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Meibomian gland dysfunction and primary Sjögren's syndrome dry eye: a protocol for systematic review and meta-analysis

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ABSTRACT

Introduction: Primary Sjögren's syndrome(pSS) is a systematic autoimmune disorder that primarily affects exocrine glands like lacrimal and salivary glands. Dry eye disease is one of the most prevalent manifestations of pSS. Sjögren's syndrome dry eye(SSDE) is generally described as aqueous-deficient dry eye. As leading pathophysiological mechanism of evaporative dry eye, meibomian gland dysfunction(MGD) also has influence on SSDE presented in the latest studies. We speculate that SSDE is more than aqueous-deficient dry eye. Due to lack of evidence-based association of MGD with SSDE, we will conduct a systematic review and meta-analysis to derive a better estimation of the connection, and investigate whether MGD has relationship with the severity of SSDE.

Methods and analysis: The Preferred Reporting items for Systematic Reviews and Meta-Analysis for Protocols(PRISMA-P) 2015 statement was used to implement this protocol. PubMed, Embase, Web of Science, Cochrane Database, China National Knowledge Infrastructure, Wan Fang database will be searched from their inception to 30 April 2021 with restriction of publications in English or Chinese. Two reviewers will independently carry out data extraction and quality assessment. Quality of included studies will be judged by the Newcastle-Ottawa Quality Scale (NOS). We will carry out this meta-analysis via RevMan V.5.4.1. The odds ratio (OR) with 95% confidence interval (CI) will be contained as primary outcome.

Ethics and dissemination: Ethical approval is not required since this meta-analysis is performed based on the published studies. The results will be published in a peer-reviewed journal.

PROSPERO registration number: PROSPERO submission under review.

Strengths and limitations of this study

- This is the first systematic review and meta-analysis to evaluate the relationship between meibomian gland dysfunction and primary Sjögren's syndrome dry eye.
- Different types of design, diagnostic criteria of pSS, and various evaluation tools of MGD and DED will give a limit to this study, which may restrict quality of the evidence.
- Subgroup analysis may decrease these restrictions.

INTRODUCTION

Primary Sjögren's syndrome(pSS) is a female dominated, systematic autoimmune disorder characterized by a widely clinical manifestations ranging from exocrine glands symptoms to extraglandular involvements. Prevalence of pSS is the second highest among rheumatic diseases, next to Rheumatoid Arthritis. As a systematic disease, multidisciplinary cooperation is required, especially department of rheumatology and ophthalmology. Dry eye disease(DED) is usually classified into aqueous-deficient dry eye due to lack of tear secretion and evaporative dry eye which results from tear evaporating too quickly.[1] The mechanism of Sjögren's syndrome dry eye(SSDE) currently remains unclear. In the majority of literatures, SSDE is described as aqueous-deficient dry eye.[2-5] The focus of SSDE turns from pathophysiology of lacrimal glands to eye lids in recent researches,[6] which is stated that meibomian gland dysfunction(MGD) is responsible for SSDE as well.

The International Workshop on Meibomian Gland Dysfunction defines MGD as a chronic, diffuse abnormality of meibomian glands that is commonly characterized by terminal duct obstruction or qualitative or quantitative changes in glandular secretion.[6] As leading pathophysiological mechanism of evaporative dry eye,[7] MGD causes a lesion to tear film lipid layer, and increased tear evaporation and tear hyperosmolarity have been observed, eventually giving rise to onset of dry eye.[8]

To date, assessment for severity of dry eye in pSS has no recognized standards.[9] Symptoms and signs/tests of tear function are included to evaluate it.[10] Nevertheless, there is a discordance between symptoms and signs in SSDE.[11] Currently, proofs have been illustrated that MGD also has influence on SSDE.[12-15] On the basis of these premises, we speculate that SSDE is more than aqueous-deficient dry eye. Owing to lack of evidence-based association of MGD with SSDE, we will conduct a systematic review and meta-analysis to derive a better estimation of the connection, and investigate whether MGD has relationship with the severity of SSDE.

METHODS

Registration

This protocol has been registered on the PROSPERO on the 13/12/2020. The Preferred Reporting items for Systematic Reviews and Meta-Analysis for Protocols(PRISMA-P) 2015 statement was used to perform this protocol.[16]

Patient and public involvement

No patient is involved in this study.

