BMJ Open

Prevalence and incidence of dry eye in the United States: a systematic review protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-056203
Article Type:	Protocol
Date Submitted by the Author:	05-Aug-2021
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Keywords:	Corneal and external diseases < OPHTHALMOLOGY, EPIDEMIOLOGY, PUBLIC HEALTH

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Title: Prevalence and incidence of dry eye in the United States: a systematic review protocol

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ARTICLE SUMMARY

Strengths and limitations of this study

- This systematic review and meta-analysis aims to report the prevalence and incidence of dry in the United States.
- We aim to overcome limitations in previous reviews of dry eye epidemiology reports.
- We will use contemporaneous data and comprehensive methods to enhance transparency and reproducibility.
- We anticipate high levels of heterogeneity in prevalence and incidence estimates, however we aim to explore the reasons for heterogeneity.
- We may rely on prevalence and incidence estimates from secondary data for epidemiological research such as electronic health records which are not primarily designed for research purposes.

ABSTRACT

Introduction: Dry eye is a multifactorial chronic condition characterized by tear film insufficiency and instability, and inflammation of the ocular surface. The prevalence and incidence of dry eye are major determinants of the magnitude of economic and societal costs of the disease. This protocol proposes a systematic review and meta-analysis of the prevalence and incidence of dry eye in the United States.

Methods and analysis: Working with an information specialist, we will develop search strategies for Ovid Medline and Embase for population-based cross-sectional and cohort studies that report the prevalence and/or incidence of dry eye. We will include studies involving persons of all ages from 1 January 2010 to the current date with no language restrictions. We will also hand-search references of included studies, dry eye epidemiology-related systematic reviews, clinical practice guidelines, and literature provided by agencies and organizations.

Two investigators will independently screen the titles and abstracts, and then full text reports to determine eligibility. One investigator will extract study data and perform risk of bias assessments using tools designed specifically for prevalence and incidence studies. A second investigator will verify all extracted study data and risk of bias assessments. We will assess heterogeneity, qualitatively and quantitatively. When appropriate, we will meta-analyse prevalence and incidence estimates.

Ethics and dissemination: This review does not require approval by an Ethics Committee because it will use published studies. We will publish our results in a peer-reviewed journal and present at relevant conferences.

Prospero registration number: ID256934 (submitted 27 July 2021)

Word Count: 3,017

Keywords: Dry eye, prevalence, incidence, epidemiology, systematic review, United States

INTRODUCTION

Dry eye disease (DED) is defined by the Tear Film and Ocular Surface Society (TFOS) Dry Eye Workshop II (DEWS-II) as "a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles."[1] Because there is no gold standard definition of DED, the term "dry eye" is used to describe various presentations of ocular discomfort and tear film abnormalities. Dry eye is frequently referred to as DED once it is clinically diagnosed.[2]

Irrespective of a clinical diagnosis of DED, dry eye causes considerable burden to patients and society. Patient burden includes decreased quality of life due to symptoms, such as foreign body sensation, itching, irritation, soreness, and visual disturbance, which interfere with reading, driving, and work productivity, and cause physical and emotional distress.[3–5] Burdens to society include direct economic costs (e.g., healthcare professional visits, treatment costs),[6] non-direct economic costs (e.g., work productivity loss),[7] and intangible personal costs (e.g., impaired social, emotional, and physical functioning).[8,9] In 2011, the estimated direct economic cost to the U.S. healthcare system for DED therapy was $3.8 billion per year and the estimated total societal cost in the U.S. was $55.4 billion per year.[6] Comparative analyses have demonstrated that DED-related costs in the U.S. are broadly comparable with other countries.[10] However, in the U.S., personal costs may be higher because treatments, such as ocular lubricants, may not be adequately covered by health insurance, and drug costs tend to be higher in the United States (US).[6,11] With introduction of newer and more costly therapies, an even larger societal economic burden of dry eye can be expected.[12,13] Furthermore, despite being a significant public health problem, dry eye remains underdiagnosed, highlighting the likelihood that there is a significant undiagnosed burden of disease.[2,14,15]

In 2017, a comprehensive epidemiology report by the TFOS DEWS-II ("TFOS epidemiology report") reviewed population-based studies that enrolled at least 500 participants to estimate the prevalence and incidence of dry eye stratified by definition of disease, age, sex, and worldwide geographical region.[16] The findings of the TFOS report showed that, globally, the prevalence of dry eye ranged from 5% to 50% with various definitions of DED.

However, in dry eye, as well as in other ophthalmic diseases, applying differing definitions of disease to epidemiological datasets can result in widely varying estimates of prevalence.[17]

In addition to disease definition, various factors may contribute to differences in prevalence of dry eye.[16] The prevalence has been reported to increase with age, especially in women.[14,16,18] To our knowledge, few studies have reported prevalence in people younger than 21 years old, and none were in US-based populations.[18–20] This lack of data is problematic because young people are also at risk of dry eye due to generally longer screen time (e.g., video monitors, digital tablets), and contact lens wear.[19] The TFOS report found no clear pattern of dry eye associated with latitude, globally.[16] However, in the US, there is indirect evidence of an association with latitude, with higher prevalence of dry eye reported in southern regions of the country.[2,14] Furthermore, other geo-environmental factors, such as higher atmospheric pressure, air pollution, humidity, and wind speed, have all been shown to be risk factors for dry eye.[21] As the US comprises an expansive land mass with great variation in climate across latitudinal and topographical regions, and given that climatic factors are influential risk factors for dry eye, it is important to consider these factors when estimating prevalence and incidence of dry eye.

The literature search for the TFOS Epidemiology report covered a 10-year period from 2005 to 2015 (last updated on September 17, 2015). However, it is unclear whether the TFOS epidemiology report strictly followed critical steps in the systematic review process, such as protocol development, risk of bias assessment, and appropriate meta-analysis.[16] Furthermore, the TFOS Epidemiology report is now relatively dated because more dry eye-related epidemiological studies have been performed in the US since its publication.[2,22]

Systematic reviews of dry eye-related epidemiology have been published for other populations and global regions but,[23,24] to our knowledge, there are no existing systematic reviews of dry eye epidemiology within the US. As the prevalence and incidence of dry eye are major determinants of the magnitude of the personal, societal, and economic costs of the disease, examining these epidemiological indices can help health policymakers estimate the burden of dry eye in the US and consequently allocate resources to risk mitigation and treatment as needed.

