FACULTEIT GENEESKUNDE EN GEZONDHEIDSWETENSCHAPPEN

VAGINAL DRYNESS AND SEXUAL DYSFUNCTION IN PRIMARY SJÖGREN'S SYNDROME: A SCOPING REVIEW

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I. Preface

We, Zita Goossens and Charlotte Van der Hauwaert, two medical students, have dedicated time and effort to create this master's thesis. Driven by our passion for the field of medicine, we researched this interesting subject and proudly present our work. We were grateful for the guidance and support from professionals in the field, Dr. Isabelle Peene, Prof. Dr. Hans Verstraelen and Dr. Helena Achten. Their mentorship provided us with insightful perspectives and constructive feedback that enhanced the depth and quality of our research. We would like to express our appreciation for the pleasant cooperation and the intellectually stimulating research environment they offered. We aspire for this thesis to showcase our academic journey and we're motivated to make more contributions to the field of medicine in the future.

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Abstract

Background

Primary Sjögren's syndrome (pSS) is a chronic inflammatory autoimmune disease that leads to dysfunction of the secretory glands because of lymphocytic infiltration. This results in dryness of the eyes and/or the oral cavity, called sicca symptoms. Patients also suffer from vaginal dryness and sexual dysfunction which in turn affects their quality of life.

Objective

This scoping review aimed to comprehensively map what studies have been undertaken to investigate the relationships between vaginal dryness and sexual dysfunction in adult women with pSS, both pre- and postmenopausal. Six topics were defined and covered: epidemiology, pathogenesis, methods of assessment, treatment, correlation with symptoms and determinants, and the impact on quality of life.

Materials and methods

The PRISMA guidelines for scoping review were followed and this research was registered in Open Science Framework. PubMed, Embase, Web of Science and Scopus were searched for relevant articles. No time frame was applied. All study designs in English that described pSS in adult women were included. Selection excluded studies that either did not report information about vaginal dryness or sexual dysfunction in pSS or involved minors.

Results

The study selection resulted in 50 included studies, divided over the six topics. *Methods of assessment*: questionnaires were used to assess vaginal dryness. Six different questionnaires were used to measure sexual dysfunction of which Female Sexual Function Index (FSFI) was most popular. *Epidemiology*: a higher prevalence of vaginal dryness and sexual dysfunction in women with pSS was found. *Pathogenesis*: two theories were found. The first described the relationship with peripheral neuropathy. The second theory referred to lymphocytic vasculitis. Both theories described an inhibition of the production of transudate. *Treatment*: only symptomatic treatments were advised, such as lubricants and hormone replacement therapy. A positive effect of pelvic floor training was also described. *Correlations with symptoms and determinants*: correlations between vaginal dryness and sexual dysfunction were contradictory. The majority of studies showed a correlation between vaginal dryness or sexual dysfunction and sicca symptoms. Only two out of six studies found an association between EULAR Sjögren's Syndrome Disease Index (ESSDAI) domains and sexual dysfunction. Sexual dysfunction was positively correlated with age in six out of seven studies and with menopause in one out of two studies. One study found a correlation between vaginal dryness and age. *Impact on quality of life*: three out of four studies found a correlation between the Hospital Anxiety and Depression Scale (HADS) domains and sexual dysfunction. The results examined by the other questionnaires were contradictory.

Conclusion

This scoping review provided a broad summary of the existing literature on the aspects vaginal dryness and sexual dysfunction within pSS. Future research including larger study populations to provide more statistically supported evidence of the complex relationship between vaginal dryness, sexual dysfunction and pSS, would be useful.

Abstract (Nederlands)

Achtergrond

Het primaire syndroom van Sjögren (pSS) is een chronische inflammatoire auto-immuunziekte die leidt tot disfunctie van de exocriene klieren als gevolg van lymfocytaire infiltratie. Dit resulteert in droogheid van de ogen en/of de mondholte, de zogenaamde Sicca symptomen. Patiënten hebben ook last van vaginale droogheid en seksuele disfunctie, wat op zijn beurt invloed heeft op de kwaliteit van leven.

Doel

Deze scoping review had als doel om in kaart te brengen welke onderzoeken naar de relaties tussen vaginale droogheid en seksuele disfunctie bij volwassen vrouwen met pSS reeds werden uitgevoerd. Zes onderwerpen werden gedefinieerd en uitgebreid behandeld: epidemiologie, pathogenese, methodes van vaststellen, behandeling, correlatie met symptomen en determinanten, en de invloed op de kwaliteit van leven.

Materialen en methoden

De PRISMA-richtlijnen voor scoping reviews werden gevolgd en dit onderzoek werd geregistreerd in Open Science Framework. Relevante studies werden gezocht op PubMed, Embase, Web of Science en Scopus. Er werd geen tijdsbestek toegepast. Alle Engelstalige studies die pSS bij volwassen vrouwen beschreven werden geïncludeerd. Studies die geen informatie gaven over vaginale droogheid of seksuele disfunctie bij pSS of waarbij minderjarigen betrokken waren, werden uitgesloten van de selectie.

Resultaten

De screening resulteerde in 50 geïncludeerde onderzoeken, verdeeld over de zes onderwerpen. *Methodes van vaststellen*: er werden vragenlijsten gebruikt om vaginale droogheid te beoordelen. Ook werden zes verschillende vragenlijsten gebruikt om seksuele disfunctie te meten, waarvan de Female Sexual Function Index (FSFI) de meest populaire was. *Epidemiologie*: er werd een hogere prevalentie van vaginale droogheid en seksuele disfunctie bij vrouwen met pSS gevonden. *Pathogenese*: er werden twee theorieën gevonden. De eerste beschreef de relatie tussen vaginale droogte en perifere neuropathie. De tweede theorie verwees naar lymfocytaire vasculitis. Beide theorieën beschreven een remming van de productie van transsudaat. *Behandeling*: er werden alleen symptomatische behandelingen geadviseerd, zoals glijmiddel en hormonale substitutietherapie. Er werd ook een positief effect van bekkenbodemtraining beschreven. *Correlaties met symptomen en determinanten*: correlaties tussen vaginale droogheid en seksuele disfunctie waren tegenstrijdig. De meerderheid van de onderzoeken toonde een correlatie tussen vaginale droogheid of seksuele disfunctie en Sicca symptomen. Slechts twee van de zes onderzoeken vonden een verband tussen de EULAR Sjögren's Syndrome Disease Index (ESSDAI) domeinen en seksuele disfunctie. Seksuele disfunctie was positief gecorreleerd met leeftijd in zes van de zeven onderzoeken en met menopauze in één van de twee onderzoeken. Eén onderzoek vond een verband tussen vaginale droogheid en leeftijd. *Impact op levenskwaliteit*: drie van de vier onderzoeken vonden een correlatie tussen de domeinen van de Hospital Anxiety and Depression Scale (HADS) en seksuele disfunctie. De resultaten van de andere vragenlijsten waren tegenstrijdig.

Conclusie

Deze scoping review gaf een brede samenvatting van de bestaande literatuur over de aspecten vaginale droogte en seksuele disfunctie binnen pSS. Toekomstig onderzoek met grotere onderzoekspopulaties om meer statistisch onderbouwd bewijs te leveren van de complexe relatie tussen vaginale droogheid, seksuele disfunctie en pSS, zou nuttig zijn.