Search strategy

PubMed, Embase, Web of Science, Cochrane Database, China National Knowledge Infrastructure, Wan Fang database will be searched from their inception to 30 April 2021 by two reviewers(TH and YR) independently. Combination of Medical Subject Headings(MeSH) and free terms are utilized to search for potentially qualified publications(Table 1). Reference lists of original and review articles will be screened manually.

Table 1 Search strategy of PubMed
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#2 “Meibomian Gland Dysfunction” OR “Dysfunction, Meibomian Gland” OR “Meibomian Gland Dysfunctions” OR “MG Dysfunction” OR “MG Dysfunctions”
#3 #1 AND #2
#4 “Dry Eye Syndromes” OR “Dry Eye Syndrome” OR “Dry Eye Disease” OR “Dry Eye Diseases” OR “Dry Eye” OR “Dry Eyes” OR “Evaporative Dry Eye Disease” OR “Evaporative Dry Eye Syndrome” OR “Evaporative Dry Eye” OR “Dry Eye, Evaporative” OR “Evaporative Dry Eyes
#5 #3 AND #4

Eligibility criteria

Study design

prospective and retrospective cohort studies, case-control studies published in English or Chinese will be incorporated in this meta-analysis. In case of similar essays delivered by the same author in different journals, the latest or study with the largest number of participants will be included.

Participants

The patients with clinical diagnosed pSS connected with dry eye and meibomian gland dysfunction will be involved, regardless of age, gender and race. The diagnosis of pSS will meet standard diagnostic criteria, such as ACR/EULAR or AECG(no matter what edition it is). For lack of a diagnostic gold standard of MDG and DED currently,[17-18] appraisement of them is based on evaluation tools made by specialists.

Outcome

The primary outcome defining association of MGD and SSDE is incident of meibomian gland dysfunction in SSDE patients. The secondary outcomes estimating the severity of SSDE are tear-film break up time (BUT), Schirmer I test, corneal fluorescein staining(CFS) and ocular surface disease index (OSDI).

Study selection and data extraction

Study selection

Two reviewers(TH and YR) will independently conduct study selection. Initial screening of literatures is based on title and abstract to eliminate that cannot meet the inclusion criteria. During the process of full-text screening, all potentially eligible studies will be retrieved for inclusion. Any disagreement will be resolved by discussion. Consulting a third reviewer(YG) to reach a consensus if an agreement still cannot be reached by discussion. The study selection process is demonstrated in a PRISMA flow diagram (figure 1). Literatures meet the standards will be imported into Endnote X9.

Data extraction

The detailed data extracted in an excel spreadsheet by two researchers(HY and QH) and checked for accuracy by YG are as follows: first author's name, year of publication, country of publication, study design, sample size, age, gender, duration of pSS, duration of follow-up, diagnostic criteria, evaluation tools of MGD and DED, outcomes, quality assessment (Newcastle–Ottawa Scale). Authors of primary studies will be contacted to obtain missing data.

Quality assessment

Quality of contained studies will be estimated by two reviewers (HY and QH) with the Newcastle-Ottawa Quality Scale (NOS) adapted for observational studies. The scale awards 0-9 star based on the selection, comparability and outcome(cohort) or exposure(case-control). Studies with 0-3 stars, 4-6 stars, or 7-9 stars are considered as a low-, moderate-, or high-quality. Controversies between two reviewers will be settled by discussion or consulting YG.

Data synthesis and statistical analysis

At least 5 studies of same outcomes in similar populations will be pooled to perform the meta-analysis by RevMan V.5.4.1. Otherwise, a systematic review will be implemented. For categorical variables, the odds ratio (OR) with 95% confidence interval (CI) will be selected from publications contained or could be calculated from original data. For continuous variables, standard mean difference (SMD) with 95%CI will be obtained.

Assessment of heterogeneity

Chi-square statistic and the I^2 test are utilized to estimate the statistical heterogeneity among included studies. P□ 0.1 is considered as representative of statistically heterogeneity.[19] I^2 values of <25%, 25%-50% and >50% representing low, medium and high heterogeneity.[20] For a significant heterogeneity(I^2 □ 50%,P<0.1), a random-effect model will be selected to synthesize the data. Otherwise, a fixed effect model will be used.

