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

Journal:	<i>BMJ Open</i>
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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33 **ARTICLE SUMMARY**

34 **Strengths and limitations of this study**

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38 44 • This systematic review and meta-analysis aims to report the prevalence and
39
40 45 incidence of dry in the United States.
41
42 46 • We aim to overcome limitations in previous reviews of dry eye epidemiology reports.
43
44 47 • We will use contemporaneous data and comprehensive methods to enhance
45
46 48 transparency and reproducibility.
47
48 49 • We anticipate high levels of heterogeneity in prevalence and incidence estimates,
49
50 50 however we aim to explore the reasons for heterogeneity.
51
51 51 • We may rely on prevalence and incidence estimates from secondary data for
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52 52 epidemiological research such as electronic health records which are not primarily
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53 53 designed for research purposes.
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2
3 55 **ABSTRACT**
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5 56 **Introduction:** Dry eye is a multifactorial chronic condition characterized by tear film
6
7 57 insufficiency and instability, and inflammation of the ocular surface. The prevalence and
8
9 58 incidence of dry eye are major determinants of the magnitude of economic and societal
10
11 59 costs of the disease. This protocol proposes a systematic review and meta-analysis of the
12
13 60 prevalence and incidence of dry eye in the United States.

14
15 61 **Methods and analysis:** Working with an information specialist, we will develop search
16
17 62 strategies for Ovid Medline and Embase for population-based cross-sectional and cohort
18
19 63 studies that report the prevalence and/or incidence of dry eye. We will include studies
20
21 64 involving persons of all ages from 1 January 2010 to the current date with no language
22
23 65 restrictions. We will also hand-search references of included studies, dry eye epidemiology-
24
25 66 related systematic reviews, clinical practice guidelines, and literature provided by agencies
26
27 67 and organizations.

28
29 68 Two investigators will independently screen the titles and abstracts, and then full text
30
31 69 reports to determine eligibility. One investigator will extract study data and perform risk of
32
33 70 bias assessments using tools designed specifically for prevalence and incidence studies. A
34
35 71 second investigator will verify all extracted study data and risk of bias assessments. We will
36
37 72 assess heterogeneity, qualitatively and quantitatively. When appropriate, we will meta-
38
39 73 analyse prevalence and incidence estimates.

40
41 74 **Ethics and dissemination:** This review does not require approval by an Ethics Committee
42
43 75 because it will use published studies. We will publish our results in a peer-reviewed journal
44
45 76 and present at relevant conferences.

46
47 77 **Prospero registration number:** ID256934 (submitted 27 July 2021)

48
49 78 **Word Count:** 3,017

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51 79 **Keywords:** Dry eye, prevalence, incidence, epidemiology, systematic review, United States
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80 INTRODUCTION

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

89 Irrespective of a clinical diagnosis of DED, dry eye causes considerable burden to patients
90 and society. Patient burden includes decreased quality of life due to symptoms, such as
91 foreign body sensation, itching, irritation, soreness, and visual disturbance, which interfere
92 with reading, driving, and work productivity, and cause physical and emotional distress.[3–
93 5] Burdens to society include direct economic costs (e.g., healthcare professional visits,
94 treatment costs),[6] non-direct economic costs (e.g., work productivity loss),[7] and
95 intangible personal costs (e.g., impaired social, emotional, and physical functioning).[8,9] In
96 2011, the estimated direct economic cost to the U.S. healthcare system for DED therapy was
97 \$3.8 billion per year and the estimated total societal cost in the U.S. was \$55.4 billion per
98 year.[6] Comparative analyses have demonstrated that DED-related costs in the U.S. are
99 broadly comparable with other countries.[10] However, in the U.S., personal costs may be
100 higher because treatments, such as ocular lubricants, may not be adequately covered by
101 health insurance, and drug costs tend to be higher in the United States (US).[6,11] With
102 introduction of newer and more costly therapies, an even larger societal economic burden
103 of dry eye can be expected.[12,13] Furthermore, despite being a significant public health
104 problem, dry eye remains underdiagnosed, highlighting the likelihood that there is a
105 significant undiagnosed burden of disease.[2,14,15]