1. Introduction

1.1 Sjögren's Syndrome

Sjögren's syndrome (SS) is a chronic inflammatory autoimmune disease leading to dysfunction of the secretory glands due to lymphocytic infiltration, resulting in dryness of the eyes and/or oral cavity. The following cluster of symptoms: dryness of the eyes, oral cavity, pharynx, larynx and/or vagina, is known as sicca syndrome. Primary Sjögren's syndrome (pSS) is not associated with other diseases and therefore differentiated from secondary Sjögren's syndrome (sSS), which is presented with previous or current underlying autoimmune disease, such as rheumatoid arthritis, lupus erythematosus or systemic sclerosis. This review focuses on pSS of which the prevalence rate is 0.1 to 4.8% (1). The syndrome has a male: female ratio of 1:9 (2). pSS has a first peak incidence between 20 and 30 years of age and a second mid-50 years of age.

1.2 Clinical presentation

Notwithstanding sicca syndrome is the dominant clinical presentation of pSS, up to 20% of patients also develop extraglandular manifestations such as cutaneous, musculoskeletal, pulmonary, renal, hematological, gynecological, gastro-intestinal, and neurological problems. Around 5% of patients will develop lymphoma, the most severe complication of the disease (3). In addition, pSS patients often suffer from profound fatigue, anxiety, depression and impaired sexual health (4). Sexual health is, according to the World Health Organization, viewed as fundamental to the overall health and well-being of individuals, couples and families and defined as "a state of physical, emotional, mental and social well-being in relation to sexuality, and not merely the absence of disease, dysfunction or infirmity." Furthermore, gynecological symptoms such as vaginal dryness, itching, genital pain, increased susceptibility to infection and dysuria may occur as well in pSS (1,5). Although women with pSS often complain about these gynecological manifestations, they are mostly left out of consideration in the overall approach of patients with pSS.

1.3 Pathogenesis

There are several factors considered possibly responsible for the disease. Firstly, genetic predisposition for pSS has been suggested, which includes certain human leukocyte antigen allele subtypes as well as some specific gene polymorphisms (4,6–10). A second factor may be exposure to environmental factors such as Epstein-Barr virus, hepatitis C and cytomegalovirus, but no clear association has been found (4,8–10). The pathophysiology of pSS is complex and remains partly elusive. However, it is known that both the innate and the adaptive immune system are involved, reinforcing each other. T helper 1 (Th1) and T helper 17 (Th17) cells appear to be involved, activated by antigen presenting cells and initiating an immune response by releasing cytokines (4,11,12). Furthermore, the activated immune system seems to induce a type I interferon response, which in turn, contributes to the activation of autoreactive B cells with production of autoantibodies. The most common autoantibodies found in pSS patients are anti-Sjögren's syndrome A (SSA)/RO and anti-Sjögren's syndrome B (SSB)/LA, which are present in 50-70% of patients (9,11). Another important finding is the formation of ectopic germinal centers (GCs) formed by lymphoid infiltrates, in the epithelium of salivary glands (12,13). Research suggests that B cell hyperreactivity and GCs increase the risk for B cell lymphoma development. Furthermore, the epithelial cells are no longer seen as merely bystanders and target of the immune response, but also as important players in pSS pathophysiology. All these models however leave many aspects of pSS unexplained. Lastly, to understand the pathogenesis of vaginal dryness in

pSS, it is important to know the mechanisms of lubrication of the vagina. During the sexually stimulated state, the intra-vaginal moisture is the result of transudate sourced from the blood vessels in the vaginal wall and is therefore hardly originating from production of fluids by local glands. In the sexually unstimulated state, the vaginal moisture consists of a combination of this transudate and mucus from the endocervical epithelium (5). This knowledge shows that vaginal dryness in pSS is probably not caused by the destruction of local glands which is the case in salivary and lacrimal glands, and thus another explanation for the pathophysiology is needed.

1.4 Diagnosis

Patients with sicca symptoms need to pass through different disciplines such as rheumatology, dentistry, ophthalmology, radiology, and otolaryngology (14). To have a clinical diagnosis of pSS, five main items are examined based on the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) criteria. The physical examination of the eye consists of the tear composition with a Schirmer test (6,15). A measurement for xerostomia can be done by rating the unstimulated salivary flow rate. A non-invasive method such as ultrasonography of the major salivary glands can also be done. To clinically determine the diagnosis of pSS, sicca symptoms need to be reported for more than three months (6). Patients who test positive for antibodies to the anti-SSA which can be detected objectively through blood testing, are strongly suggested of having the clinical diagnosis of pSS (16) These markers are not specific for pSS as they may be present in other diseases such as systemic lupus erythematosus (14). Twenty to 40% of people diagnosed with pSS doesn't produce these antibodies (16). The severity of most common symptoms, dryness, fatigue and pain, are also assessed by the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI), a questionnaire which is often used in studies as well. A similar questionnaire, the EULAR Sjögren's Syndrome Disease Index (ESSDAI), exists for measuring disease activity in the following other organ systems: cutaneous, respiratory, renal, articular, muscular, peripheral nervous system, central nervous system, hematological, glandular, constitutional, lymphadenopathic and biological system. Furthermore, whether women with pSS suffer from vaginal dryness, is not queried or examined by default, since it's not included in EULAR or ACR criteria. Lastly, sexual dysfunction in patients with pSS is assessed by self-administered questionnaires but these are not routinely used in clinical practice. Examples of these are the Female Sexual Function Index (FSFI) and the Female Sexual Distress Scale (FSDS) (2).

1.5 Treatment

At present, there's no curative treatment available that slows progression or treats all aspects of pSS. Thus, treatment of the disease is symptomatic. Since clinical picture of pSS is variable, the treatment differs from patient to patient. It depends on disease activity and presence of extraglandular manifestations. The main aim however, improving quality of life, stays the same. EULAR drew up recommendations for the management of the disease. It starts with handling dryness, fatigue and pain followed by the treatment of extraglandular symptoms. To fight xerostomia, oral topical therapies such as saliva substitutes and other kind of stimulants are available. When this treatment does not have the desired effect, it is possible to add or transfer to pharmacological stimulation, more specifically muscarine agonists (17,18).

As quoted several times above, research on the gynecological aspect of pSS seems limited at first glance despite the frequent occurrence of vaginal dryness and sexual dysfunction in women with pSS. These gynecological symptoms possibly have an impact on the quality of life and, as a patient, it could

be a gain if this study gives a clearer answer. Further on it could be reassuring if this issue gets a place in the care plan of pSS. This scoping review aims to provide the reader with a comprehensive picture of what studies have been undertaken to investigate the relationships between vaginal dryness and sexual dysfunction in adult women with pSS, both pre- and postmenopausal. This review maps the reported research on this topic and identifies existing knowledge gaps. Six topics have been covered, including epidemiology, pathogenesis, methods of assessment, treatment, correlation with symptoms and determinants, and, ultimately, the impact on quality of life. This way, this scoping review offers to clinicians and researchers an overview of the state of the art in pSS research and points out which study directions should be followed to provide guidelines to assess, manage and treat vaginal dryness and sexual dysfunction in women with pSS.

2. Methods

The PRISMA guidelines for scoping review (19) were followed and this research was registered in Open Science Framework (20).