Subgroup analysis

Subgroup analysis is applied to high heterogeneity among publications included with following aspects, such as age, sex, diagnostic criteria for pSS, study design, different evaluation tools of MGD and DED.

Sensitivity analysis

Eliminating literatures one by one to conduct sensitivity analysis, possible major source of heterogeneity may be found.

Assessment of publication bias

Visual assessment of the funnel plot will be applied to appraise publication bias if more than 10 articles contained.[21]

Quality of evidence

The Grading of Recommendations Assessment, Development and Evaluation(GRADE) will be used to assess the strength evidence for each outcome, which will be divided into high, moderate, low and very low level.[22]

Ethics and dissemination

Ethical approval is not required since this meta-analysis is performed based on the published studies. The results will be published in a peer-reviewed journal.

DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis to evaluate the relationship between meibomian gland dysfunction and primary Sjögren's syndrome dry eye. Different types of design, diagnostic criteria of pSS, and various evaluation tools of MGD and DED will give a limit to this study, which may restrict quality of the evidence. Yet subgroup analysis may decrease these restrictions.

Contributors CZ and QH are joint first authors.CZ designed the study protocol and registered the protocol on the PROSPERO database. CZ and QH drafted the manuscript. TH and YR will search, select studies independently, and HY with QH will extract data and assess 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.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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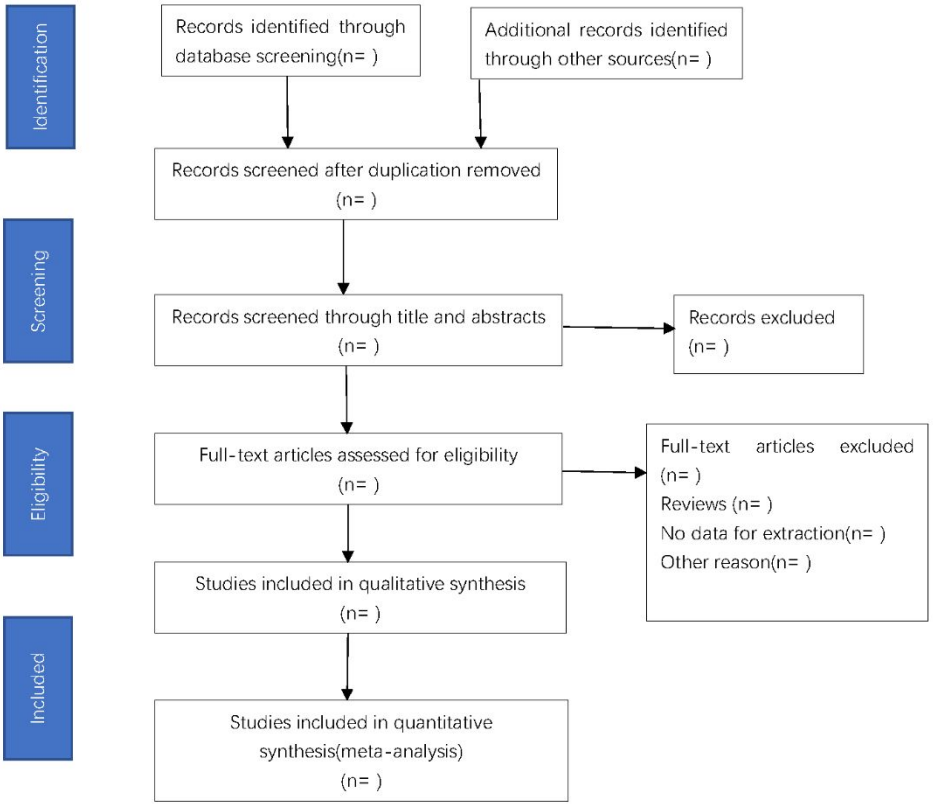

Figure 1 Flow chart and descriptions of study selection.