Primary Objective

The primary objective of this systematic review and meta-analysis is to summarize the prevalence and incidence of dry eye in persons of all ages in the US.

Secondary Objectives

1. Estimate the prevalence and incidence of dry eye in the US by disease definition, age group, sex, study location, and geo-environmental factors.
2. Assess heterogeneity in the prevalence and incidence of dry eye within the US and factors potentially explaining the heterogeneity.
3. Report epidemiological factors associated with dry eye.

METHODS AND ANALYSIS

We have registered for this systematic review protocol with the PROSPERO international register for systematic reviews (ID256934) and we report it in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) 2015 statement. We will conduct and report the review with guidance from the Joanna Briggs Institute Manual for Evidence Synthesis,[25] the Cochrane Handbook for Systematic Reviews of Interventions,[26] the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines,[27] the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) statement,[28] and a meta-epidemiological study on the assessment of prevalence study quality by Migliavaca et al.[29] Patient stakeholders have input into the development of our research strategies as part of our review group advisory board (Cochrane Eyes and Vision, National Eye Institute, National Institutes of Health, UG1EY020522).

Criteria for considering studies for this review

We used the populations, context, and condition (PCC) framework for the systematic review of prevalence and incidence to formulate the eligibility criteria.[30]

Population and Context

We will investigate the prevalence and incidence of dry eye in the US population. Prevalence is the proportion of the population with dry eye at a given time (point or period of time). Cumulative incidence is the proportion of persons in the at-risk population who develop a

new diagnosis of dry eye during a given follow-up period. Incidence rate is the number of new cases of dry eye divided by the observed person-time during a given observation period. We aim to explore the influence of demographic factors (e.g., age, sex), environmental exposures (e.g., air pollution, screen time), meteorological exposures (e.g., temperature, wind speed, relative humidity, atmospheric pressure), and underlying risk factors of disease (e.g., co-morbidities, topical and systemic medications) on these epidemiological indices.

Condition

We will use definitions of dry eye outlined in the included primary studies. We will aim to consolidate similar case definitions across studies into homogenous definitions when appropriate. In the TFOS report, case definitions of DED included: (1) Women's Health Study (WHS) criteria (i.e., self-reported physician diagnosis and/or self-reported 'constant' or 'often' symptoms),[14] (2) dry eye symptoms alone (e.g., measured by the Ocular Surface Disease Index), (3) dry eye clinical signs alone (e.g., tear break up time), (4) a combination of dry eye signs and symptoms (distinct from WHS criteria), and (5) Meibomian gland dysfunction.[16] We will also consider including the definition of dry eye based on relevant International Classification of Disease codes.

Types of Studies

We will include population-based observational studies (i.e., cross-sectional studies and cohort studies) that reported prevalence or incidence of dry eye in the US. We will not exclude studies based on characteristics such as sampling frame or sampling methods, but these will be assessed as part of the risk of bias assessment of included studies. We will exclude case reports, case series, case-control studies, and interventional studies. We will exclude population-based studies with fewer than 73 total participants because estimates from samples with less than 73 participants would produce 95% confidence intervals greater than ±0.05 when the anticipated minimum population proportion is estimated to be 0.05.[31] However, if we find studies on specific population subgroups (e.g., native Americans) that have fewer than 73 total participants we will consider them for inclusion.

Search methods for identification of studies

Electronic Searches

Working with an information specialist, we will develop search strategies for Ovid Medline, and Embase for population-based studies that report the prevalence and/or incidence of dry eye. We will include studies involving persons with all ages from 1 January 2010 to the current date with no language restrictions.

The search strategy will include text word as well as controlled vocabulary (e.g., medical subject headings, Emtree) terms for epidemiological concepts, such as “epidemiology”, “prevalence”, “incidence”, and “burden of disease”, combined with dry eye-related concepts, such as “dry eye syndromes” (see Supplementary File).

Other Sources

We will hand-search references of included studies, dry eye epidemiology-related systematic reviews, and clinical practice guidelines for additional studies. Conference abstracts will be searched as part of our electronic search of Embase. We will search literature provided by agencies including the World Health Organization. We will contact study authors for complete data to calculate prevalence and/or incidence when required.

Data collection and analysis

Selection of studies

We will remove duplicate records and import the search results into Covidence®, a web-based review management software.[32] Then, two investigators will independently screen each title and abstract. Investigators will classify each record as 'yes' (relevant), 'maybe' (possibly relevant) and 'no' (not relevant) for further full-text review. During title/abstract screening, studies that meet the eligibility criteria for population, context, and condition will be included for full text screening.

We will retrieve the full-text articles for records considered 'relevant' or 'possibly relevant'. Then, two investigators will independently screen the full-text articles for eligibility and classify articles as 'to be included' or 'to be excluded'. If there are questions regarding the eligibility of a given study, we will contact its authors to obtain additional information. If the

authors do not respond to three emails within 4 weeks, we will use information available from study reports to determine eligibility.

During the screening process, we will exclude but tag studies of non-US-based populations that otherwise meet the eligibility criteria. This will prove useful should the population eligibility criteria be broadened (e.g., other North American populations) due to sparsity of US-based studies.

We will review studies in languages other than English that reach full text review based on their title and abstract following translation by Google Translate when possible. We will report reasons for exclusion of full texts in an 'Excluded Studies' table. We will classify studies that meet eligibility criteria but have not yet been completed or have not published full text reports within two years of completion as 'ongoing'. We will resolve discrepancies regarding the classification of the studies by discussion and, where needed, adjudication by a third investigator.

Data Extraction and Management

One investigator will extract all relevant study characteristics and other information from included studies into a data collection form using a platform such as the Systematic Review Data Repository Plus (SRDR+). An independent investigator will verify the information for accuracy.[33] We will resolve discrepancies by consensus or, if consensus can't be reached, by adjudication by a third investigator. Where available, we will extract the following data: article information (first author's name, year of publication, country and region where the study was conducted), study design, source population, study population, participant inclusion and exclusion criteria, sampling method, sample size at baseline, index date, dates of follow up, follow up period, region(s) where the participants were recruited, case definition(s), participant characteristics (e.g., age, sex), prevalence, prevalence period, cumulative incidence, incidence rate, and measures of precision. We will extract from each study, all factors included in association analyses (e.g., age and sex are associated with increased prevalence/incidence of dry eye). We will extract estimates (e.g., relative risk) and their precisions for unadjusted and adjusted factors associated with disease. We will record which covariates were included in the multivariable adjusted models of disease association.

