


# BMJ Open Prevalence and incidence of dry eye in the USA: a systematic review protocol

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## ABSTRACT

**Introduction** Dry eye is a multifactorial chronic condition characterised 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 USA.

**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 organisations. 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.

## 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 characterised 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.’<sup>1</sup> Because there is no gold standard diagnostic test for DED, the term ‘dry eye’ is used to describe various presentations of

## Strengths and limitations of this study

- 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.

ocular discomfort and tear film abnormalities. Dry eye is frequently referred to as DED once it is clinically diagnosed.<sup>2</sup>

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.<sup>3-5</sup> Burdens to society include direct economic costs (eg, healthcare professional visits, treatment costs),<sup>6</sup> non-direct economic costs (eg, work productivity loss)<sup>7</sup> and intangible personal costs (eg, impaired social, emotional and physical functioning).<sup>8,9</sup> In 2011, the estimated direct economic cost to the US healthcare system for DED therapy was US\$3.8 billion per year and the estimated total societal cost in the USA was US\$55.4 billion per year.<sup>6</sup> Comparative analyses have demonstrated that DED-related costs in the USA are broadly comparable with other countries.<sup>10</sup> However, in the USA, 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 USA.<sup>6,11</sup> With introduction of newer and more costly therapies, an even larger societal and personal economic burden of dry eye can be expected.<sup>12-14</sup> Furthermore, despite being a significant public health problem, dry eye remains underdiagnosed, highlighting the

likelihood that there is a significant undiagnosed burden of disease.<sup>2 15 16</sup>

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.<sup>17</sup> 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.<sup>18</sup>

In addition to disease definition, various factors may contribute to differences in prevalence of dry eye.<sup>17</sup> The prevalence has been reported to increase with age, especially in women.<sup>15 17 19</sup> To our knowledge, few studies have reported prevalence in people younger than 21 years old, and none were in US-based populations.<sup>19–21</sup> This lack of data is problematic because young people are also at risk of dry eye due to generally longer screen time (eg, video monitors, digital tablets), and contact lens wear.<sup>20</sup> The TFOS report found no clear pattern of dry eye associated with latitude, globally.<sup>17</sup> However, in the USA, there is indirect evidence of an association with latitude, with higher prevalence of dry eye reported in southern regions of the country.<sup>2 15</sup> 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.<sup>22</sup> As the USA 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 17 September 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.<sup>17</sup> Furthermore, the TFOS epidemiology report is now relatively dated because more dry eye-related epidemiological studies have been performed in the USA since its publication.<sup>2 23</sup>

Systematic reviews of dry eye-related epidemiology have been published for other populations and global regions but,<sup>24 25</sup> to our knowledge, there are no existing systematic reviews of dry eye epidemiology within the USA. 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 policy-makers estimate the burden of dry eye in the USA 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 summarise the prevalence and incidence of dry eye in persons of all ages in the USA.

## Secondary objectives

1. Estimate the effect of disease definition, age group, sex, US region and geoenvironmental factors on prevalence and incidence of dry eye in the USA by using metaregression methods.
2. Assess heterogeneity in the prevalence and incidence of dry eye within the USA 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 2015 statement (see online supplemental file 1). We will conduct and report the review with guidance from the Joanna Briggs Institute Manual for Evidence Synthesis,<sup>26</sup> the Cochrane Handbook for Systematic Reviews of Interventions,<sup>27</sup> the Meta-analysis of Observational Studies in Epidemiology guidelines,<sup>28</sup> the Guidelines for Accurate and Transparent Health Estimates Reporting statement<sup>29</sup> and a meta-epidemiological study on the assessment of prevalence study quality by Migliavaca *et al.*<sup>30</sup>

## Patient and public involvement

No patient involved.

## Criteria for considering studies for this review

We used the populations, context and condition framework for the systematic review of prevalence and incidence to formulate the eligibility criteria.<sup>31</sup>

## Population and context

We will investigate the prevalence and incidence of dry eye in the US population (ie, 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 (eg, age, sex), environmental exposures (eg, air pollution, screen time), meteorological exposures (eg, temperature, wind speed, relative humidity, atmospheric pressure) and underlying risk factors of disease (eg, comorbidities, topical and systemic medications) on these epidemiological indices. Our source populations will be from studies conducted within the USA and studies conducted outside the USA are not eligible. However, the target population may be

broadened to Continental North American populations if there is a sparsity of US-based studies (ie, 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 (ie, self-reported physician diagnosis and/or self-reported 'constant' or 'often' symptoms),<sup>15</sup> (2) dry eye symptoms when signs were not measured (eg, measured by the Ocular Surface Disease Index), (3) dry eye clinical signs when symptoms were not measured (eg, tear break up time), (4) a combination of dry eye signs and symptoms (distinct from WHS criteria) and (5) Meibomian gland dysfunction.<sup>17</sup> We will also include dry eye definitions based on relevant International Classification of Disease codes.

### Types of studies

We will include population-based observational studies (ie, cross-sectional studies and cohort studies) that reported prevalence or incidence of dry eye in the USA. 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% CIs greater than  $\pm 0.05$  when the anticipated minimum population proportion is estimated to be 0.05.<sup>32</sup> However, if we find studies on specific population subgroups (eg, 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 (eg, 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 online supplemental 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 WHO. 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.<sup>33</sup> 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 (ie, 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 2 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. An independent investigator will verify the information for accuracy.<sup>34</sup> We will resolve discrepancies by consensus or, if consensus cannot 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



(eg, 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 (eg, age and sex). We will extract estimates (eg, 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.<sup>34</sup> 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.*<sup>35</sup> Items 1–4 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 5–10 assess internal validity (items 5–9 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.<sup>36</sup> 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 (ie, high risk of bias).

#### Data synthesis

We will summarise from each study, sample characteristics and prevalence and incidence data with precision estimates, in structured tables.<sup>37</sup> We will also present all reported potential risk factors for dry eye including their definitions (eg, age grouping) and effect estimates for each potential risk factor, including specific risk factors such as geo-environmental factors and screen time when data are available. We will document prevalence and incidence of dry eye severity using previously defined classifications

when reported in the primary studies.<sup>38,39</sup> 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 ( $\tau^2$ ) and the contribution of heterogeneity to the total variability across studies ( $I^2$ ).<sup>40</sup>

#### 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 analyse 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 summarise 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 can be fitted in the generalised linear mixed model modules available in many popular statistical packages such as SAS, R and Stata.<sup>41</sup>

#### Metaregression

If there are sufficient risk factor data within-sample (ie, from the primary studies) and out-of-sample (eg, 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.<sup>42</sup> 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.<sup>42–44</sup> 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

DED 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 WHO has emphasised that dry eye must not be overlooked when addressing global eye care needs.<sup>45</sup> With demographic ageing,<sup>46</sup> lifestyle changes,<sup>24</sup> climate changes<sup>2 15 22</sup> and the introduction of newer and more costly therapies,<sup>13</sup> 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 policy-makers and research funding bodies to 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 USA and in comparable settings by patients, physicians, health policy-makers, 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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**Contributors** PMM: concept, design, drafting, final submission. AGA: statistical and methodological design, drafting. DGG, SH and Cl: design, drafting. S-HL: methodological design, drafting. IS: methodological design, drafting, final submission. TL: concept, design, drafting, final submission, guarantor.

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