate
Van Nimwegen et al. [14]	*	–	*	*	*	–	**	–	*	–	*	*	High
Prior et al. [13]	*	*	–	*	–	*	**	–	*	*	*	*	High

0–4 Poor; 5–7 moderate; 8–10 high; 11–13 very high.

Mod Rheumatol, 2017; 27(4): 623–629

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 [13,14,21]. 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 analyzed studies [13,14,21] 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 analyzed 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) [24], but is associated more with the self-reported symptoms of the syndrome as rated by the EULAR Sjögren's Syndrome Patients' Reported Index (ESSPRI) [25]. 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 summarized 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. [6]. 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 [26,27] therefore, we concluded that pSS has

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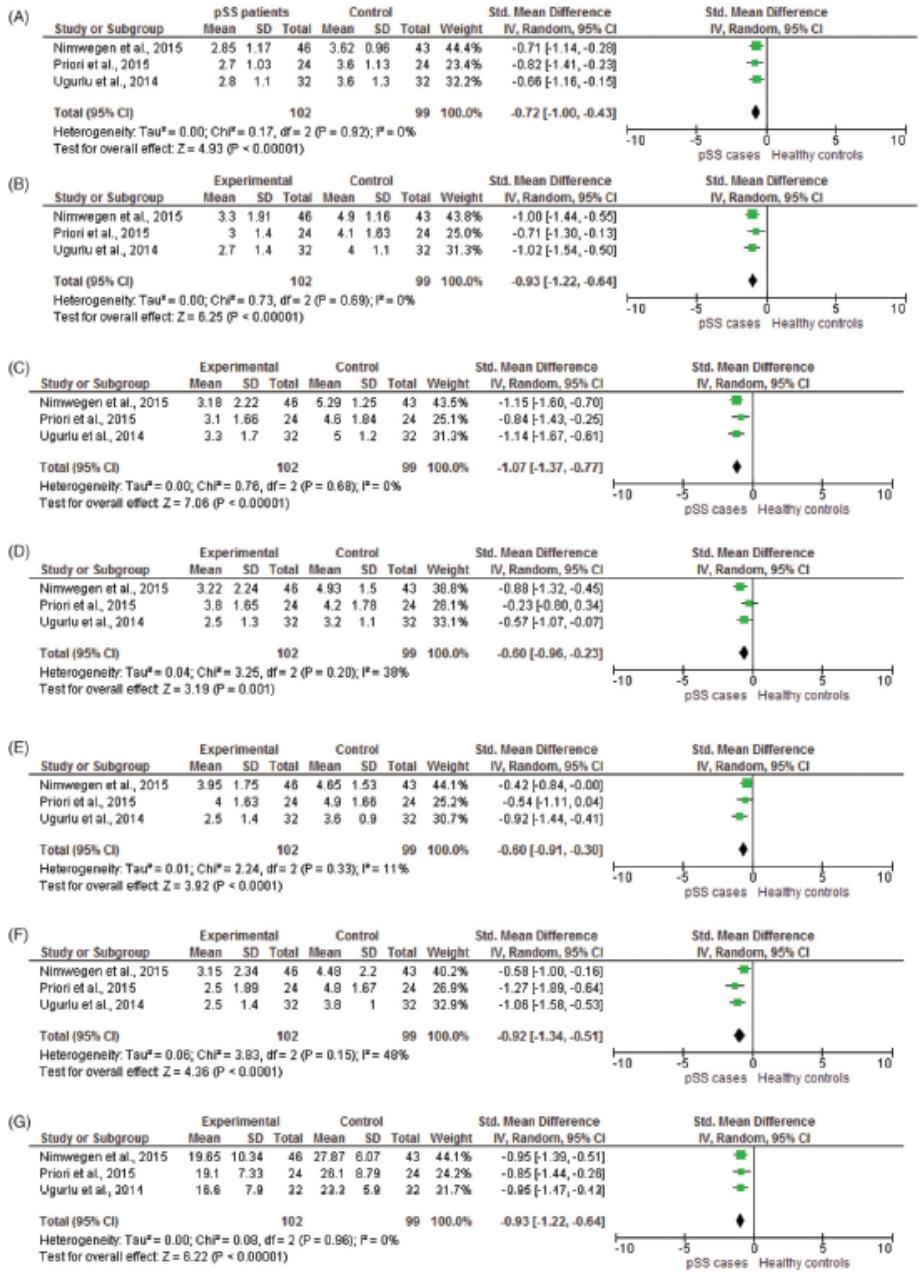

Figure 2. Forest plots of the sexual function A–G assessed by FSFI. (A) Desire, (B) Arousal, (C) Lubrication, (D) Orgasm, (E) Satisfaction, (F) Pain, and (G) total FSFI. Quality of life (H and I) assessed by SF-12, SF-36 and RAND-36, (H) Physical component, (I) Mental component. Mental health well-being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