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

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3 111 However, in dry eye, as well as in other ophthalmic diseases, applying differing definitions of
4
5 112 disease to epidemiological datasets can result in widely varying estimates of prevalence.[17]
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7 113 In addition to disease definition, various factors may contribute to differences in prevalence
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9 114 of dry eye.[16] The prevalence has been reported to increase with age, especially in
10
11 115 women.[14,16,18] To our knowledge, few studies have reported prevalence in people
12
13 116 younger than 21 years old, and none were in US-based populations.[18–20] This lack of data
14
15 117 is problematic because young people are also at risk of dry eye due to generally longer
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17 118 screen time (e.g., video monitors, digital tablets), and contact lens wear.[19] The TFOS
18
19 119 report found no clear pattern of dry eye associated with latitude, globally.[16] However, in
20
21 120 the US, there is indirect evidence of an association with latitude, with higher prevalence of
22
23 121 dry eye reported in southern regions of the country.[2,14] Furthermore, other geo-
24
25 122 environmental factors, such as higher atmospheric pressure, air pollution, humidity, and
26
27 123 wind speed, have all been shown to be risk factors for dry eye.[21] As the US comprises an
28
29 124 expansive land mass with great variation in climate across latitudinal and topographical
30
31 125 regions, and given that climatic factors are influential risk factors for dry eye, it is important
32
33 126 to consider these factors when estimating prevalence and incidence of dry eye.

34 127 The literature search for the TFOS Epidemiology report covered a 10-year period from 2005
35
36 128 to 2015 (last updated on September 17, 2015). However, it is unclear whether the TFOS
37
38 129 epidemiology report strictly followed critical steps in the systematic review process, such as
39
40 130 protocol development, risk of bias assessment, and appropriate meta-analysis.[16]

41 131 Furthermore, the TFOS Epidemiology report is now relatively dated because more dry eye-
42
43 132 related epidemiological studies have been performed in the US since its publication.[2,22]

44
45 133 Systematic reviews of dry eye-related epidemiology have been published for other
46
47 134 populations and global regions but,[23,24] to our knowledge, there are no existing
48
49 135 systematic reviews of dry eye epidemiology within the US. As the prevalence and incidence
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51 136 of dry eye are major determinants of the magnitude of the personal, societal, and economic
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53 137 costs of the disease, examining these epidemiological indices can help health policymakers
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55 138 estimate the burden of dry eye in the US and consequently allocate resources to risk
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57 139 mitigation and treatment as needed.
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3 **140 Primary Objective**
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5 141 The primary objective of this systematic review and meta-analysis is to summarize the
6
7 142 prevalence and incidence of dry eye in persons of all ages in the US.
8

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10 **143 Secondary Objectives**
11

- 12 144 1. Estimate the prevalence and incidence of dry eye in the US by disease definition, age
13
14 145 group, sex, study location, and geo-environmental factors.
15
16 146 2. Assess heterogeneity in the prevalence and incidence of dry eye within the US and
17
18 147 factors potentially explaining the heterogeneity.
19
20 148 3. Report epidemiological factors associated with dry eye.
21

