ABSTRACT

Introduction Primary Sjögren’s syndrome (pSS) is a systemic autoimmune disorder that primarily affects the exocrine glands such as the lacrimal and the salivary glands. Dry eye disease (DED) is one of the most prevalent manifestations of pSS and is usually classified into aqueous-deficient dry eye and evaporative dry eye. Sjögren’s syndrome dry eye (SSDE) is generally described as aqueous-deficient dry eye. However, as the leading pathophysiological mechanism of evaporative dry eye, meibomian gland dysfunction (MGD) also has influence on SSDE, which has been shown in recent studies. We speculate that SSDE is more than just an aqueous-deficient dry eye. While no related systematic review and meta-analysis has been published, the present study is designed to derive a better understanding of the association between MGD and SSDE.

Methods and analysis The Preferred Reporting items for Systematic Reviews and Meta-Analysis for Protocols 2015 statement was used to prepare this protocol. PubMed, Embase, Web of Science, Cochrane Database, China National Knowledge Infrastructure and Wan Fang Database will be searched from their inception to 31 October 2021, with restrictions to publications in English or Chinese. Two reviewers will independently carry out data extraction and quality assessment. The diagnosis of pSS will meet the standard diagnostic criteria, such as American College of Rheumatology/European League against Rheumatism Classification Criteria (ACR/EULAR) or American-European Consensus Group Classification criteria (AECG), and the definition of MGD and DED will differ between studies. The quality of included studies will be judged using the Newcastle-Ottawa Quality Scale. We will carry out this meta-analysis using RevMan V.5.5.4.1. The incidence of MGD in patients with SSDE will be indicated as OR with 95% CI.

Ethics and dissemination Ethical approval is not required as this meta-analysis is performed based on published studies and does not involve human participants. The results will be published in a peer-reviewed journal.

PROSPERO registration number CRD42021226017.

INTRODUCTION

Primary Sjögren’s syndrome (pSS) is a female-dominated, systemic autoimmune disorder characterised by wide clinical manifestations, extending from exocrine gland symptoms to extraglandular involvement. As a systemic disease, multidisciplinary cooperation is required, especially from the departments of rheumatology, immunology and ophthalmology. Dry eye disease (DED) is usually classified into aqueous-deficient dry eye and evaporative dry eye. The mechanism of Sjögren’s syndrome dry eye (SSDE) currently remains unclear. In majority of the literature, SSDE is classified as aqueous-deficient dry eye, with much attention being paid to the lack of aqueous tear production. However, meibomian gland dysfunction (MGD) has been diagnosed in patients with pSS.

The International Workshop on Meibomian Gland Dysfunction defines MGD as a chronic, diffuse abnormality of the meibomian glands, commonly characterised by terminal duct obstruction or qualitative or quantitative changes in glandular secretion. As the leading pathophysiological mechanism of evaporative dry eye, MGD causes a lesion to the tear film lipid layer, affecting the rate of tear evaporation and tear hyperosmolarity, eventually triggering onset of dry eye. Currently, evidence has shown that MGD has influence on SSDE.
these premises, we speculate that SSDE is more than just an aqueous-deficient dry eye. In this protocol, we aim to perform a comprehensive review of the association between MGD and SSDE.
considered to be representative of statistical heterogeneity. I² values of <25%, 25%–50% and >50% represent low, medium and high heterogeneity. For a significant heterogeneity (I²>50%, p<0.1), a random-effect model will be selected to synthesise the data. Otherwise, a fixed-effect model will be used.

**Subgroup analysis**
Subgroup analysis will be conducted among publications with high heterogeneity including the following aspects: diagnostic criteria for pSS, study design and different evaluation tools for MGD and DED.

**Sensitivity analysis**
Sensitivity analysis will be conducted, eliminating studies one by one. Possible major source of heterogeneity may be found.

**Assessment of publication bias**
Visual assessment of funnel plot will be applied to appraise publication bias if more than 10 articles are included.

**Quality of evidence**
The Grading of Recommendations Assessment, Development and Evaluation will be used to assess the strength of evidence for each outcome and will be divided into high, moderate, low and very low level of evidence.

**DISCUSSION**
Symptoms of MGD have a significant impact on quality of life, causing not only ocular irritation, but also sequelae of ocular surface inflammation and resultant deficits in visual function. SSDE is a complicated disease that needs
multidisciplinary participation. More attention should be paid to MGD. To our knowledge, this is the first systematic review and meta-analysis to evaluate the relationship between MGD and pSS dry eye. Different types of design, diagnostic criteria for pSS and various evaluation tools for MGD and DED will give a limit to this study, which may restrict the quality of the evidence. Subgroup analysis may reduce these restrictions.

Contributors CZ designed the study protocol and registered the protocol in the PROSPERO database. CZ and QH drafted the manuscript. TH and YR will search and select studies independently, and HY with QH will extract the data and assess the quality of studies included. YG will be the third reviewer for study selection, data extraction and quality assessment. CZ and QH revised the final study. All authors reviewed and approved the final manuscript for submission.