2.1 Eligibility criteria

To make sure no relevant studies were missed, no time frame was applied and all study designs written in the English language, were included. Only studies that described the primary version of the syndrome in adult women, both pre- and postmenopausal, were included. If no clear distinction was made between primary and secondary SS, the article was considered and assessed if valuable information could be found on pSS. Studies that did not report information about vaginal dryness or sexual dysfunction in pSS or studies involving minors were excluded.

2.2 Information sources and search strategy

The focus was put on electronic databases covering fields of health science. PubMed, Embase, Web of Science and Scopus were searched during the month of April 2023 for relevant articles and all articles were merged. Because of the limited literature on the gynecological aspect of Sjogren Syndrome, the search strategy remained broad. The following keywords were used: “Sjögren”, “vaginal dryness” and “sexual dysfunction". To make sure all articles on this topic were included, advanced search was used. A search string containing all synonyms was created in PubMed. The following synonyms for Sjögren syndrome were used: Sicca syndrome, Sjoegren syndrome, Sjögrens’s disease. The following synonyms for vaginal dryness and sexual dysfunction were used: ‘vaginal disease’, ‘sexual intercourse’, ’vulvar disease’, ‘dyspareunia’, ‘vulvodynia’. MeSH terms in PubMed and Emtree terms in Embase were used for extended search. Free text words were sought in title and abstract. The complete search strategy is described in table 1.

Table 1: search strategy

PubMed	(“Sjogren’s syndrome”[Mesh] OR "sjogren*”[TIAB] OR "sjoegren*"[TIAB] OR “sicca” [TIAB]) AND ("Sexual Dysfunction, Physiological"[Mesh] OR "Sexual Dysfunctions, Psychological"[Mesh] OR “Vagina”[Mesh] OR "Vaginal Diseases"[Mesh] OR "Dyspareunia"[Mesh] OR "Sexual Behavior"[Mesh] OR "Vulvodynia"[Mesh] OR "Vulvar Diseases"[Mesh] OR "vaginal*"[TIAB] OR "vagina*"[TIAB] OR "sexual*"[TIAB] OR "dry vagina"[TIAB] OR "vulvovaginal atrophy" [TIAB])

Embase	('sjoegren syndrome'/exp OR sicca:ab,ti OR sjoegren*:ab,ti OR sjogren*:ab,ti) AND ('vaginal dryness'/exp OR 'sexual dysfunction'/exp OR 'vagina disease'/exp OR 'dyspareunia'/exp OR 'vulva disease'/exp OR 'pyschosexual disorder'/exp OR 'female sexual dysfunction'/exp OR 'vagina* atrophy':ab,ti OR 'sexual*':ab,ti OR 'vagina* dry*':ab,ti OR 'vulva*':ab,ti OR 'sexual dysfunction':ab,ti)
Scopus	(TITLE-ABS-KEY (sjogren*) OR TITLE-ABS-KEY (sicca*)) AND (TITLE-ABS-KEY (vagina*) OR TITLE-ABS-KEY (sexual*) OR TITLE-ABS-KEY (dyspareunia) OR TITLE-ABS-KEY (vulvodynia) OR TITLE-ABS-KEY (vulvovaginal AND atrophy) OR TITLE-ABS-KEY (vulva*) OR TITLE-ABS-KEY (dry AND vagina))
Web of Science	(TS= Sicca* OR TS=sjogren* OR TS=sjoegren*) AND (TS=sexual* OR TS=dyspareunia OR TS=vagina* OR TS=vulvodynia OR TS=vulva*)

2.3 Data charting process and data items

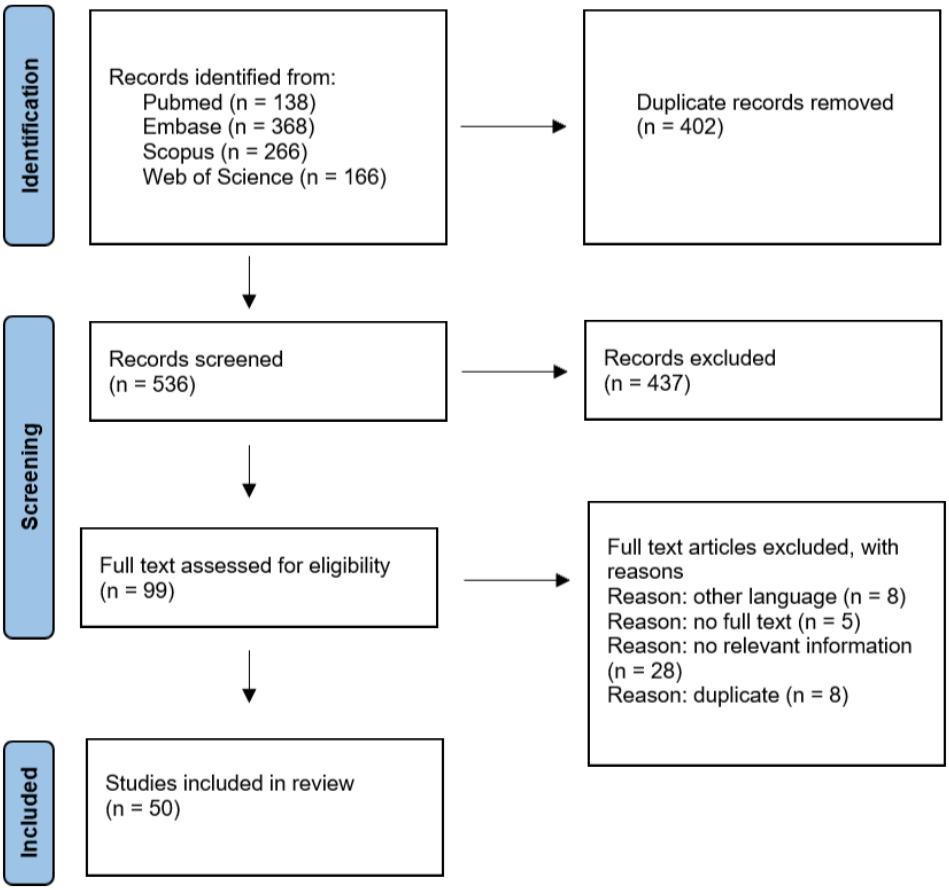
Data from 50 included studies were extracted by two reviewers independently, and subsequently merged in a predetermined Excel file (attached file 1) which was jointly, in advance developed by two reviewers (Goossens Z., Van der Hauwaert C.). When certain data of the two reviewers differed, the respective study was jointly reviewed. From each study, the following study characteristics were charted: author, year of publication, journal and its impact factor, country where the study was carried out, study design, study period, study population, total number of study participants and their age (range). The following information about the main topics: epidemiology, pathogenesis, methods of assessment and treatment of vaginal dryness and sexual dysfunction, was also charted. Furthermore, the correlation between vaginal dryness and sexual dysfunction mutually and the correlation between vaginal dryness or sexual dysfunction with symptoms such as oral and ocular dryness, the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) and the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) domains, and determinants such as age and menopause, were extracted. Lastly, the impact of vaginal dryness or sexual dysfunction on patients' quality of life was charted. The extracted information was summarized for descriptive analysis.