Assessment of Risk of Bias in Included Studies

One review author will assess the risk of bias in each included study using specific risk of bias tools for prevalence and incidence studies. Another investigator will independently verify the information.[33] Any conflicts will be resolved by discussion or by adjudication by a third investigator. We will provide tool guides *a priori* for consistent and transparent use of each tool among investigators.

For prevalence studies, we will use the tool proposed by Hoy et al.[34] Items 1 to 4 of the tool assess the external validity of the study (items 1 and 2 assess sampling bias, and items 3 and 4 assess non-response bias). For item 1, we will address the extent to which the study population represents the general US population with respect to factors that influence prevalence and incidence of dry eye. Items 5 to 10 assess internal validity (items 5 to 9 assess ascertainment bias, and item 10 assesses bias related to the analysis). The study is rated as "high" or "low" risk of bias for each of the 10 items; there is no 'unclear' option. Once all 10 items are rated, we will evaluate the overall risk of bias in the summary assessment. The summary assessment is a subjective judgement and is not calculated as an overall sum of the items. There are three options for the summary assessment: 'high', 'moderate', and 'low' risk of bias.

For incidence studies, we will use the Joanna Briggs Institute Critical Appraisal Checklist for Cohort Studies.[35] The checklist has 11 items, and each item has 'yes', 'no', 'unclear', and 'not applicable' options. There is an additional overall appraisal item with 'include', 'exclude' and 'seek further info' options, and a comment section for the 'reason of exclusion'. We will not exclude studies from the systematic review based on the 'exclude' response in the overall appraisal item, but we will interpret this response as 'high risk of bias'. We will consider excluding studies from meta-analysis based on an 'exclude' response in the overall appraisal item (i.e., high risk of bias).

Data Synthesis

We will summarize from each study sample characteristics and prevalence and incidence data with precision estimates, in structured tables.[36] We will also present all reported potential risk factors for dry eye including their definitions (e.g., age grouping) and

estimates for each potential risk factor. All data will be stratified by case definition whenever feasible.

Investigation of Heterogeneity

We will qualitatively investigate sources of heterogeneity of the data by assessing risk of bias and other aspects of the design of each study (methodological heterogeneity) and examining the characteristics of the populations (clinical heterogeneity) in each study, including age, sex, case definition, and sociodemographic profiles. We will display the estimates and their uncertainty from each study in forest plots (separately for prevalence and incidence). We will quantitatively assess statistical heterogeneity by calculating the amount of heterogeneity (τ^2) and the contribution of heterogeneity to the total variability across studies (I^2).[37]

Meta-Analyses

When appropriate, we will conduct meta-analyses of prevalence and incidence estimates. We will combine data if the study estimates have acceptable heterogeneity, both qualitatively and quantitatively. If a study uses more than one case definition and reports several prevalence and incidence estimates, we will stratify the estimates by case definition and analyze them in separate subgroup meta-analyses. We will use our clinical expertise and the literature to judge which case definitions are compatible for pooling in subgroup meta-analyses. We will also consider stratifying meta-analyses by levels of risk of bias. We will consider meta-analysis of measures of association for common risk factor covariates across studies. Whether or not we conduct meta-analyses, we will qualitatively summarize the findings across studies in a summary of findings table.

We will meta-analyse prevalence and cumulative incidence proportions using separate random-intercept binomial models with a logistic link function via the exact likelihood method as follows:

$$\text{logit}(P(\Upsilon_{ik} = 1)) = \Theta + b_i \text{ with } b_i \sim N(0,\tau^2) \quad (1)$$

We will combine incidence rate using a random-intercept Poisson regression model as follows:

$$\Upsilon_i \sim \text{Poisson}(\mu_i) \text{ with } \log(\mu_i) = \beta_0 + b_i + \log(T_i) \text{ and } b_i \sim N(0,\tau^2) \quad (2)$$

Both models (1) and (2) can be fitted in the Generalized Linear Mixed Model (GLMM) modules available in many popular statistical packages such as SAS, R, and Stata.[38]

DISCUSSION

Dry eye disease is a chronic symptomatic condition that is costly to society, reduces quality of life and is among the leading reasons for presentation to eye care services worldwide. For this reason, the World Health Organization has emphasized that dry eye must not be overlooked when addressing global eye care needs.[39] With demographic ageing,[40] lifestyle changes,[23] climate changes,[2,14,21] and the introduction of newer and more costly therapies,[12] dry eye-related economic costs to the US society can be expected to increase considerably. Hence, contemporaneous burden of disease estimates are necessary to enable health policymakers and research funding bodies make decisions regarding public health interventions and adequate resource allocation.

Our systematic review and meta-analysis will overcome some of the limitations in previous reviews of dry eye epidemiology reports as we will use contemporaneous data and comprehensive methods to enhance transparency and reproducibility. However, we do anticipate challenges and limitations in our study. Some of the most important limitations will be the anticipated high levels of heterogeneity in prevalence and incidence estimates. But this will provide the opportunity to explore and report the reasons for heterogeneity such as clinical and methodological variations. Other limitations may include reliance on secondary data for epidemiological research such as healthcare utilization databases and electronic health records which are not primarily designed for research purposes.[22,41]

Despite these limitations, the information gathered from this study is likely to be widely used by patients, physicians, health policymakers, researchers, and custodians to obtain and allocate funds and other resources to target the prevention and treatment of dry eye.

ETHICS AND DISSEMINATION

This review does not require the approval of an Ethics Committee because it will use previously published studies. We will publish our results in a peer-reviewed journal and present at relevant conferences.

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AUTHOR STATEMENT:

Paul McCann: Concept, design, drafting, final submission

Alison Abraham: Statistical and methodological design, drafting

Darren Gregory: Design, drafting

Scott Hauswirth: Design, drafting

Cristos Ifantides: Design, drafting

Su-Hsun Liu: Methodological design, drafting

Ian J. Saldanha: Methodological design, drafting, final submission

Tianjing Li: Concept, design, drafting, final submission, guarantor

DATA STATEMENT: Data will be made available upon reasonable request.