22 **149 METHODS AND ANALYSIS**
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24 150 We have registered for this systematic review protocol with the PROSPERO international
25
26 151 register for systematic reviews (ID256934) and we report it in accordance with the Preferred
27
28 152 Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) 2015
29
30 153 statement. We will conduct and report the review with guidance from the Joanna Briggs
31
32 154 Institute Manual for Evidence Synthesis,[25] the Cochrane Handbook for Systematic Reviews
33
34 155 of Interventions,[26] the Meta-analysis of Observational Studies in Epidemiology (MOOSE)
35
36 156 guidelines,[27] the Guidelines for Accurate and Transparent Health Estimates Reporting
37
38 157 (GATHER) statement,[28] and a meta-epidemiological study on the assessment of
39
40 158 prevalence study quality by Migliavaca et al.[29] Patient stakeholders have input into the
41
42 159 development of our research strategies as part of our review group advisory board
43
44 160 (Cochrane Eyes and Vision, National Eye Institute, National Institutes of Health,
45
46 161 UG1EY020522).
47

48 **162 Criteria for considering studies for this review**
49

50 163 We used the populations, context, and condition (PCC) framework for the systematic review
51
52 164 of prevalence and incidence to formulate the eligibility criteria.[30]
53

54 **165 Population and Context**
55

56 166 We will investigate the prevalence and incidence of dry eye in the US population. Prevalence
57
58 167 is the proportion of the population with dry eye at a given time (point or period of time).
59
60 168 Cumulative incidence is the proportion of persons in the at-risk population who develop a

1
2
3 169 new diagnosis of dry eye during a given follow-up period. Incidence rate is the number of
4
5 170 new cases of dry eye divided by the observed person-time during a given observation
6
7 171 period. We aim to explore the influence of demographic factors (e.g., age, sex),
8
9 172 environmental exposures (e.g., air pollution, screen time), meteorological exposures (e.g.,
10
11 173 temperature, wind speed, relative humidity, atmospheric pressure), and underlying risk
12
13 174 factors of disease (e.g., co-morbidities, topical and systemic medications) on these
14
15 175 epidemiological indices.

16 176 Condition

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18
19 177 We will use definitions of dry eye outlined in the included primary studies. We will aim to
20
21 178 consolidate similar case definitions across studies into homogenous definitions when
22
23 179 appropriate. In the TFOS report, case definitions of DED included: (1) Women's Health Study
24
25 180 (WHS) criteria (i.e., self-reported physician diagnosis and/or self-reported 'constant' or
26
27 181 'often' symptoms),[14] (2) dry eye symptoms alone (e.g., measured by the Ocular Surface
28
29 182 Disease Index), (3) dry eye clinical signs alone (e.g., tear break up time), (4) a combination of
30
31 183 dry eye signs and symptoms (distinct from WHS criteria), and (5) Meibomian gland
32
33 184 dysfunction.[16] We will also consider including the definition of dry eye based on relevant
34
35 185 International Classification of Disease codes.

36 186 Types of Studies

37
38 187 We will include population-based observational studies (i.e., cross-sectional studies and
39
40 188 cohort studies) that reported prevalence or incidence of dry eye in the US. We will not
41
42 189 exclude studies based on characteristics such as sampling frame or sampling methods, but
43
44 190 these will be assessed as part of the risk of bias assessment of included studies. We will
45
46 191 exclude case reports, case series, case-control studies, and interventional studies. We will
47
48 192 exclude population-based studies with fewer than 73 total participants because estimates
49
50 193 from samples with less than 73 participants would produce 95% confidence intervals greater
51
52 194 than ± 0.05 when the anticipated minimum population proportion is estimated to be
53
54 195 0.05.[31] However, if we find studies on specific population subgroups (e.g., native
55
56 196 Americans) that have fewer than 73 total participants we will consider them for inclusion.
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197 **Search methods for identification of studies**

198 Electronic Searches

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

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

207 Other Sources

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

213 **Data collection and analysis**

214 Selection of studies

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

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

1
2
3 225 authors do not respond to three emails within 4 weeks, we will use information available
4
5 226 from study reports to determine eligibility.
6

7 227 During the screening process, we will exclude but tag studies of non-US-based populations
8
9 228 that otherwise meet the eligibility criteria. This will prove useful should the population
10
11 229 eligibility criteria be broadened (e.g., other North American populations) due to sparsity of
12
13 230 US-based studies.
14