3. Results

3.3 Study selection

All 938 records were exported to Rayyan, and 402 duplicates were removed. Two reviewers (Goossens Z., Van der Hauwaert C.) screened the remaining 536 records independently by title and abstract and excluded 437 records that did not meet the eligibility criteria. Full text was assessed by two reviewers independently for the remaining 99 records and eligibility criteria were reapplied. Forty-nine records that did not give relevant information about vaginal dryness or sexual dysfunction, did not include pSS patients, were written in another language, had no full text or were duplicates, were removed. Disagreements on whether or not studies included relevant information were verbally resolved by consensus. The study selection resulted in 50 included studies and a flowchart is shown in figure 1.

Figure 1: Flowchart of study selection process



3.4 Study characteristics

The 50 included studies (1,2,5,21–67) are categorized in table 2. For ease of interpretation, a distinction was made in topics raised and study design. Publication year ranged from 1988 to 2023. Most studies discussed more than one topic and are therefore mentioned in multiple rows. In total, there are ten reviews, three case reports, nine case control studies, two randomised control trials (RCT) and 23 cross-sectional studies. Other study designs include: one cohort study, one comment on a case control study, one overview of treatment options and one congress abstract about an online forum. The investigations took place in 11 different countries. In total, 18 studies discussed epidemiology, 10 pathogenesis, 26 methods of assessment, 13 treatment, 24 correlations with symptoms and determinants and 21 the impact on quality of life. The total number of study participants, both pSS patients as healthy controls if present, of each study, excluding reviews, is mentioned in table 2. A summary of all study characteristics can be found in the attached file. Since the included reviews (scoping and systematic) based their investigation on articles included in this scoping review as well, they were usually not mentioned in the results below.

Table 2: study characteristics

	Review (n (ref))	Case report (n (ref (**participants-**	Case control (n (ref (**participants**	RCT (n (ref (**participants -healthy controls**))	Cross sectional study (n (ref (**participants-healthy controls**))	Other study designs (n (ref)	Total (n)

			healthy controls))	**-healthy controls**))				
1.	Epidemiology	2 (Oliveira 2021, Goules 2012)		5 (Isik 2019 (**46-47**), Isik 2017 (**46-47**), Van Nimwegen 2015 (**46-43**), Haga 2005 (**58-157**), Valtysdottir 2003 (**21-15**))		11 (McCready 2023 (**98-0**), Al-Ezzi 2022 (**65-62**), Priori 2015 (**24-24**), Bongi 2013 (**62-50**), Bowman 2009 (**35-0**), Marton 2008 (**335-0**), Saad 1999 (**28-0**), Marchesoni 1995 (**36-43**), Lehrer 1994 (**539-0**), Skopouli 1994 (**51-57**), Capriello 1988 (**26-0**))		18
2.	Pathogenesis	1 (Schoofs 2003)	2 (Mulherin 1997 (**7-0**), Tayal 1996 (**1-0**))	3 (Van Nimwegen 2020 (**9-8**), Van der Meulen 2019 (**9-8**), Van Nimwegen 2017 (**9-5**))		3 (Farenhorst 2022 (**199-0**), Bongi 2016 (**112-0**), Skopouli 1994 (**51-57**))	1 (Khan 2020)	10
3.	Methods of assessment	4 (Minopoulou 2023, Oliveira 2021, Al-Ezzi 2017, Del Rosso 2014)		6 (Van Nimwegen 2020 (**9-8**), Isik 2017 (**46-47**), Van Nimwegen 2017 (**9-5**), Yildiz 2017 (**31-27**), Van Nimwegen 2015 (**46-43**), Valtysdottir 2003 (**21-15**))	2 (Aydin 2022 (**49-0**), Van Nimwegen 2017(**52-0**))	14 (McCready 2023 (**98-0**), Giardina 2022 (**40-0**), Al-Ezzi 2022 (**65-62**), Gözüküçük 2021 (**68-132**), Cetin 2020 (**94-94**), Gonen 2019 (**23-0**), Li 2017 (**102-101**), Al-Ezzi 2016 (**65-62**), Bongi 2016 (**112-0**), Priori 2015 (**24-24**), Ugurlu 2014 (**32-32**), Bongi 2013 (**62-50**), Marton 2008 (**335-0**), Saad 1999 (**28-0**))		26
4.	Treatment	5 (Oliveira 2021, Piccioni 2020, Baer 2017, Del Rosso 2014, Schoofs 2003)	2 (Sartore 2003 (**1-0**), Tayal 1996 (**1-0**))	2 (Van Nimwegen 2020 (**9-8**), Isik 2017(**46-47**))	1 (Aydin 2022(**49-0**))	1 (Albornoz 2023 (**22-31**))	2 (McCready 2020, Fox 2012)	13

5.	Correlations with symptoms and determinants	4 (Oliveira 2021, Miyamoto 2020, Al-Ezzi 2017, Tristano 2009)		4 (Isik 2017 (**46-47**), Yildiz 2017 (**31-27**), Van Nimwegen 2015 (**46-43**), Valtysdottir 2003 (**21-15**))	1 (Van Nimwegen 2017 (**52-0**))	14 (McCready 2023 (**98-0**), Farenhorst 2022 (**199-0**), Giardina 2022 (**40-0**), Al-Ezzi 2022 (**65-62**), Cetin 2020 (**94-94**), Gonen 2019 (**23-0**), Li 2017 (**102-101**), Al-Ezzi 2016 (**65-62**), Bongi 2016 (**112-0**), Priori 2015 (**24-24**), Bongi 2013 (**62-50**), Cirpan 2007 (**33-67**), Marchesoni 1995 (**36-43**), Skopouli 1994 (**51-57**))	1 (McCready 2020)	24
6.	Impact on quality of life	4 (Miyamoto 2020, Piccioni 2020, Al-Ezzi 2017, Del Rosso 2014)		3 (Isik 2019 (**46-47**), Isik 2017 (**46-47**), Van Nimwegen 2015 (**46-43**))		13 (McCready 2023 (**98-0**), Farenhorst 2022 (**199-0**), Giardina 2022 (**40-0**), McCoy 2022 (**2961-0**), Al-Ezzi 2022 (**65-62**), Gözüküçük 2021 (**68-132**), Gonen 2019 (**23-0**), Li 2017 (**102-101**), Al-Ezzi 2016 (**65-62**), Priori 2015 (**24-24**), Ugurlu 2014 (**32-32**), Bongi 2013 (**62-50**), Bowman 2009 (**35-0**))	1 (McCready 2020)	21

3.5 Findings from the selected publications

3.5.1 Methods of assessment

As shown in table 3, the symptom vaginal dryness was self-reported by participants in most studies (23,25–29,32,34–36,46,56,60). One study from Van Nimwegen *et al.* used a numeric rating scale (range 0-10) which participants had to fill in (41,42). Furthermore, two studies from the same research team used the vaginal health index (VHI) which was assessed by gynaecologists, and which included five domains: elasticity of the vaginal mucosa, fluid secretion, pH, appearance of the epithelial mucosa, and moisture. Each of these domains was scored on a scale of 1 to 5, resulting in a score of 5-25. Low scores (≤ 15) corresponded to low vaginal health (42,43). Furthermore, Bongi *et al.* measured, aside from subjective vaginal dryness, objective genital dryness as well. Although, no mention was made of how this measurement was carried out (46).