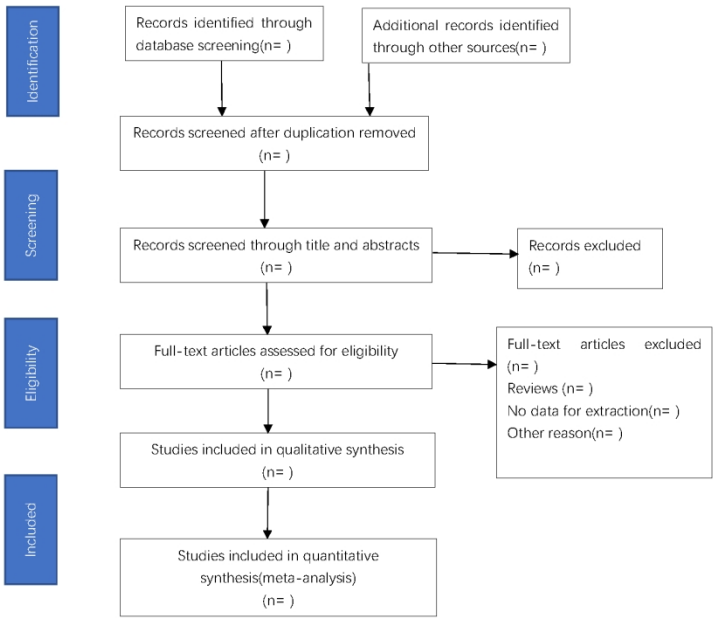

Figure 1 Flow chart and descriptions of study selection.

210x297mm (200 x 200 DPI)

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	page1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	N/A

Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	page2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	page1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	page 8
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support			
Sources	#5a	Indicate sources of financial or other support for the review	page 8
Sponsor	#5b	Provide name for the review funder and / or sponsor	page 8
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	page 8
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is	page 3

		already known	
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	page 3,5
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	page 4-5
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	page 4
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	page 4
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	page 5
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	page 5
Study records - data collection	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any	page 5-6

process		processes for obtaining and confirming data from investigators	
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	page 6
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	page 5
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	page 6
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	page 6
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	page 6
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	page 6-7
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	page 6
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within	page 7

		studies)	
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	page 7

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ABSTRACT

Introduction: Primary Sjögren's syndrome(pSS) is a systematic autoimmune disorder that primarily affects exocrine glands like lacrimal and salivary glands. Dry eye disease(DED) is one of the most prevalent manifestations of pSS and 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 leading pathophysiological mechanism of evaporative dry eye, meibomian gland dysfunction(MGD) also has influences on SSDE, which are presented in the latest studies. We speculate that SSDE is more than just aqueous-deficient dry eye. While no related systematic review and meta-analysis has been published, the present study is design to derive a better understanding of the connection between MGD and SSDE.

Methods and analysis: The Preferred Reporting items for Systematic Reviews and Meta-Analysis for Protocols(PRISMA-P) 2015 statement was used to prepare this protocol. PubMed, Embase, Web of Science, Cochrane Database, China National Knowledge Infrastructure, Wan Fang database will be searched from their inception to 31 October 2021 with restrictions of publications in English or Chinese. Two reviewers will independently carry out data extraction and quality assessment. The diagnosis of pSS will meet standard diagnostic criteria, such as ACR/EULAR or AECG. The definition of MDG and DED will differ between studies. Quality of included studies will be judged by the Newcastle-Ottawa Quality Scale (NOS). We will carry out this meta-analysis via RevMan V.5.4.1. The incidence of meibomian gland dysfunction in patients with Sjögren's syndrome dry eye will be indicated as odds ratio (OR) with 95% confidence interval (95% CI).

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

PROSPERO registration number: CRD42021226017

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INTRODUCTION

Primary Sjögren's syndrome(pSS) is a female dominated, systematic autoimmune disorder characterized by a widely clinical manifestations extending from exocrine glands symptoms to extraglandular involvements. As a systematic disease, multidisciplinary cooperation is required, especially department of rheumatology, immunology and ophthalmology. Dry eye disease(DED) is usually classified into aqueous-deficient dry eye and evaporative dry eye.[1] The mechanism of Sjögren's syndrome dry eye(SSDE) currently remains unclear. In the majority of literatures, SSDE is classified as aqueous-deficient dry eye, with much attention being paid to the lack of aqueous tear production.[2-5] However, meibomian gland dysfunction(MGD) also has been diagnosed in patients with pSS.[6]

The International Workshop on Meibomian Gland Dysfunction defines MGD as a chronic, diffuse abnormality of meibomian glands, commonly characterized by terminal duct obstruction or qualitative or quantitative changes in glandular secretion.[7] As leading pathophysiological mechanism of evaporative dry eye,[8] MGD causes a lesion to tear film lipid layer, which affects the rate of tear evaporation and tear hyperosmolarity, eventually triggering onset of dry eye.[9]

Currently, proofs have been illustrated that MGD has influences on SSDE.[10-13] On the basis of these premises, we speculate that SSDE is more than just aqueous-deficient dry eye. In this protocol, we aim to perform a comprehensive review of association between MGD and SSDE.