15 231 We will review studies in languages other than English that reach full text review based on
16
17 232 their title and abstract following translation by Google Translate when possible. We will
18
19 233 report reasons for exclusion of full texts in an 'Excluded Studies' table. We will classify
20
21 234 studies that meet eligibility criteria but have not yet been completed or have not published
22
23 235 full text reports within two years of completion as 'ongoing'. We will resolve discrepancies
24
25 236 regarding the classification of the studies by discussion and, where needed, adjudication by
26
27 237 a third investigator.
28

29 238 Data Extraction and Management

30
31 239 One investigator will extract all relevant study characteristics and other information from
32
33 240 included studies into a data collection form using a platform such as the Systematic Review
34
35 241 Data Repository Plus (SRDR+). An independent investigator will verify the information for
36
37 242 accuracy.[33] We will resolve discrepancies by consensus or, if consensus can't be reached,
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39 243 by adjudication by a third investigator. Where available, we will extract the following data:
40
41 244 article information (first author's name, year of publication, country and region where the
42
43 245 study was conducted), study design, source population, study population, participant
44
45 246 inclusion and exclusion criteria, sampling method, sample size at baseline, index date, dates
46
47 247 of follow up, follow up period, region(s) where the participants were recruited, case
48
49 248 definition(s), participant characteristics (e.g., age, sex), prevalence, prevalence period,
50
51 249 cumulative incidence, incidence rate, and measures of precision. We will extract from each
52
53 250 study, all factors included in association analyses (e.g., age and sex are associated with
54
55 251 increased prevalence/incidence of dry eye). We will extract estimates (e.g., relative risk) and
56
57 252 their precisions for unadjusted and adjusted factors associated with disease. We will record
58
59 253 which covariates were included in the multivariable adjusted models of disease association.
60

254 Assessment of Risk of Bias in Included Studies

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

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

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

279 Data Synthesis

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

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

285 Investigation of Heterogeneity

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

294 Meta-Analyses

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

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

$$308 \quad \text{logit}(P(Y_{ik} = 1)) = \theta + b_i \text{ with } b_i \sim N(0, \tau^2) \quad (1)$$

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

$$311 \quad Y_i \sim \text{Poisson}(\mu_i) \text{ with } \log(\mu_i) = \beta_0 + b_i + \log(T_i) \text{ and } b_i \sim N(0, \tau^2) \quad (2)$$

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2
3 312 Both models (1) and (2) can be fitted in the Generalized Linear Mixed Model (GLMM)
4
5 313 modules available in many popular statistical packages such as SAS, R, and Stata.[38]
6

7 314 **DISCUSSION**

8
9 315 Dry eye disease is a chronic symptomatic condition that is costly to society, reduces quality
10 316 of life and is among the leading reasons for presentation to eye care services worldwide. For
11 317 this reason, the World Health Organization has emphasized that dry eye must not be
12 318 overlooked when addressing global eye care needs.[39] With demographic ageing,[40]
13 319 lifestyle changes,[23] climate changes,[2,14,21] and the introduction of newer and more
14 320 costly therapies,[12] dry eye-related economic costs to the US society can be expected to
15 321 increase considerably. Hence, contemporaneous burden of disease estimates are necessary
16 322 to enable health policymakers and research funding bodies make decisions regarding public
17 323 health interventions and adequate resource allocation.

18 324 Our systematic review and meta-analysis will overcome some of the limitations in previous
19 325 reviews of dry eye epidemiology reports as we will use contemporaneous data and
20 326 comprehensive methods to enhance transparency and reproducibility. However, we do
21 327 anticipate challenges and limitations in our study. Some of the most important limitations
22 328 will be the anticipated high levels of heterogeneity in prevalence and incidence estimates.
23 329 But this will provide the opportunity to explore and report the reasons for heterogeneity
24 330 such as clinical and methodological variations. Other limitations may include reliance on
25 331 secondary data for epidemiological research such as healthcare utilization databases and
26 332 electronic health records which are not primarily designed for research purposes.[22,41]
27 333 Despite these limitations, the information gathered from this study is likely to be widely
28 334 used by patients, physicians, health policymakers, researchers, and custodians to obtain and
29 335 allocate funds and other resources to target the prevention and treatment of dry eye.