Sexual dysfunction was assessed using questionnaires. Several questionnaires emerged, but one called Female Sexual Function Index (FSFI) was clearly most popular as it was used in 14 different studies (1,2,21,24,27–29,41,42,44,48,49,52,53,55–57). The validated FSFI measured sexual functioning over

the last 30 days and consisted of the following six domains: desire, arousal, lubrication, orgasm, sexual function and pain. These domains were scored between 0 or 1 and 6, resulting in a score of 2-36. Higher scores indicated a more optimal sexual functioning.
A second validated questionnaire called the Female Sexual Distress Scale (FSDS) was used in 2 studies, on top of FSFI, to measure sexually related levels of distress in patients with sexual dysfunction (2,27). FSDS consisted of 13 questions scored on a scale 0-4. A score of 11 or more discriminates between women with sexual distress and no sexual distress.
Del Rosso *et al.* (50) and Bongi *et al.* (30) assessed sexual dysfunction by the Hill Questionnaire which was originally created to evaluate the impact of rheumatoid arthritis on sexual activity, relationships with a partner and communication about sex issues. Both studies modified the questionnaire to one that is applicable for women with pSS but was not validated yet. Bongi and colleagues executed this by adding four questions to the questionnaire investigating the presence of a sexual relationship and the influence of the disease on frequency of intercourse and satisfaction and pleasure during sexual activity. Del Rosso *et al.* didn't mention how the questionnaire was modified.
Fourthly, Giardina *et al.* translated, from French into Italian, and adapted the Qualisex questionnaire, originally created for Rheumatoid Arthritis patients, to one for women with pSS. This 10-question numeric rating scale (range 0-10) questionnaire tested the sexual function over the last three months. Higher scores indicated a greater negative impact of pSS on sexual functioning. The study does not describe a detailed explanation about the adaptations but the Italian version of the Qualisex questionnaire was validated and considered a reliable and useful tool (51).
Fifthly, Valtysdottir *et al.* measured sexual life of patients with the Swedish version of the McCoy Female Sexuality questionnaire (MFSQ), which covers sexual experience and responsiveness during the past 30 days. This validated questionnaire was originally designed to discover if and how female sexuality is affected by changing sex hormone levels during menopausal transition (26).
Lastly, a study carried out by Gonen *et al*, investigated the relation between pelvic floor and sexual dysfunction and evaluated sexual life by the Pelvic Organ Prolapsed/Urinary Incontinence Sexual Questionnaire (PISQ-12), specifically designed for women with pelvic floor disorders. The questionnaire measures three domains, behavioural-emotive, physical, and partner-related and the 12 responses range from 0 (always) to 4 (never) (54).
A summary of methods of assessment and its number of uses can be found in table 3.

Table 3: methods of assessment of vaginal dryness and sexual dysfunction

	Number of uses	**Reference**
Vaginal dryness		
Self-reported	13	McCready 2023, Al-Ezzi 2022, Isik 2019, Bongi 2016, Priori 2015, Bongi 2013, Márton 2008, Haga 2005, Valtysdottir 2003, Sartore 2003, Saad 1999, Marchesoni 1995, Lehrer 1994
Numeric rating scale	1	Van Nimwegen 2020
Vaginal health index	2	Van Nimwegen 2020, Van Nimwegen 2017
Sexual dysfunction		
FSFI	14	McCready 2023, Aydin 2022, Al-Ezzi 2022, Gözüküçük 2021, Cetin 2020, Van Nimwegen 2020, Isik 2017, Li 2017, Van Nimwegen 2017, Yildiz

		2017, Priori 2015, Van Nimwegen 2015, Ugurlu 2014
FSDS	2	McCready 2023, Van Nimwegen 2015
Hill questionnaire	2	Del Rosso 2014, Bongi 2013
Qualisex	1	Giardina 2022
McCoy scale	1	Valtysdottir 2003
PISQ-12	1	Gonen 2019

3.5.2 Epidemiology

The epidemiology of vaginal dryness, sexual dysfunction and dyspareunia was extracted from the included articles and all percentages can be found in table 4. The method of assessment, how the study got to this percentage, was also added in table 4.

The prevalence of vaginal dryness varied across different studies that mentioned this aspect (23–30,32,34–36,42,46). Both controlled and uncontrolled studies were included in this scoping review as seen in table 4. The prevalence of vaginal dryness in healthy controls ranged from 12.5% to 33%, and from 18.1% to 92.9% among women with pSS. A study of Marchesoni *et al.* studied 36 pSS patients, 18 pre- and 18 postmenopausal, and 43 healthy controls. They found that vaginal dryness was present in 18% of premenopausal pSS patients and in 47% of postmenopausal pSS patients (35). Capriello *et al.* found that 9 out of 17 premenopausal patients and all 9 postmenopausal patients suffered from vaginal dryness (38). Isik *et al.* investigated premenopausal women only and showed a prevalence of 80.4% in women with pSS compared to 8.5% in women without pSS.

Secondly, it became clear that sexual dysfunction is more common in patients with pSS compared to healthy women. As previously mentioned for vaginal dryness, both controlled as uncontrolled studies were performed. The prevalence of sexual dysfunction among women with pSS, mostly measured by FSFI, ranged from 36.3% to 89% (2,24,27,28,33,41)

Lastly, a few articles examined the prevalence of dyspareunia, a common symptom of sexual dysfunction, which ranged from 28.6% to 100% (24,26,29,35,37,42,46). Whether this symptom was present was questioned through self-administered questionnaires or in one of the domains of the questionnaires of sexual dysfunction, such as FSFI or the McCoy Scale. Four studies were controlled, and the prevalence in healthy controls ranged from 25% to 39% (29,35,37,42). Capriello *et al.* distinguished between pre- and postmenopausal patients and concluded dyspareunia was present in 70.6% (n=17) and in 66.6% (n=9) respectively (38). Skopouli *et al.* made the same distinction and found a prevalence of dyspareunia in 40% of premenopausal patients, compared to 58.6% in postmenopausal patients (37). Marchesoni *et al.* differentiated both groups as well and observed significantly more dyspareunia in postmenopausal patients compared to premenopausal patients (35)

Table 4: epidemiology of vaginal dryness, sexual dysfunction and dyspareunia and its method of assessment

	pSS	**Healthy controls**	**Method of assessment**	**Reference**
Vaginal dryness	92.9%	-	Self-reported	McCready 2023
	87.0%	-	Self-reported	Al-Ezzi 2022
	55.6%	12.5%	Numeric rating scale	Van Nimwegen 2020
	63.0%	31.0%	Self-reported	Işik 2019