METHODS

Registration

This protocol has been registered on the PROSPERO on the 13/12/2020. The Preferred Reporting items for Systematic Reviews and Meta-Analysis for Protocols(PRISMA-P) 2015 statement was used to perform this protocol.[14]

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Search items
#1 "Sjogren's Syndrome" OR "Sjogrens Syndrome" OR "Syndrome, Sjogren's" OR "Sjogren Syndrome" OR "Sicca Syndrome" OR "Syndrome, Sicca"
#2 "Meibomian Gland Dysfunction" OR "Dysfunction, Meibomian Gland" OR "Meibomian Gland Dysfunctions" OR "MG Dysfunction" OR "MG Dysfunctions"
#3 #1 AND #2
#4 "Dry Eye Syndromes" OR "Dry Eye Syndrome" OR "Dry Eye Disease" OR "Dry Eye Diseases" OR "Dry Eye" OR "Dry Eyes" OR "Evaporative Dry Eye Disease" OR "Evaporative Dry Eye Syndrome" OR "Evaporative Dry Eye" OR "Dry Eye, Evaporative" OR "Evaporative Dry Eyes
#5 #3 AND #4

Eligibility criteria

Study design

prospective and retrospective cohort studies, case-control studies published in English or Chinese will be incorporated in this meta-analysis. In case of similar essays delivered by the same author in

different journals, the latest or study with the largest number of participants will be included.

Participants

The patients with clinical diagnosed pSS connected with dry eye and meibomian gland dysfunction will be involved, regardless of age, gender and race. The diagnosis of pSS will meet AECG criteria in 2002[15] or ACR criteria in 2012[16] or ACR/EULAR criteria in 2016.[17] The diagnostic tools for DED and MGD will differ between studies and be grouped into three categories: symptom questionnaires, objective ocular testing and biomarkers or other emerging diagnostic techniques.[18-19]

Outcomes

The primary outcome is incident of meibomian gland dysfunction in SSDE patients. The secondary outcomes mainly include the following aspects: tear-film break up time (BUT), Schirmer I test, corneal fluorescein staining(CFS) and ocular surface disease index (OSDI).

Study selection and data extraction

Study selection

Two reviewers(TH and YR) will independently conduct study selection. Based on title and abstract, initial screening of literatures will eliminate that cannot meet the inclusion criteria. During the process of full-text screening, all potentially eligible studies will be retrieved for inclusion. Any disagreement will be resolved by discussion. Consulting a third reviewer(YG) to reach a consensus if an agreement still cannot be reached by discussion. The study selection process is demonstrated in a PRISMA flow diagram (figure 1). Literatures meet the standards will be imported into Endnote X9.

Data extraction

The detailed data extracted in an excel spreadsheet by two researchers(HY and QH) and checked for accuracy by YG are as follows: first author's name, year of publication, country of publication, study design, sample size, age, gender, duration of pSS, duration of follow-up, diagnostic criteria,

evaluation tools of MGD and DED, outcomes, quality assessment (Newcastle–Ottawa Scale). Authors of primary studies will be contacted to obtain missing data.

Quality assessment

Quality of contained studies will be estimated by two reviewers (HY and QH) with the Newcastle-Ottawa Quality Scale (NOS) adapted for observational studies. The scale awards 0-9 star based on the selection, comparability and outcome(cohort) or exposure(case-control). Studies with 0-3 stars, 4-6 stars, or 7-9 stars are considered as a low-, moderate-, or high-quality. Controversies between two reviewers will be settled by discussion or consulting YG.

Data synthesis and statistical analysis

At least 5 studies of same outcomes in similar populations will be pooled to perform the meta-analysis by RevMan V.5.4.1. Otherwise, a systematic review will be implemented. For categorical variables, the odds ratio (OR) with 95% confidence interval (CI) will be used. For continuous variables, we will choose mean difference (MD) or standardized mean difference (SMD) with 95% CI , depending on whether the measurement scale is consistent or not.