FUNDING: This work was supported by National Eye Institute, National Institutes of Health, grant number UG1EY020522. The funding body had no role in developing the protocol.

CONFLICTS OF INTEREST: None to declare.

ACKNOWLEDGEMENTS: We would like to acknowledge the contribution of Kristen Desanto, our information specialist, who assisted us with developing the draft search strategy for electronic databases.

Supplementary File

Search strategy draft

MEDLINE (via Ovid MEDLINE® ALL)

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2	exp Keratoconjunctivitis Sicca/
3	exp Xerophthalmia/
4	exp Meibomian Glands/
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6	((keratoconjunctivitis or kerato-conjunctivitis) adj1 sicca).tw,kf.
7	xerophthalmi*.tw,kf.
8	meibomian gland dysfunction.tw,kf.
9	exp Sjogren's Syndrome/
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11	(9 or 10) and (exp Eye/ or eye*.mp. or ocular*.mp. or ophthalm*.mp.)
12	or/1-8,11
13	exp Epidemiology/
14	exp Epidemiologic Methods/
15	epidemiology.fs.
16	burden of disease.tw,kf.
17	DALY*.tw,kf.
18	death rate*.tw,kf.
19	Disability Adjusted Life Years.tw,kf.
20	disease burden.tw,kf.
21	endemic*.tw,kf.
22	epidemic*.tw,kf.
23	epidemiolog*.tw,kf.
24	frequency.tw,kf.
25	incidence*.tw,kf.
26	morbidities.tw,kf.
27	morbidity.tw,kf.
28	occurrence.tw,kf.
29	outbreak*.tw,kf.
30	prevalence.tw,kf.
31	surveillance.tw,kf.
32	survival rate*.tw,kf.
33	years lived with disability.tw,kf.
34	years of life lost.tw,kf.
35	YLD*.tw,kf.
36	YLL*.tw,kf.
37	or/13-36

509	38	12 and 37
510	39	38 NOT (exp animals/ NOT exp humans/)
511	40	limit 39 to yr="2010 -Current"
512	**Embase (via Elsevier)**	
513	#1	'dry eye'/exp
514	#2	'dry eye syndrome'/exp
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517	#5	'xerophthalmia'/exp
518	#6	'meibomian gland'/exp
519	#7	(dry* NEAR/3 eye*):ab,ti,kw
520	#8	((keratoconjunctivitis or kerato-conjunctivitis) NEAR/1 sicca):ab,ti,kw
521	#9	xerophthalmi*:ab,ti,kw
522	#10	'meibomian gland dysfunction':ab,ti,kw
523	#11	'Sjoegren syndrome'/exp
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525	#13	(#11 OR #12) AND ('eye'/exp OR eye* OR ocular* OR ophthalm*)
526	#14	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #13
527	#15	'epidemiology'/exp
528	#16	epidemiology:lnk
529	#17	'burden of disease':ab,ti,kw
530	#18	DALY*:ab,ti,kw
531	#19	'death rate*':ab,ti,kw
532	#20	'Disability Adjusted Life Years':ab,ti,kw
533	#21	'disease burden':ab,ti,kw
534	#22	endemic*:ab,ti,kw
535	#23	epidemic*:ab,ti,kw
536	#24	epidemiolog*:ab,ti,kw
537	#25	frequency:ab,ti,kw
538	#26	incidence*:ab,ti,kw
539	#27	morbidities:ab,ti,kw
540	#28	morbidity:ab,ti,kw
541	#29	occurrence:ab,ti,kw
542	#30	outbreak*:ab,ti,kw
543	#31	prevalence:ab,ti,kw
544	#32	surveillance:ab,ti,kw
545	#33	'survival rate*':ab,ti,kw
546	#34	'years lived with disability':ab,ti,kw
547	#35	'years of life lost':ab,ti,kw
548	#36	YLD*:ab,ti,kw
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#38 #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37

#39 #14 AND #38

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	✓
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	✓
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	✓
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	✓
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	✓
Sponsor	5b	Provide name for the review funder and/or sponsor	✓
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	✓
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is 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)	✓ (PCC)
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	✓
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	✓
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	✓
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Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	✓
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)	✓
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any 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	✓
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	✓
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	✓
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	✓
	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 I^2, Kendall's τ)	✓
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Supplementary File

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#25 frequency:ab,ti,kw
#26 incidence*:ab,ti,kw
#27 morbidities:ab,ti,kw
#28 morbidity:ab,ti,kw
#29 occurrence:ab,ti,kw
#30 outbreak*:ab,ti,kw
#31 prevalence:ab,ti,kw
#32 surveillance:ab,ti,kw
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Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	✓
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BMJ Open

Prevalence and incidence of dry eye in the United States: a systematic review protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-056203.R1
Article Type:	Protocol
Date Submitted by the Author:	13-Oct-2021
Complete List of Authors:	McCann, Paul; University of Colorado - Anschutz Medical Campus, Department of Ophthalmology Abraham, Alison; University of Colorado - Anschutz Medical Campus, Department of Epidemiology, Colorado School of Public Health, and Department of Ophthalmology Gregory, Darren G.; University of Colorado - Anschutz Medical Campus, Department of Ophthalmology Hauswirth, Scott; University of Colorado - Anschutz Medical Campus, Department of Ophthalmology Ifantides, Cristos; University of Colorado - Anschutz Medical Campus, Department of Ophthalmology Liu, Su-Hsun; University of Colorado - Anschutz Medical Campus, Department of Ophthalmology Saldanha, Ian; Brown University School of Public Health, Health Services, Policy and Practice Li, Tianjing; University of Colorado - Anschutz Medical Campus, Department of Ophthalmology
Primary Subject Heading:	Ophthalmology
Secondary Subject Heading:	Epidemiology
Keywords:	Corneal and external diseases < OPHTHALMOLOGY, EPIDEMIOLOGY, PUBLIC HEALTH

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Title: Prevalence and incidence of dry eye in the United States: a systematic review protocol

Authors: Paul McCann[1], Alison G. Abraham[1,2], Darren G. Gregory[1], Scott Hauswirth[1], Cristos Ifantides[1], Su-Hsun Liu[1], Ian J. Saldanha[3,4], Tianjing Li[1,2]

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Co-authors

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Tianjing Li: Department of Ophthalmology, School of Medicine, University of Colorado Anschutz Medical Campus, 1675 Aurora Ct., F731, Aurora, CO 80045, USA, email: tianjing.li@cuanschutz.edu

ABSTRACT

Introduction: Dry eye is a multifactorial chronic condition characterized by tear film insufficiency and instability, and ocular symptoms including foreign body sensation, itching, irritation, soreness, and visual disturbance. The prevalence and incidence of dry eye are major determinants of the magnitude of economic and societal costs of the disease. This protocol proposes a systematic review and meta-analysis of the prevalence and incidence of dry eye in the United States.