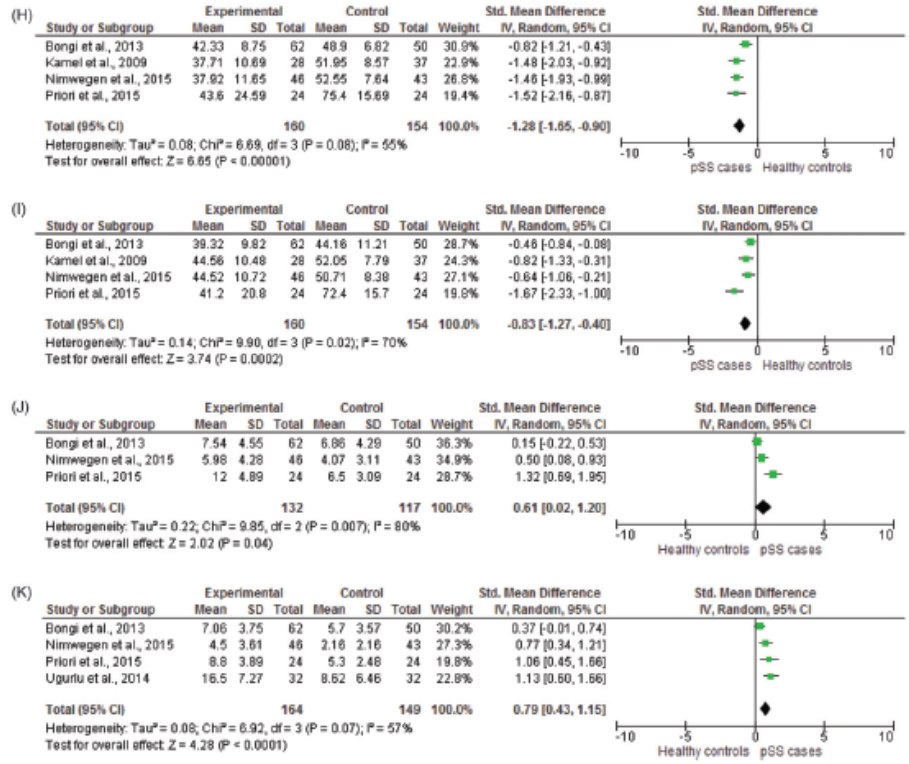

Figure 2. Continued.

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 analyzing 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.

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Conflict of interest

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Appendix 27

Table A Coefficients' table of the impact of the oral dryness assessed by USFR on the gustatory function of taste in the total population

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	15.615	1.128		13.837	.000	13.380	17.850
USSFR	2.589	.886	.241	2.922	.004	.835	4.344
Age	-.101	.018	-.468	-5.686	.000	-.136	.066
Smoking	-1.449	.986	-.103	-1.469	.145	-3.403	505
Alcohol	-.210	.486	-.103	-.432	.666	-3.403	.752
Mouthwash	-.945	.480	-.137	-1.970	.051	-1.895	005
Appliances	-.771	.645	-.086	-1.196	.234	-2.047	506

R^2=0.45

Dependent Variable: Gustatory function of taste

Table B Coefficients' table of the impact of the oral dryness assessed by SSFR on the gustatory function of taste in the total population

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	16.403	1.182		13.872	.000	14.061	18.746
SSFR	.542	.313	.145	1.733	.086	-.077	1.161
Age	-.112	.018	-.521	-6.291	.000	-.147	-.077
Smoking	-1.276	1.018	-.091	-1.254	.212	-3.292	.740
Alcohol	-.165	.502	-.024	-.328	.744	-1.160	.830
Mouthwash	-.899	.495	-.130	-1.817	.072	-1.880	.081
Appliances	-.847	.668	-.094	-1.269	.207	-2.170	.476

R^2=0.42

Dependent Variable: Gustatory function of taste

Table C Coefficients' table of the impact of the oral dryness assessed by CODS on the gustatory function of taste in the total population

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	16.418	.846		19.397	.000	14.742	18.095
CODS	-.470	.094	-.416	-5.020	.000	-.656	-.285
Age	-.076	.018	-.353	-4.319	.000	-.111	-.041
Smoking	-.724	.917	-.052	-.789	.431	-2.541	1.093
Alcohol	-.180	.456	-.026	-.394	.694	-1.083	.724
Mouthwash	-.474	.459	-.069	-1.033	.304	-1.384	.436
Appliances	-.525	.608	-.058	-.864	.389	-1.729	.679

R^2=0.51

Dependent Variable: Gustatory function of taste

Appendix 28

Beta change when the predictor is USFR and the outcome is the gustatory function of taste in pSS patients

Variables	Standardised coefficients Beta	Beta change of USFR
USFR	0.492	----
USFR, Age	0.240	0.252
USFR, Age, Mouthwash	0.237	0.003