30 336 **ETHICS AND DISSEMINATION**

31 337 This review does not require the approval of an Ethics Committee because it will use
32 338 previously published studies. We will publish our results in a peer-reviewed journal and
33 339 present at relevant conferences.
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3 453 **AUTHOR STATEMENT:**
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5 454 Paul McCann: Concept, design, drafting, final submission
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8 455 Alison Abraham: Statistical and methodological design, drafting
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10 456 Darren Gregory: Design, drafting
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12 457 Scott Hauswirth: Design, drafting
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14 458 Cristos Ifantides: Design, drafting
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16 459 Su-Hsun Liu: Methodological design, drafting
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18 460 Ian J. Saldanha: Methodological design, drafting, final submission
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20 461 Tianjing Li: Concept, design, drafting, final submission, guarantor
21

22 462 **DATA STATEMENT:** Data will be made available upon reasonable request.
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24 463 **FUNDING:** This work was supported by National Eye Institute, National Institutes of Health,
25
26 464 grant number UG1EY020522. The funding body had no role in developing the protocol.
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28 465 **CONFLICTS OF INTEREST:** None to declare.
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30 466 **ACKNOWLEDGEMENTS:** We would like to acknowledge the contribution of Kristen Desanto,
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32 467 our information specialist, who assisted us with developing the draft search strategy for
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34 468 electronic databases.
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3 469 Supplementary File
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6 470 Search strategy draft
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8 471 **MEDLINE (via Ovid MEDLINE® ALL)**
9 472 1 exp Dry Eye Syndromes/
10 473 2 exp Keratoconjunctivitis Sicca/
11 474 3 exp Xerophthalmia/
12 475 4 exp Meibomian Glands/
13 476 5 (dry* adj3 eye*).tw,kf.
14 477 6 ((keratoconjunctivitis or kerato-conjunctivitis) adj1 sicca).tw,kf.
15 478 7 xerophthalmi*.tw,kf.
16 479 8 meibomian gland dysfunction.tw,kf.
17 480 9 exp Sjogren's Syndrome/
18 481 10 ((Sjogren* or Sjogren*) adj1 (syndrom* or disease*)).tw,kf.
19 482 11 (9 or 10) and (exp Eye/ or eye*.mp. or ocular*.mp. or ophthalm*.mp.)
20 483 12 or/1-8,11
21 484 13 exp Epidemiology/
22 485 14 exp Epidemiologic Methods/
23 486 15 epidemiology.fs.
24 487 16 burden of disease.tw,kf.
25 488 17 DALY*.tw,kf.
26 489 18 death rate*.tw,kf.
27 490 19 Disability Adjusted Life Years.tw,kf.
28 491 20 disease burden.tw,kf.
29 492 21 endemic*.tw,kf.
30 493 22 epidemic*.tw,kf.
31 494 23 epidemiolog*.tw,kf.
32 495 24 frequency.tw,kf.
33 496 25 incidence*.tw,kf.
34 497 26 morbidities.tw,kf.
35 498 27 morbidity.tw,kf.
36 499 28 occurrence.tw,kf.
37 500 29 outbreak*.tw,kf.
38 501 30 prevalence.tw,kf.
39 502 31 surveillance.tw,kf.
40 503 32 survival rate*.tw,kf.
41 504 33 years lived with disability.tw,kf.
42 505 34 years of life lost.tw,kf.
43 506 35 YLD*.tw,kf.
44 507 36 YLL*.tw,kf.
45 508 37 or/13-36