Methods and analysis: Working with an information specialist, we will develop search strategies for Ovid Medline and Embase for population-based cross-sectional and cohort studies involving US-based populations that report the prevalence and/or incidence of dry eye. We will include studies involving persons of all ages from 1 January 2010 to the current date with no language restrictions. We will also hand-search references of included studies, dry eye epidemiology-related systematic reviews, clinical practice guidelines, and literature provided by agencies and organizations.

Two investigators will independently screen the titles and abstracts, and then full text reports to determine eligibility. One investigator will extract study data and perform risk of bias assessments using tools designed specifically for prevalence and incidence studies. A second investigator will verify all extracted study data and risk of bias assessments. We will assess heterogeneity, qualitatively and quantitatively. When appropriate, we will meta-analyse prevalence and incidence estimates.

Ethics and dissemination: This review does not require approval by an Ethics Committee because it will use published studies. We will publish our results in a peer-reviewed journal and present at relevant conferences.

Prospero registration number: CRD42021256934

Word Count: 3,716

Keywords: Dry eye, prevalence, incidence, epidemiology, systematic review, United States

ARTICLE SUMMARY

Strengths and limitations of this study

- This systematic review and meta-analysis aims to report the prevalence and incidence of dry in the United States.
- We aim to overcome limitations in previous reviews of dry eye epidemiology reports.
- We will use contemporaneous data and comprehensive methods to enhance transparency and reproducibility.
- We anticipate high levels of heterogeneity in prevalence and incidence estimates, however we aim to explore the reasons for heterogeneity.

INTRODUCTION

Dry eye disease (DED) is defined by the Tear Film and Ocular Surface Society (TFOS) Dry Eye Workshop II (DEWS-II) as "a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles."[1] Because there is no gold standard diagnostic test for DED, the term "dry eye" is used to describe various presentations of ocular discomfort and tear film abnormalities. Dry eye is frequently referred to as DED once it is clinically diagnosed.[2]

Irrespective of a clinical diagnosis of DED, dry eye causes considerable burden to patients and society. Patient burden includes decreased quality of life due to symptoms, such as foreign body sensation, itching, irritation, soreness, and visual disturbance, which interfere with reading, driving, and work productivity, and cause physical and emotional distress.[3–5] Burdens to society include direct economic costs (e.g., healthcare professional visits, treatment costs),[6] non-direct economic costs (e.g., work productivity loss),[7] and intangible personal costs (e.g., impaired social, emotional, and physical functioning).[8,9] In 2011, the estimated direct economic cost to the United States (US) healthcare system for DED therapy was $3.8 billion per year and the estimated total societal cost in the U.S. was $55.4 billion per year.[6] Comparative analyses have demonstrated that DED-related costs in the U.S. are broadly comparable with other countries.[10] However, in the US, personal costs may be higher because treatments, such as ocular lubricants, may not be adequately covered by health insurance, and drug costs tend to be higher in the US.[6,11] With introduction of newer and more costly therapies, an even larger societal and personal economic burden of dry eye can be expected.[12–14] Furthermore, despite being a significant public health problem, dry eye remains underdiagnosed, highlighting the likelihood that there is a significant undiagnosed burden of disease.[2,15,16]

In 2017, a comprehensive epidemiology report by the TFOS DEWS-II ("TFOS epidemiology report") reviewed population-based studies that enrolled at least 500 participants to estimate the prevalence and incidence of dry eye stratified by definition of disease, age, sex, and worldwide geographical region.[17] The findings of the TFOS report showed that, globally, the prevalence of dry eye ranged from 5% to 50% with various definitions of DED.

However, in dry eye, as well as in other ophthalmic diseases, applying differing definitions of disease to epidemiological datasets can result in widely varying estimates of prevalence.[18]

In addition to disease definition, various factors may contribute to differences in prevalence of dry eye.[17] The prevalence has been reported to increase with age, especially in women.[15,17,19] To our knowledge, few studies have reported prevalence in people younger than 21 years old, and none were in US-based populations.[19–21] This lack of data is problematic because young people are also at risk of dry eye due to generally longer screen time (e.g., video monitors, digital tablets), and contact lens wear.[20] The TFOS report found no clear pattern of dry eye associated with latitude, globally.[17] However, in the US, there is indirect evidence of an association with latitude, with higher prevalence of dry eye reported in southern regions of the country.[2,15] Furthermore, other geo-environmental factors, such as higher atmospheric pressure, air pollution, humidity, and wind speed, have all been shown to be risk factors for dry eye.[22] As the US comprises an expansive land mass with great variation in climate across latitudinal and topographical regions, and given that climatic factors are influential risk factors for dry eye, it is important to consider these factors when estimating prevalence and incidence of dry eye.

The literature search for the TFOS Epidemiology report covered a 10-year period from 2005 to 2015 (last updated on September 17, 2015). However, it is unclear whether the TFOS epidemiology report strictly followed critical steps in the systematic review process, such as protocol development, risk of bias assessment, and appropriate meta-analysis.[17] Furthermore, the TFOS Epidemiology report is now relatively dated because more dry eye-related epidemiological studies have been performed in the US since its publication.[2,23]

Systematic reviews of dry eye-related epidemiology have been published for other populations and global regions but,[24,25] to our knowledge, there are no existing systematic reviews of dry eye epidemiology within the US. As the prevalence and incidence of dry eye are major determinants of the magnitude of the personal, societal, and economic costs of the disease, examining these epidemiological indices can help health policymakers estimate the burden of dry eye in the US and consequently allocate resources to risk mitigation and treatment as needed.