	80.4% (premenopausal)	8.5% (premenopausal)	Self-reported	Işik 2017
	61.9%	-	Self-reported	Bongi 2016
	87.5%	-	Self-reported	Priori 2015
	56.4%	28%	Self-reported	Bongi 2013
	14.0%	-	Self-reported	Màrton 2008
	52.9%	28.3%	Self-reported	Haga 2005
	59.0%	-	Self-reported	Valtysdottir 2003
	18.1%	-	Self-reported	Saad 1999
	52.0%	33.0%	Self-reported	Marchesoni 1995
	76.0%	-	Self-reported	Lehrer 1994
Sexual dysfunction	85.2%	-	FSFI	McCready 2023
	82.1%	33.3%	FSFI	Al-Ezzi 2022
	66.2%	-	FSFI	Gözüküçük 2021
	80.4%	38.5%	FSFI	Işik 2017
	89.0%	-	FSFI	Van Nimwegen 2017
	56.0%	-	FSFI	Van Nimwegen 2015
Dyspareunia	100.0%	25.0%	Domain of FSFI	Van Nimwegen 2020
	57.0%	-	Domain of FSFI	Işik 2017
	28.6%	-	Self-administered questionnaire	Bongi 2016
	79.2%	33.3%	Domain of FSFI	Priori 2015
	53.0%	-	Domain of McCoy Scale	Valtysdottir 2003
	56.9%	36.8%	Self-administered questionnaire	Skopouli 1994
	61.0%	39.0%	Self-administered questionnaire	Marchesoni 1995

3.5.3 Pathogenesis

Firstly, relevant knowledge was brought by Schoofs *et al.* saying that vaginal atrophy, when the vaginal epithelium becomes thinner and less elastic, leads to vaginal dryness and is a normal evolution in healthy perimenopausal and postmenopausal women. This is due to lack of oestrogens and occurs independently of pSS (39). Lack of oestrogens cannot be the only cause of vaginal dryness in women with pSS, since vaginal dryness appears in both pre- as postmenopausal patients (42).

Furthermore, a study performed by Van der Meulen and colleagues indicated that the vaginal microbiota composition, mainly lactobacilli, was not affected by the disease in nine premenopausal pSS patients, claiming that pSS-associated vaginal dryness does not negatively influence the homeostasis of the vaginal ecosystem. However, in postmenopausal women, both healthy and those with pSS, a difference was observed in the vaginal microbiota composition. The cause may be the loss of oestrogen in postmenopausal women. To clarify, in premenopausal women, glycogen is deposited in the epithelium of the vagina under the influence of oestrogen and degraded to lactic acid by lactobacilli. This contributes to the vaginal pH and this way inhibits the growth of other bacteria (45).

A first theory on the pathogenesis of vaginal dryness was initiated by Farenhorst *et al*. who investigated the relationship between vaginal dryness and other clinical parameters in 199 pSS patients. They claimed to have found an association between peripheral neuropathy, measured by the Sjögren's Syndrome Disease Damage Index (SSDDI), and vaginal dryness. 16 patients with peripheral neuropathy showed a higher severity of vaginal dryness (5). During sexual arousal in healthy women, the activated

central nervous system stimulates the peripheral nerves in the vaginal wall to secrete certain neuropeptides, nitric oxygen and vasoactive intestinal peptide, which cause vasodilatation of the vessels. This increases the vaginal blood flow which in turn provides genital vasocongestion and increases the production of transudate. When women with pSS suffer from peripheral neuropathy, vasodilation may not occur properly, and the production of transudate remains absent or limited (5).

A second theory claims that vascular dysfunction caused by lymphocytic vasculitis in the vaginal wall is responsible for vaginal dryness. Skopouli *et al.* did a histological examination of the vaginal mucosa in four women with pSS and showed an inflammatory lymphocytic infiltration of the underlying stroma, which was more prominent around the vessels (37). Bongi *et al.* showed an inflammatory infiltrate as well in 100% (n=21) of the biopsies taken from women with pSS. According to their findings, the infiltration was composed by T lymphocytes (CD3+), sparse CD20+ B cells and mean CD4:CD8 T-cell ratio of 1.5 (46). A third research group examining this subject, Van Nimwegen *et al.*, found a peri-epithelial infiltration in the vaginal wall of four pSS patients. More specifically, their finding included a higher number of CD45+ cells. The lymphocytic infiltrate would damage capillaries and post-capillary venules and interfere with the production of transudate. Furthermore, Van Nimwegen *et al.* suggested that an interferon-induced chemokine, CXCL10, is involved in the migration of lymphocytes to the vaginal wall. Increased levels of this chemokine were already reported in samples of saliva, tear fluid and serum. Therefor a dominant role of this chemokine in the pathogenesis of oral, ocular and vaginal dryness is suspected. A third important finding of Van Nimwegen and colleagues was the observation of lower numbers of vascular smooth muscle cells in the vaginal wall of their pSS patients. Given the important role of these cells in the regulon of blood flow, a decrease possibly disturbs the production of transudate (43).

3.5.4 Treatment

The same variety of therapeutic approaches were used for both vaginal dryness and sexual dysfunction. Firstly, the most common treatment were non-hormonal vaginal lubricants of which the use was mentioned in six studies (2,21,24,39,42,67).Only one study investigated the effect of non-hormonal vaginal lubricants and found a positive correlation with sexual function according (24). Fox *et al.* created guidelines and advised the use of water-soluble and non-irritating sterile lubricants (63). Other examples of lubrication were vit E oil and olive oil, used in and around the vagina, which effectively helped against vaginal dryness (68). Schoofs *et al.* mentioned Polycarbophil, found in a vaginal moisturizer, in their review which worked effectively for 72 hours by releasing water. This way the epithelial cells rehydrated, and vaginal moisture could be maintained (39). The last form of lubrication was Coconut oil, of which one study investigated the benefits for dyspareunia and found a significant decrease in pain during intercourse (61).

Secondly, three studies (60,63,68) discussed the use of hormone replacement therapy. Sartore *et al.* described a case of a 55-year-old woman diagnosed with pSS who initiated hormone replacement therapy, taking tibolone daily. Because of the estrogenic and androgenic activity of tibolone, a beneficial effect on vaginal and oral mucosa was seen (60). The guidelines created by Fox *et al.* also advised the use of vaginal topical oestrogen cream in peri- and postmenopausal women. Baer *et al*. mentioned in their review that topical oestrogen cream may help if the patients' symptoms didn't improve using vaginal lubricants (68).

A third treatment option was pelvic floor training of which Aydin *et al.* investigated the effect on sexual dysfunction in 49 patients with pSS. The research team observed less sexual dysfunction, measured by FSFI, among the intervention group, while the control group showed no improvement (44).
Lastly, McCready *et al.* (2020) developed a forum on which women with pSS discussed increased cognitive effort and behavioural changes regarding sexual activity in one of the themes. Many women revealed they planned sexual activity considering their symptoms and implemented self-management strategies before, during and after sexual activity (62).

3.5.5 Correlations with symptoms and determinants

This topic was divided in three main groups. Firstly, the correlation between vaginal dryness and sexual dysfunction, secondly the correlation between vaginal dryness and symptoms or determinants (sicca symptoms, EULAR Sjögren's Syndrome Disease Index (ESSDAI) criteria, age and menopause) and thirdly, the correlation between sexual dysfunction and symptoms or determinants (sicca symptoms, ESSDAI criteria, age and menopause). Sicca symptoms were objectively measured in some studies and subjectively reported by patients through the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) in other. ESSDAI criteria included total disease duration and total disease activity. In one study the peripheral nervous system was discussed. An overview of the three main groups can be found in table 5.

Vaginal dryness was often correlated with sexual dysfunction, since four research groups found a positive correlation between two parameters, saying that vaginal dryness contributed to sexual dysfunction (24,27,30,41). Conversely, three other research groups found no association between the two parameters (26,28,37).