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3 509 38 12 and 37
4 510 39 38 NOT (exp animals/ NOT exp humans/)
5 511 40 limit 39 to yr="2010 -Current"
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7 512 **Embase (via Elsevier)**
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9 513 #1 'dry eye'/exp
10 514 #2 'dry eye syndrome'/exp
11 515 #3 'evaporative dry eye disease'/exp
12 516 #4 'keratoconjunctivitis sicca'/exp
13 517 #5 'xerophthalmia'/exp
14 518 #6 'meibomian gland'/exp
15 519 #7 (dry* NEAR/3 eye*):ab,ti,kw
16 520 #8 ((keratoconjunctivitis or kerato-conjunctivitis) NEAR/1 sicca):ab,ti,kw
17 521 #9 xerophthalmi*:ab,ti,kw
18 522 #10 'meibomian gland dysfunction':ab,ti,kw
19 523 #11 'Sjogren syndrome'/exp
20 524 #12 ((Sjogren* or Sjogren*) NEAR/1 (syndrom* or disease*)):ab,ti,kw
21 525 #13 (#11 OR #12) AND ('eye'/exp OR eye* OR ocular* OR ophthalm*)
22 526 #14 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #13
23 527 #15 'epidemiology'/exp
24 528 #16 epidemiology:lnk
25 529 #17 'burden of disease':ab,ti,kw
26 530 #18 DALY*:ab,ti,kw
27 531 #19 'death rate*':ab,ti,kw
28 532 #20 'Disability Adjusted Life Years':ab,ti,kw
29 533 #21 'disease burden':ab,ti,kw
30 534 #22 endemic*:ab,ti,kw
31 535 #23 epidemic*:ab,ti,kw
32 536 #24 epidemiolog*:ab,ti,kw
33 537 #25 frequency:ab,ti,kw
34 538 #26 incidence*:ab,ti,kw
35 539 #27 morbidities:ab,ti,kw
36 540 #28 morbidity:ab,ti,kw
37 541 #29 occurrence:ab,ti,kw
38 542 #30 outbreak*:ab,ti,kw
39 543 #31 prevalence:ab,ti,kw
40 544 #32 surveillance:ab,ti,kw
41 545 #33 'survival rate*':ab,ti,kw
42 546 #34 'years lived with disability':ab,ti,kw
43 547 #35 'years of life lost':ab,ti,kw
44 548 #36 YLD*:ab,ti,kw
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552 #37
553 #39 #14 AND #38
554 #40 #39 NOT ([animals]/lim NOT [humans]/lim)
555 #41 #40 AND [2010-2021]/py
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558 **PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis**
 559 **Protocols) 2015 checklist: recommended items to address in a systematic review**
 560 **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	✓
Study records:			
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)	✓
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	✓
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	✓
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	✓
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	n/a

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

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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 23 epidemiolog*.tw,kf.
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 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.
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 34 years of life lost.tw,kf.
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 36 YLL*.tw,kf.
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- 40 limit 39 to yr="2010 -Current"
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- #2 'dry eye syndrome'/exp
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- #5 'xerophthalmia'/exp
- #6 'meibomian gland'/exp
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- #8 ((keratoconjunctivitis or kerato-conjunctivitis) NEAR/1 sicca):ab,ti,kw
- #9 xerophthalmi*:ab,ti,kw
- #10 'meibomian gland dysfunction':ab,ti,kw
- #11 'Sjogren syndrome'/exp
- #12 ((Sjogren* or Sjogren*) 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

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11 #41 #40 AND [2010-2021]/py
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1 **PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis**
2 **Protocols) 2015 checklist: recommended items to address in a systematic review**
3 **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	✓
Study records:			
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)	✓
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	✓
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	✓
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	✓
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	n/a

4 *** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and**
5 **Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol**
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BMJ Open

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

Journal:	<i>BMJ Open</i>
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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44 **ABSTRACT**