Primary Objective

The primary objective of this systematic review and meta-analysis is to summarize the prevalence and incidence of dry eye in persons of all ages in the US.

Secondary Objectives

1. Estimate the effect of disease definition, age group, sex, US region, and geo-environmental factors on prevalence and incidence of dry eye in the US by using meta-regression methods.
2. Assess heterogeneity in the prevalence and incidence of dry eye within the US and factors potentially explaining the heterogeneity.
3. Report epidemiological factors associated with dry eye.

METHODS AND ANALYSIS

We have registered for this systematic review protocol with the PROSPERO international register for systematic reviews (CRD42021256934) and we report it in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) 2015 statement (see Supplementary File 1). We will conduct and report the review with guidance from the Joanna Briggs Institute Manual for Evidence Synthesis,[26] the Cochrane Handbook for Systematic Reviews of Interventions,[27] the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines,[28] the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) statement,[29] and a meta-epidemiological study on the assessment of prevalence study quality by Migliavaca et al.[30]

Patient and Public Involvement

No patient involved.

Criteria for considering studies for this review

We used the populations, context, and condition (PCC) framework for the systematic review of prevalence and incidence to formulate the eligibility criteria.[31]

Population and Context

We will investigate the prevalence and incidence of dry eye in the US population (i.e., the target population). Prevalence is the proportion of the population with dry eye at a given time (point or period of time). Cumulative incidence is the proportion of persons in the at-

risk population who develop a new diagnosis of dry eye during a given follow-up period. Incidence rate is the number of new cases of dry eye divided by the observed person-time during a given observation period. We aim to explore the influence of demographic factors (e.g., age, sex), environmental exposures (e.g., air pollution, screen time), meteorological exposures (e.g., temperature, wind speed, relative humidity, atmospheric pressure), and underlying risk factors of disease (e.g., co-morbidities, topical and systemic medications) on these epidemiological indices. Our source populations will be from studies conducted within the US and studies conducted outside the US are not eligible. However, the target population may be broadened to Continental North American populations if there is a sparsity of US-based studies (i.e., less than two US-based studies) although this is not expected.

Condition

We will use definitions of dry eye outlined in the included primary studies. We will aim to consolidate similar case definitions across studies into homogenous definitions when appropriate. In the TFOS report, case definitions of DED included: (1) Women's Health Study (WHS) criteria (i.e., self-reported physician diagnosis and/or self-reported 'constant' or 'often' symptoms),[15] (2) dry eye symptoms when signs were not measured (e.g., measured by the Ocular Surface Disease Index), (3) dry eye clinical signs when symptoms were not measured (e.g., tear break up time), (4) a combination of dry eye signs and symptoms (distinct from WHS criteria), and (5) Meibomian gland dysfunction.[17] We will also include dry eye definitions based on relevant International Classification of Disease codes.

Types of *S*tudies

We will include population-based observational studies (i.e., cross-sectional studies and cohort studies) that reported prevalence or incidence of dry eye in the US. We will not exclude studies based on characteristics such as sampling frame or sampling methods, but these will be assessed as part of the risk of bias assessment of included studies. We will exclude case reports, case series, case-control studies, and interventional studies. We will exclude population-based studies with fewer than 73 total participants because estimates from samples with less than 73 participants would produce 95% confidence intervals greater than ±0.05 when the anticipated minimum population proportion is estimated to be

0.05.[32] However, if we find studies on specific population subgroups (e.g., native Americans) that have fewer than 73 total participants we will consider them for inclusion.

Search methods for identification of studies

Electronic Searches

Working with an information specialist, we will develop search strategies for Ovid Medline, and Embase for population-based studies that report the prevalence and/or incidence of dry eye. We will include studies involving persons with all ages from 1 January 2010 to the current date with no language restrictions. The search strategy will include text word as well as controlled vocabulary (e.g., medical subject headings, Emtree) terms for epidemiological concepts, such as “epidemiology”, “prevalence”, “incidence”, and “burden of disease”, combined with dry eye-related concepts, such as “dry eye syndromes” (see Supplementary File 2).

Other Sources

We will hand-search references of included studies, dry eye epidemiology-related systematic reviews, and clinical practice guidelines for additional studies. Conference abstracts will be searched as part of our electronic search of Embase. We will search literature provided by agencies including the World Health Organization. We will contact study authors for complete data to calculate prevalence and/or incidence when required.

Data collection and analysis

Selection of studies

We will remove duplicate records and import the search results into Covidence®, a web-based review management software.[33] Then, two investigators will independently screen each title and abstract. Investigators will classify each record as 'yes' (relevant), 'maybe' (possibly relevant) and 'no' (not relevant) for further full-text review. During title/abstract screening, studies that meet the eligibility criteria for population, context, and condition will be included for full text screening.

We will retrieve the full-text articles for records considered 'relevant' or 'possibly relevant'. Then, two investigators will independently screen the full-text articles for eligibility and classify articles as 'to be included' or 'to be excluded'. If there are questions regarding the

eligibility of a given study, we will contact its authors to obtain additional information. If the authors do not respond to three emails within 4 weeks, we will use information available from study reports to determine eligibility.

During the screening process, we will exclude but tag studies of non-US-based populations that otherwise meet the eligibility criteria. This will prove useful should the population eligibility criteria be broadened (i.e., Continental North American populations) due to sparsity of US-based studies.

We will review studies in languages other than English that reach full text review based on their title and abstract following translation by Google Translate when possible. We will report reasons for exclusion of full texts in an 'Excluded Studies' table. We will classify studies that meet eligibility criteria but have not yet been completed or have not published full text reports within two years of completion as 'ongoing'. We will resolve discrepancies regarding the classification of the studies by discussion and, where needed, adjudication by a third investigator.