Funding This work was supported by the Science and Technology Development Fund of the Hospital of Chengdu University of Traditional Chinese Medicine (19LW19, 18MZ12).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is credited and any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Changyan Zi http://orcid.org/0000-0001-5369-6812
Qun Huang http://orcid.org/0000-0002-0544-1273

REFERENCES
1. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II definition and classification report. *Ocul Surf* 2017;15:276–83.
2. Akpek EK, Bunya VY, Saldañha U. Sjögren’s syndrome: more than just dry eye. *Cornea* 2019;38:658–61.
3. Vijmali T, Chen FYT, Chen YT, et al. Topical administration of interleukin-1 receptor antagonist as a therapy for aqueous-deficient dry eye in autoimmune disease. *Mol Vis* 2013;19:1957–65.
4. Liew MSH, Zhang M, Kim E, et al. Prevalence and predictors of Sjögren’s syndrome in a prospective cohort of patients with aqueous-deficient dry eye. *Br J Ophthalmol* 2012;96:1498–503.
5. Jung HH, Ji YS, Sung MS, et al. Long-term outcome of treatment with topical corticosteroids for severe dry eye associated with Sjögren’s syndrome. *Chonnam Med J* 2015;51:26–32.
6. Menzies KL, Srinivasan S, Prokopich CL, et al. Infrared imaging of meibomian glands and evaluation of the lipid layer in Sjögren’s syndrome patients and non-dry eye controls. *Invest Ophthalmol Vis Sci* 2015;56:836–41.
7. Vérali C, BD, Sinizadz-J, Benitez-del-Castillo JM, et al. The international workshop on meibomian gland dysfunction: report of the definition and classification subcommittee. *Invest Ophthalmol Vis Sci* 2011;52:1930–7.
8. Vehof J, Utheim TP, Bootsma H. Advances, limitations and future perspectives on the classification and management of dry eye in Sjögren’s syndrome. *Clinical and Experimental Rheumatology* 2020;38:S301–9.
9. Chan TCY, Chow SSW, Wan KHN, et al. Update on the association between dry eye disease and meibomian gland dysfunction. *Hong Kong Med J* 2019;25:39–47.
10. Shimazaki J, Goto E, Ono M, et al. Meibomian gland dysfunction in patients with Sjögren syndrome. *Ophthalmology* 1998;105:1485–8.
11. Zang S, Cui Y, Cui Y, et al. Meibomian gland dropout in Sjögren’s syndrome and non-Sjögren’s dry eye patients. *Eye* 2018;32:1681–7.
12. Wang Y, Qin Q, Liu B, et al. Clinical analysis: Aqueous-deficient and meibomian gland dysfunction in patients with primary Sjögren’s syndrome. *Front Med* 2019;6:291.
13. Goto E, Matsumoto Y, Kamoi M, et al. Tear evaporation rates in Sjögren syndrome and non-Sjögren dry eye patients. *Am J Ophthalmol* 2007;144:81–5.
14. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
15. Iotubi C, Bombardier S, Jonsson R, et al. Classification criteria for Sjögren’s syndrome: a revised version of the European criteria proposed by the American-European consensus group. *Ann Rheum Dis* 2002;61:554–8.
16. Shiboski SC, Shiboski CH, Criswell LA, et al. American College of Rheumatology classification criteria for Sjögren’s syndrome: a data-driven, expert consensus approach in the Sjögren’s international collaborative clinical alliance cohort. *Arthritis Care Res* 2012;64:475–87.
17. Shiboski CH, Shiboski SC, Seror R, American College of Rheumatology/European League Against Rheumatism classification criteria for Primary Sjögren’s Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts. *Arthritis Rheumatol* 2016;70:35–45.
18. Beckman KA, Luchs J, Milner MS. Making the diagnosis of Sjogren’s syndrome in patients with dry eye. *Clin Ophthalmol* 2016;10:43–53.
19. Yoo Y-S, Na K-S, Kim DY, et al. Morphological evaluation for diagnosis of dry eye related to meibomian gland dysfunction. *Exp Eye Res* 2017;163:72–7.
20. Pandis N. The chi-square test. *Am J Orthod Dentofacial Orthop* 2016;150:898–9.
21. Melsen WG, Bootsma MCJ, Rovers MM, et al. Data-driven, expert consensus approach for Sjögren’s syndrome patients and non-dry eye controls. *Eur J Rheumatol* 2015;2:26–32.
22. Debray TPA, Moons KGM, Riley RD. Detecting small-study effects and funnel plot asymmetry in meta-analysis of survival data: a comparison of new and existing tests. *Res Synth Methods* 2018;9:1–50.
23. Guyatt G, Oxman AD, Akl EA, et al. Grade guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;64:383–94.
24. Sabeti S, Kheirkhah A, Yin J, et al. Management of meibomian gland dysfunction: a review. *Surv Ophthalmol* 2020;65:205–17.