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

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

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

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

67 **Prospero registration number:** CRD42021256934

68 **Word Count:** 3,716

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

70 **ARTICLE SUMMARY**

71 **Strengths and limitations of this study**

- 1
2
3 72 • This systematic review and meta-analysis aims to report the prevalence and
4 incidence of dry in the United States.
5 73
6
7 74 • We aim to overcome limitations in previous reviews of dry eye epidemiology reports.
8
9 75 • We will use contemporaneous data and comprehensive methods to enhance
10 transparency and reproducibility.
11 76
12 77 • We anticipate high levels of heterogeneity in prevalence and incidence estimates,
13 however we aim to explore the reasons for heterogeneity.
14 78
15
16 79

For peer review only

80 INTRODUCTION

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

89 Irrespective of a clinical diagnosis of DED, dry eye causes considerable burden to patients
90 and society. Patient burden includes decreased quality of life due to symptoms, such as
91 foreign body sensation, itching, irritation, soreness, and visual disturbance, which interfere
92 with reading, driving, and work productivity, and cause physical and emotional distress.[3–
93 5] Burdens to society include direct economic costs (e.g., healthcare professional visits,
94 treatment costs),[6] non-direct economic costs (e.g., work productivity loss),[7] and
95 intangible personal costs (e.g., impaired social, emotional, and physical functioning).[8,9] In
96 2011, the estimated direct economic cost to the United States (US) healthcare system for
97 DED therapy was \$3.8 billion per year and the estimated total societal cost in the U.S. was
98 \$55.4 billion per year.[6] Comparative analyses have demonstrated that DED-related costs
99 in the U.S. are broadly comparable with other countries.[10] However, in the US, personal
100 costs may be higher because treatments, such as ocular lubricants, may not be adequately
101 covered by health insurance, and drug costs tend to be higher in the US.[6,11] With
102 introduction of newer and more costly therapies, an even larger societal and personal
103 economic burden of dry eye can be expected.[12–14] Furthermore, despite being a
104 significant public health problem, dry eye remains underdiagnosed, highlighting the
105 likelihood that there is a significant undiagnosed burden of disease.[2,15,16]

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

1
2
3 111 However, in dry eye, as well as in other ophthalmic diseases, applying differing definitions of
4 112 disease to epidemiological datasets can result in widely varying estimates of prevalence.[18]
5
6
7 113 In addition to disease definition, various factors may contribute to differences in prevalence
8
9 114 of dry eye.[17] The prevalence has been reported to increase with age, especially in
10
11 115 women.[15,17,19] To our knowledge, few studies have reported prevalence in people
12
13 116 younger than 21 years old, and none were in US-based populations.[19–21] This lack of data
14
15 117 is problematic because young people are also at risk of dry eye due to generally longer
16
17 118 screen time (e.g., video monitors, digital tablets), and contact lens wear.[20] The TFOS
18
19 119 report found no clear pattern of dry eye associated with latitude, globally.[17] However, in
20
21 120 the US, there is indirect evidence of an association with latitude, with higher prevalence of
22
23 121 dry eye reported in southern regions of the country.[2,15] Furthermore, other geo-
24
25 122 environmental factors, such as higher atmospheric pressure, air pollution, humidity, and
26
27 123 wind speed, have all been shown to be risk factors for dry eye.[22] As the US comprises an
28
29 124 expansive land mass with great variation in climate across latitudinal and topographical
30
31 125 regions, and given that climatic factors are influential risk factors for dry eye, it is important
32
33 126 to consider these factors when estimating prevalence and incidence of dry eye.
34
35 127 The literature search for the TFOS Epidemiology report covered a 10-year period from 2005
36
37 128 to 2015 (last updated on September 17, 2015). However, it is unclear whether the TFOS
38
39 129 epidemiology report strictly followed critical steps in the systematic review process, such as
40
41 130 protocol development, risk of bias assessment, and appropriate meta-analysis.[17]
42
43 131 Furthermore, the TFOS Epidemiology report is now relatively dated because more dry eye-
44
45 132 related epidemiological studies have been performed in the US since its publication.[2,23]
46
47 133 Systematic reviews of dry eye-related epidemiology have been published for other
48
49 134 populations and global regions but,[24,25] to our knowledge, there are no existing
50
51 135 systematic reviews of dry eye epidemiology within the US. As the prevalence and incidence
52
53 136 of dry eye are major determinants of the magnitude of the personal, societal, and economic
54
55 137 costs of the disease, examining these epidemiological indices can help health policymakers
56
57 138 estimate the burden of dry eye in the US and consequently allocate resources to risk
58
59 139 mitigation and treatment as needed.
60