Data Extraction and Management

One investigator will extract all relevant study characteristics and other information from included studies into a data collection form using a platform such as the Systematic Review Data Repository Plus (SRDR+). An independent investigator will verify the information for accuracy.[34] We will resolve discrepancies by consensus or, if consensus can't be reached, by adjudication by a third investigator. Where available, we will extract the following data: article information (first author's name, year of publication, country and region where the study was conducted), study design, source population, study population, participant inclusion and exclusion criteria, sampling method, sample size at baseline, index date, dates of follow up, follow up period, region(s) where the participants were recruited, case definition(s), participant characteristics (e.g., age, sex), prevalence, prevalence period, cumulative incidence, incidence rate, and measures of precision. We will extract from each study, all factors included in association analyses (e.g., age and sex are associated with increased prevalence/incidence of dry eye). We will extract estimates (e.g., relative risk) and their precisions for unadjusted and adjusted factors associated with disease. We will record which covariates were included in the multivariable adjusted models of disease association.

Assessment of Risk of Bias in Included Studies

One review author will assess the risk of bias in each included study using specific risk of bias tools for prevalence and incidence studies. Another investigator will independently verify the information.[34] Any conflicts will be resolved by discussion or by adjudication by a third investigator. We will provide tool guides *a priori* for consistent and transparent use of each tool among investigators.

For prevalence studies, we will use the tool proposed by Hoy et al.[35] Items 1 to 4 of the tool assess the external validity of the study (items 1 and 2 assess sampling bias, and items 3 and 4 assess non-response bias). For item 1, we will address the extent to which the study population represents the general US population with respect to factors that influence prevalence and incidence of dry eye. Items 5 to 10 assess internal validity (items 5 to 9 assess ascertainment bias, and item 10 assesses bias related to the analysis). The study is rated as "high" or "low" risk of bias for each of the 10 items; there is no 'unclear' option. Once all 10 items are rated, we will evaluate the overall risk of bias in the summary assessment. The summary assessment is a subjective judgement and is not calculated as an overall sum of the items. There are three options for the summary assessment: 'high', 'moderate', and 'low' risk of bias.

For incidence studies, we will use the Joanna Briggs Institute Critical Appraisal Checklist for Cohort Studies.[36] The checklist has 11 items, and each item has 'yes', 'no', 'unclear', and 'not applicable' options. There is an additional overall appraisal item with 'include', 'exclude' and 'seek further info' options, and a comment section for the 'reason of exclusion'. We will not exclude studies from the systematic review based on the 'exclude' response in the overall appraisal item, but we will interpret this response as 'high risk of bias'. We will consider excluding studies from meta-analysis based on an 'exclude' response in the overall appraisal item (i.e., high risk of bias).

Data Synthesis

We will summarize from each study, sample characteristics and prevalence and incidence data with precision estimates, in structured tables.[37] We will also present all reported potential risk factors for dry eye including their definitions (e.g., age grouping) and effect estimates for each potential risk factor, including specific risk factors such as geo-

environmental factors and screen time when data is available. We will document prevalence and incidence of dry eye severity using previously defined classifications when reported in the primary studies.[38,39] All data will be stratified by case definition whenever feasible.

Investigation of Heterogeneity

We will qualitatively investigate sources of heterogeneity of the data by assessing risk of bias and other aspects of the design of each study (methodological heterogeneity) and examining the characteristics of the populations (clinical heterogeneity) in each study, including age, sex, case definition, and sociodemographic profiles. We will display the estimates and their uncertainty from each study in forest plots (separately for prevalence and incidence). We will quantitatively assess statistical heterogeneity by calculating the amount of heterogeneity (τ^2) and the contribution of heterogeneity to the total variability across studies (I^2).[40]

Meta-Analyses

When appropriate, we will conduct meta-analyses of prevalence and incidence estimates. We will combine data if the study estimates have acceptable heterogeneity, both qualitatively and quantitatively. If a study uses more than one case definition and reports several prevalence and incidence estimates, we will stratify the estimates by case definition and analyze them in separate subgroup meta-analyses. We will use our clinical expertise and the literature to judge which case definitions are compatible for pooling in subgroup meta-analyses. We will also consider stratifying meta-analyses by levels of risk of bias. We will consider meta-analysis of measures of association for common risk factor covariates across studies. Whether or not we conduct meta-analyses, we will qualitatively summarize the findings across studies in a summary of findings table.

We will meta-analyse prevalence and cumulative incidence proportions using separate random-intercept regression models with a logistic link function via the exact likelihood method. We will combine incidence rate using a random-intercept regression model. Both models and can be fitted in the Generalized Linear Mixed Model (GLMM) modules available in many popular statistical packages such as SAS, R, and Stata.[41]

Meta-regression

If there are sufficient risk factor data within-sample (i.e., from the primary studies) and out-of-sample (e.g., from census-derived demographic data, governmental agency derived geo-environmental data), we will consider conducting a Bayesian meta-regression with integrative systems modelling using DisMod-MR software.[42] This will allow us to extrapolate nationwide prevalence and incidence estimates captured in the primary studies and stratify prevalence and incidence by factors such as age, sex, US region and geo-environmental factors.[42–44] Integrative systems modelling potentially addresses some of the notable challenges faced in this meta-analysis including, (1) diverse case-definitions, (2) variation in environmental and climatic exposures within the country, and (3) a lack of standardised age stratification), which may improve compatibility for pooling of data. We will consult with statisticians and integrative systems modelling experts to decide on the most appropriate statistical approach.

DISCUSSION

Dry eye disease is a chronic symptomatic condition that is costly to society, reduces quality of life and is among the leading reasons for presentation to eye care services worldwide. For this reason, the World Health Organization has emphasized that dry eye must not be overlooked when addressing global eye care needs.[45] With demographic ageing,[46] lifestyle changes,[24] climate changes,[2,15,22] and the introduction of newer and more costly therapies,[13] dry eye-related economic costs to the US society can be expected to increase considerably. Hence, contemporaneous burden of disease estimates are necessary to enable health policymakers and research funding bodies make decisions regarding public health interventions and adequate resource allocation.

Our systematic review and meta-analysis will overcome some of the limitations in previous reviews of dry eye epidemiology reports as we will use contemporaneous data and comprehensive methods to enhance transparency and reproducibility. However, we do anticipate challenges and limitations in our study. An important limitation will be the anticipated high levels of heterogeneity in prevalence and incidence estimates. But this will provide the opportunity to explore and report the reasons for heterogeneity such as clinical and methodological variations. Another limitation is that we will search only published literature and we acknowledge the potential of publication bias. Despite potential

limitations, the information gathered from this study is likely to be widely used in the United States and in comparable settings by patients, physicians, health policymakers, researchers, and custodians to obtain and allocate funds and other resources to target the prevention and treatment of dry eye.