Oral and ocular dryness, both among sicca symptoms, were independently correlated with vaginal dryness according to Farenhorst *et al.* (5) and Van Nimwegen *et al.* (41). This latter research team also established an association with ESSPRI total score (41). On the other hand, Marchesoni *et al.* alleged to have found no correlation with both lacrimal and salivary symptoms (35). Furthermore, Al-Ezzi *et al.* and research team indicated there was no correlation with oral dryness (28).
Regarding the ESSDAI domain peripheral nervous system, one study found a correlation between long-lasting peripheral neuropathy and vaginal dryness (5).
Furthermore, concerning the determinant 'age', one study (41) claimed to have found a correlation with vaginal dryness, saying older women have a higher chance to suffer from vaginal dryness.

The results concerning correlations of sexual dysfunction with sicca symptoms were inconsistent. Sexual dysfunction was associated with ESSPRI total score in 3 studies (2,41,51), of which one showed no correlation between sexual dysfunction and measured salivary and tear gland function (41). Following this, Skopouli *et al.* showed a correlation between dyspareunia and xeropthalmia, although this research team didn't find a correlation between dyspareunia and other glandular symptoms (37). Furthermore, one study showed that arthralgia/myalgia and fatigue affected the sexual ability in respectively 18.4% and 21% of women with pSS (30). Lastly, McCready *et al.* (2020) developed a forum on which women with SS discussed their sexual problems and concluded that symptoms of vaginal dryness, fatigue and pain were being discussed as the most debilitating of symptoms.
Regarding ESSDAI domains, the results were contradictory. While Yildiz *et al.* concluded sexual dysfunction was associated with disease duration (52), Van Nimwegen *et al*. found an association between sexual dysfunction and ESSDAI total score in premenopausal patients only (2). Furthermore,

3 studies (29,41,51) established no correlation between sexual dysfunction and disease duration nor activity. Comparable, Skopouli *et al.* didn't find a correlation between dyspareunia and systemic manifestations (37).
Among determinants 'age' and 'menopause' there was more agreement. A positive correlation was shown between sexual dysfunction and age in 6 studies (24,27,29,41,51,55), of which one also found a correlation with menopause (51). Conversely, Skopouli *et al.* showed no correlation between dyspareunia and age nor menopause (37).

Two studies investigated other subjects, apart from abovementioned main groups, which are thought to be relevant. Firstly, Valtysdottir *et al.* claimed that higher serum levels of dehydroepiandrosteronsulfaat (DHEA-S) contributed to better sexual functioning measured by the McCoy scale, suggesting androgen levels influence the sexual function in pSS patients (26). Secondly, Cetin *et al.*, showed that pelvic floor distress, measured by the pelvic floor disability index (PFDI-20), was correlated with sexual dysfunction. In addition, pelvic floor distress was more prevalent in women with pSS compared to healthy controls and increased as the disease duration increased (53).

3.5.6 Impact on quality of life

The impact of sexual dysfunction on quality of life was measured by several different questionnaires: Hospital Anxiety and Depression Scale (HADS), Health Status Questionnaire-Short Form 36 (QoL-SF 36), Mental Fatigue Index (MFI), Maudsley Marital questionnaire (MMQ) and World Health Organisation Quality of Life questionnaire (WHOQoL-Bref). Regarding vaginal dryness and its impact on quality of life, only one study attempted to find the relation between these two, using QoL-SF 36 to measure the quality of life (5). The results, listed below, were categorized by questionnaire. An overview of the correlations between sexual dysfunction/vaginal dryness and HADS domains/QoL-SF 36 domains can be found in table 5.

Regarding the two HADS domains, depression and anxiety, there were not many conflicting results. Sexual dysfunction correlated with both depressive and anxiety symptoms in 2 studies (51,55) with depressive symptoms only according to Van Nimwegen *et al.* (2) and with anxiety only as per the results of Priori *et al.* (29). The study performed by Gözüküçük *et al.* showed no significant correlation between HADS domains and sexual dysfunction (1).

A second questionnaire, QoL-SF 36, was used and correlations were searched in six studies. This questionnaire consists of 36 questions about eight domains, physical functioning, role physical, pain, general health, vitality, social function, role emotional, and mental health. The Research and Development-36 (RAND-36) questionnaire is based on the same original questionnaire as QoL SF-36 and only differs in how some items are worded and some scale scores are calculated. Farenhorst *et al.* showed an association between vaginal dryness and domains social functioning, emotional role and general health (5). Priori *et al.* did not find a significant correlation between FSFI global score and QoL SF-36 total score (29). Conversely, a case control study by Isik *et al.* with 46 premenopausal pSS patients and 47 age-matched controls found a correlation between total FSFI score and domains physical functioning, role physical and role emotional (24). According to Gözüküçük *et al.* the only existing correlation was between physical functioning and FSFI total score (1). Furthermore, Bongi *et al.* demonstrated that women with pSS who didn't have sexual relationships or didn't feel pleasure during sexual activity, showed lower scores in physical functioning, role physical, pain, and general health of QoL-SF 36 questionnaire, but they found no correlation with the other 4 domains (30). Lastly,

Van Nimwegen *et al.* only found an association between FSDS total score and RAND-36 domain mental health (2).

Van Nimwegen *et al.* also showed a positive correlation between all domains of a third questionnaire, MFI, and FSDS total score (2). MFI is a 20-item scale designed to evaluate five dimensions of fatigue: general fatigue, physical fatigue, reduced motivation, reduced activity, and mental fatigue.
Furthermore, an association was found between FSDS total score and relationship satisfaction, measured by Maudsley Marital questionnaire (MMQ)(2). This 20-item scale evaluates satisfaction with sexual contact, relationships, and life in general.

Lastly, Al-Ezzi *et al.* showed a significant correlation between sexual function in sexually active women with pSS and social domain of WHOQoL-Bref, while no such correlation was observed with the two other domains of the questionnaire, physical and psychological (28).

Table 5: Correlations between vaginal dryness and sexual dysfunction, correlations between vaginal dryness/sexual dysfunction and sicca symptoms/ESSDAI criteria/age/menopause, correlations between vaginal dryness/sexual dysfunction and HADS domains/QoL-SF 36 domains. Sicca symptoms were objectively measured or subjectively reported by patients through ESSPRI.

		Vaginal dryness (number of positive correlations/total number of studies)	**Sexual dysfunction (number of positive correlations/total number of studies)**
Sicca symptoms	ESSPRI	1/1	3/3
	Oral dryness	2/4	1/2
	Ocular dryness	2/3	2/2
ESSDAI		Peripheral neuropathy: 1/1	2/6
Gynaecological aspects	Vaginal dryness	-	4/7
	Sexual dysfunction	4/7	-
	Age	1/1	6/7
	Menopause	-	1/2
Quality of life	HADS Anxiety	-	3/4
	HADS Depression	-	3/4
	QoL-SF 36/RAND-36 total score	0/1	0/4
	Domain physical functioning	0/1	2/4
	Domain role physical	0/1	2/4
	Domain pain	0/1	1/4
	Domain general health	1/1	1/4
	Domain vitality	0/1	0/4
	Domain social function	1/1	0/4
	Domain role emotional	1/1	1/4
	Domain mental health	0/1	0/4

4. Discussion

By broadly summarising the existing literature, this scoping review allowed defining and yielding clarity on the following six aspects of vaginal dryness and sexual dysfunction in women with pSS: epidemiology, methods of assessment, pathogenesis, treatment, correlations with symptoms and

determinants and impact on quality of life. The main observations and current knowledge gaps within these aspects were further discussed below.