Assessment of heterogeneity

Chi-square statistic and the I^2 test are utilized to estimate the statistical heterogeneity among included studies. $P < 0.1$ is considered as representative of statistically heterogeneity. [20] I^2 values of <25%, 25%-50% and >50% representing low, medium and high heterogeneity.[21] For a significant heterogeneity($I^2 > 50\%$,$P<0.1$), a random-effect model will be selected to synthesize the data. Otherwise, a fixed effect model will be used.

Subgroup analysis

Subgroup analysis is applied to high heterogeneity among publications included with following aspects, such as diagnostic criteria for pSS, study design, different evaluation tools of MGD and DED.

Sensitivity analysis

Eliminate literatures one by one to conduct sensitivity analysis. possible major source of heterogeneity may be found.

Assessment of publication bias

Visual assessment of the funnel plot will be applied to appraise publication bias if more than 10 articles are contained.[22]

Quality of evidence

The Grading of Recommendations Assessment, Development and Evaluation(GRADE) will be used to assess the strength evidence for each outcome, which will be divided into high, moderate, low and very low level.[23]

Ethics and dissemination

Ethical approval is not required since this meta-analysis is performed based on the published studies. The results will be published in a peer-reviewed journal.

DISCUSSION

Symptoms of MGD have a significant impact on quality of life, causing not only ocular irritation, but also the sequelae of ocular surface inflammation and resultant deficits in visual function.[24] 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 meibomian gland dysfunction and primary Sjögren's syndrome dry eye. Different types of design, diagnostic criteria of pSS, and various evaluation tools of MGD and DED will give a limit to this study, which may restrict quality of the evidence. Yet subgroup analysis may decrease these restrictions.

Contributors CZ and QH are joint first authors.CZ designed the study protocol and registered the protocol on the PROSPERO database. CZ and QH drafted the manuscript. TH and YR will search, select studies independently, and HY with QH will extract data and assess 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.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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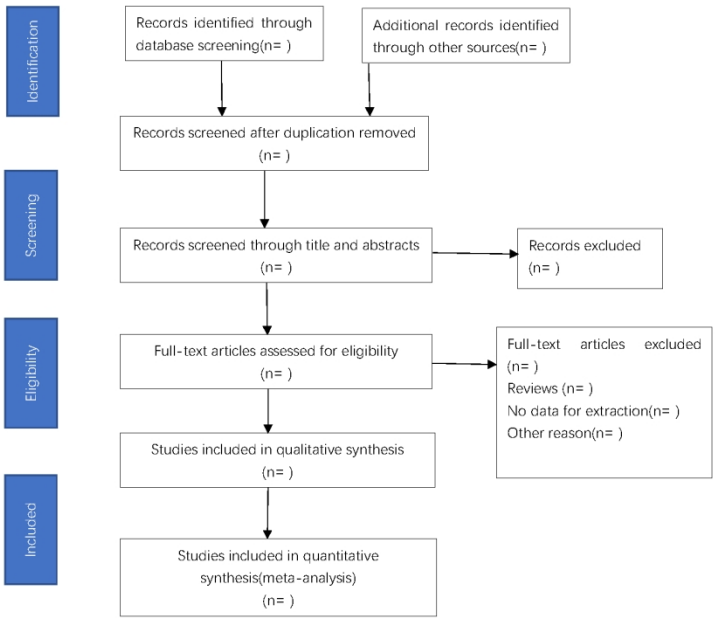

Figure 1 Flow chart and descriptions of study selection.

210x297mm (200 x 200 DPI)

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	page1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	N/A

Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	page2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	page1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	page 8
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support			
Sources	#5a	Indicate sources of financial or other support for the review	page 8
Sponsor	#5b	Provide name for the review funder and / or sponsor	page 8
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	page 8
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is	page 3

		already known	
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	page 3,5
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	page 4-5
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	page 4
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	page 4
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	page 5
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	page 5
Study records - data collection	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any	page 5-6

process		processes for obtaining and confirming data from investigators	
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	page 6
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	page 5
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	page 6
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	page 6
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	page 6
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	page 6-7
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	page 6
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within	page 7

		studies)	
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	page 7