ETHICS AND DISSEMINATION

This review does not require the approval of an Ethics Committee because it will use previously published studies. We will publish our results in a peer-reviewed journal and present at relevant conferences.

AUTHOR STATEMENT:

Paul McCann: Concept, design, drafting, final submission

Alison Abraham: Statistical and methodological design, drafting

Darren Gregory: Design, drafting

Scott Hauswirth: Design, drafting

Cristos Ifantides: Design, drafting

Su-Hsun Liu: Methodological design, drafting

Ian J. Saldanha: Methodological design, drafting, final submission

Tianjing Li: Concept, design, drafting, final submission, guarantor

CONFLICTS OF INTEREST: None to declare.

FUNDING: This work was supported by National Eye Institute, National Institutes of Health, grant number UG1EY020522. The funding body had no role in developing the protocol.

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DATA STATEMENT: Data will be made available upon reasonable request.

ACKNOWLEDGEMENTS: We would like to acknowledge the contribution of Kristen Desanto, our information specialist, who assisted us with developing the search strategy for electronic databases. We would also like to acknowledge and thank Dr Abraham Flaxman (University of Washington) for reviewing and consulting on our proposed meta-regression methods.

Supplementary File 1

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item		Page
ADMINISTRATIVE INFORMATION				
Title:				
Identification	1a	Identify the report as a protocol of a systematic review	✓	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	n/a	n/a
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	✓	3
Authors:				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	✓	1-2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	✓	15
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	n/a
Support:				
Sources	5a	Indicate sources of financial or other support for the review	✓	15
Sponsor	5b	Provide name for the review funder and/or sponsor	✓	15
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	✓	15
INTRODUCTION				
Rationale	6	Describe the rationale for the review in the context of what is already known	✓	5-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	✓ (PCC)	7-8
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	✓	3, 7-8
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	✓	9
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	✓	Suppl
Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	✓	9-10

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)	✓	9-10
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	✓	10
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	✓	10
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	✓	10
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	✓	11
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	✓	12
	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 I^2, Kendall's τ)	✓	12
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	✓	12, 13
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	✓	11-12
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	✓	13
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	n/a	n/a

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

Supplementary File 2

Search strategy draft

MEDLINE (via Ovid MEDLINE® ALL)

1	exp Dry Eye Syndromes/
2	exp Keratoconjunctivitis Sicca/
3	exp Xerophthalmia/
4	exp Meibomian Glands/
5	(dry* adj3 eye*).tw,kf.
6	((keratoconjunctivitis or kerato-conjunctivitis) adj1 sicca).tw,kf.
7	xerophthalmi*.tw,kf.
8	meibomian gland dysfunction.tw,kf.
9	exp Sjogren's Syndrome/
10	((Sjogren* or Sjoegren*) adj1 (syndrom* or disease*)).tw,kf.
11	(9 or 10) and (exp Eye/ or eye*.mp. or ocular*.mp. or ophthalm*.mp.)
12	or/1-8,11
13	exp Epidemiology/
14	exp Epidemiologic Methods/
15	epidemiology.fs.
16	burden of disease.tw,kf.
17	DALY*.tw,kf.
18	death rate*.tw,kf.
19	Disability Adjusted Life Years.tw,kf.
20	disease burden.tw,kf.
21	endemic*.tw,kf.
22	epidemic*.tw,kf.
23	epidemiolog*.tw,kf.
24	frequency.tw,kf.
25	incidence*.tw,kf.
26	morbidities.tw,kf.
27	morbidity.tw,kf.
28	occurrence.tw,kf.
29	outbreak*.tw,kf.
30	prevalence.tw,kf.
31	surveillance.tw,kf.
32	survival rate*.tw,kf.
33	years lived with disability.tw,kf.
34	years of life lost.tw,kf.

35 YLD*.tw,kf.
36 YLL*.tw,kf.
37 or/13-36
38 12 and 37
39 38 NOT (exp animals/ NOT exp humans/)
40 limit 39 to yr="2010 -Current"

Embase (via Elsevier)

#1 'dry eye'/exp
#2 'dry eye syndrome'/exp
#3 'evaporative dry eye disease'/exp
#4 'keratoconjunctivitis sicca'/exp
#5 'xerophthalmia'/exp
#6 'meibomian gland'/exp
#7 (dry* NEAR/3 eye*):ab,ti,kw
#8 ((keratoconjunctivitis or kerato-conjunctivitis) NEAR/1 sicca):ab,ti,kw
#9 xerophthalmi*:ab,ti,kw
#10 'meibomian gland dysfunction':ab,ti,kw
#11 'Sjoegren syndrome'/exp
#12 ((Sjogren* or Sjoegren*) NEAR/1 (syndrom* or disease*)):ab,ti,kw
#13 (#11 OR #12) AND ('eye'/exp OR eye* OR ocular* OR ophthalm*)
#14 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #13
#15 'epidemiology'/exp
#16 epidemiology:lnk
#17 'burden of disease':ab,ti,kw
#18 DALY*:ab,ti,kw
#19 'death rate*':ab,ti,kw
#20 'Disability Adjusted Life Years':ab,ti,kw
#21 'disease burden':ab,ti,kw
#22 endemic*:ab,ti,kw
#23 epidemic*:ab,ti,kw
#24 epidemiolog*:ab,ti,kw
#25 frequency:ab,ti,kw
#26 incidence*:ab,ti,kw
#27 morbidities:ab,ti,kw
#28 morbidity:ab,ti,kw
#29 occurrence:ab,ti,kw
#30 outbreak*:ab,ti,kw
#31 prevalence:ab,ti,kw

#32 surveillance:ab,ti,kw

#33 'survival rate*':ab,ti,kw

#34 'years lived with disability':ab,ti,kw

#35 'years of life lost':ab,ti,kw

#36 YLD*:ab,ti,kw

#37 YLL*:ab,ti,kw

#38 #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37

#39 #14 AND #38

#40 #39 NOT ([animals]/lim NOT [humans]/lim)

#41 #40 AND [2010-2021]/py