Several key findings regarding epidemiology were revealed. First, it became apparent that women with pSS suffer more often from vaginal dryness and sexual dysfunction, since every controlled study came to a higher prevalence of sexual dysfunction and vaginal dryness in women with pSS. However, the prevalences found varied widely. A reason may be the differences in study population which was determined by the classification criteria for pSS. These classification criteria have changed greatly over the past three decennia. Since the oldest study investigating epidemiology dates from 1994 and the newest one from 2023, varying prevalences may have occurred. Another reason may be the difference in sample size, which ranged from 21 to 539 included women with pSS. Furthermore, vaginal dryness in aroused state was not differentiated from vaginal dryness in non-aroused state, although this is clinically relevant. Second, two studies made a distinction between pre- and postmenopausal patients with pSS and showed a higher prevalence of vaginal dryness in postmenopausal women compared to premenopausal women. In addition, a correlation was found by Van Nimwegen *et al.* between age and vaginal dryness (41). These observations combined suggest that a higher age may be a predisposing factor for vaginal dryness, which is plausible since vaginal atrophy is a normal phenomenon in postmenopausal women. The same reasoning can be followed for sexual dysfunction, since 6 out of 7 studies found a correlation between age and sexual dysfunction. The fact that prevalence of sexual dysfunction was higher in postmenopausal patients further corroborates this (35,37). Conflicting with this, Capriello *et al.* showed the prevalence of sexual dysfunction was just slightly higher in premenopausal patients compared to postmenopausal patients. It should be noted though, that the sample size in the latter study was very small, hence these data need to be interpreted with caution.

Regarding methods of assessment, vaginal dryness was often self-reported which is subjective but provides relevant information about how women with pSS perceive this symptom. Although again, no distinction was made between vaginal dryness during aroused and non-aroused state. The vaginal health index used by Van Nimwegen *et al.* tried to objectify vaginal dryness and may be a relevant addition to the subjective measurement (41,42). A study by Gabrieli *et al.* claimed that the modified Shirmer test can be used as an objective measurement for vaginal dryness. In this test, a paper strip is placed on the vaginal opening and fluid amount is measured by the length of the moistened area of the strip (69). This study was not included in this scoping review since the study population did not include women with pSS. Further research evaluating the modified Shirmer test in women with pSS may be relevant, so the test can be used in clinical practice. Secondly, sexual dysfunction was measured by a variety of questionnaires, of which FSFI was most popular. This questionnaire is considered the golden standard to diagnose sexual dysfunction, likely because of its clear wording, scale structure, psychometric properties, and brevity (3). The Hill Questionnaire and Qualisex were specially designed for women with rheumatic diseases, which may be an advantage. However, the adapted Hill questionnaire is not yet validated and the adapted Qualisex questionnaire is only available in Italian. Consequently, both questionnaires can't be applied in clinical practice yet. The McCoy scale used by Valtysdottir *et al.* seems less interesting since it was originally designed for menopausal women, whereas a big part of women with pSS are premenopausal (26). To the best of our knowledge, there was no study comparing the questionnaires to assess sexual dysfunction in women with pSS. Hence, this may be relevant for further research.

The pathogenesis of vaginal dryness in pSS was largely subject of research from a single team from the University of Groningen in The Netherlands. They raised two findings. The first described an association between peripheral neuropathy and vaginal dryness, found in a sample size of 199 women with pSS. Yet only an association was proven so far, and the postulated hypothesis warrants further research. A second finding concerned a lymphocytic vasculitis in the vaginal wall, prominently around the blood vessels, which is thought to inhibit the passage of transudate. This was also shown by Skopouli *et al.* (37) and Bongi *et al.* (46) by histological examinations. Nonetheless, there was a difference in the composition of lymphocytes found in the different studies. These discrepancies may be explained by the small sample sizes in all three studies. In summary, regarding pathogenesis, much remains to be fathomed. This leaves much room for further research, in which inclusion of larger study populations should be an important criterion.

The above clearly indicated that the cause of vaginal dryness in women with pSS remains elusive. As a consequence, the treatments discussed in the included studies were only symptomatic. The effects and efficacy of lubricants, such as coconut oil, have been studied, with some promising outcome, but overall, with limited to no conclusive evidence. There was no evidence of hormone replacement therapy in women with pSS. Likewise, although guidelines, such as those created by Fox *et al.* may be interesting for rheumatologists to transfer to their patients, supporting evidence is still lacking.

Attempts to correlate sexual dysfunction and vaginal dryness with each other, symptoms and determinants often led to contradictory results, showing that this mechanism is very complex. For instance, vaginal dryness could not be correlated to sexual dysfunction in every study, which may infer that vaginal dryness is not the only cause of sexual dysfunction in women with pSS. Interestingly, on the forum created by McCready *et al.*, which included more than 3000 posts, users revealed they had been abstaining from sexual activity for years, forwarding vaginal dryness, dyspareunia, fatigue, and pain as reasons. In addition, arthralgia, myalgia, and fatigue influenced the sexual abilities in approximately one fifth of women with pSS (30). However, to confirm such correlations and to uncover all risk factors for sexual dysfunction, more research is needed. In contrast, many studies showed a correlation between vaginal dryness or sexual dysfunction and sicca symptoms, suggesting vaginal dryness and sexual dysfunction may worsen when sicca symptoms are more severe. If additional examination further confirms this, severe sicca symptoms may be considered a risk factor for vaginal dryness and/or sexual dysfunction.

Regarding the impact on quality of life, three out of four studies found a correlation between the Hospital Anxiety and Depression Scale (HADS) domains, anxiety and depression, and sexual dysfunction. However, the causal hierarchy remained unclear, since depression and anxiety can contribute to sexual dysfunction, and vice versa (70). Furthermore, numerous users on the forum of McCready *et al.* discussed the difficulties they experienced during kissing, as they perceived others' kisses as too wet. Since these women also revealed feelings of guilt, burden, fear of intimacy and pain, it may be assumed there is a big emotional impact because of sexual dysfunction. However, the results of the impact on quality of life of vaginal dryness and sexual dysfunction examined by QoL-SF 36, RAND-36 and WHOQoL-Bref, were contradictory. Hence, more comprehensive studies examining the impact of these gynaecological symptoms within pSS on the quality of life are missing to date.

5. Limitations

This scoping review was limited to a survey of four databases and may therefore miss some informative reports. Furthermore, included articles were limited to those in the English language, which for this topic resulted in the exclusion of 8 articles (see figure 1).

6. Conclusion

This scoping review provided a broad summary of the existing literature detailing the relationship between pSS and vaginal dryness and sexual dysfunction. Clarity was given about the existing methods of assessment, epidemiology, pathogenesis and treatment of these symptoms in women with pSS. Information about correlations with sicca symptoms, ESSDAI criteria and other determinants and the impact on the quality of these women's lives was gathered as well. Furthermore, gaps in knowledge and deficiencies in the guiding of patients have become clear and were discussed.

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