140 **Primary Objective**

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

143 **Secondary Objectives**

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

150 **METHODS AND ANALYSIS**

151 We have registered for this systematic review protocol with the PROSPERO international
152 register for systematic reviews (CRD42021256934) and we report it in accordance with the
153 Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P)
154 2015 statement (see Supplementary File 1). We will conduct and report the review with
155 guidance from the Joanna Briggs Institute Manual for Evidence Synthesis,[26] the Cochrane
156 Handbook for Systematic Reviews of Interventions,[27] the Meta-analysis of Observational
157 Studies in Epidemiology (MOOSE) guidelines,[28] the Guidelines for Accurate and
158 Transparent Health Estimates Reporting (GATHER) statement,[29] and a meta-
159 epidemiological study on the assessment of prevalence study quality by Migliavaca et al.[30]

160 **Patient and Public Involvement**

161 No patient involved.

162 **Criteria for considering studies for this review**

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

165 **Population and Context**

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

1
2
3 169 risk population who develop a new diagnosis of dry eye during a given follow-up period.
4
5 170 Incidence rate is the number of new cases of dry eye divided by the observed person-time
6
7 171 during a given observation period. We aim to explore the influence of demographic factors
8
9 172 (e.g., age, sex), environmental exposures (e.g., air pollution, screen time), meteorological
10
11 173 exposures (e.g., temperature, wind speed, relative humidity, atmospheric pressure), and
12
13 174 underlying risk factors of disease (e.g., co-morbidities, topical and systemic medications) on
14
15 175 these epidemiological indices. Our source populations will be from studies conducted within
16
17 176 the US and studies conducted outside the US are not eligible. However, the target
18
19 177 population may be broadened to Continental North American populations if there is a
20
21 178 sparsity of US-based studies (i.e., less than two US-based studies) although this is not
22
23 179 expected.

24 180 Condition

25
26 181 We will use definitions of dry eye outlined in the included primary studies. We will aim to
27
28 182 consolidate similar case definitions across studies into homogenous definitions when
29
30 183 appropriate. In the TFOS report, case definitions of DED included: (1) Women's Health Study
31
32 184 (WHS) criteria (i.e., self-reported physician diagnosis and/or self-reported 'constant' or
33
34 185 'often' symptoms),[15] (2) dry eye symptoms when signs were not measured (e.g.,
35
36 186 measured by the Ocular Surface Disease Index), (3) dry eye clinical signs when symptoms
37
38 187 were not measured (e.g., tear break up time), (4) a combination of dry eye signs and
39
40 188 symptoms (distinct from WHS criteria), and (5) Meibomian gland dysfunction.[17] We will
41
42 189 also include dry eye definitions based on relevant International Classification of Disease
43
44 190 codes.

45 191 Types of Studies

46
47 192 We will include population-based observational studies (i.e., cross-sectional studies and
48
49 193 cohort studies) that reported prevalence or incidence of dry eye in the US. We will not
50
51 194 exclude studies based on characteristics such as sampling frame or sampling methods, but
52
53 195 these will be assessed as part of the risk of bias assessment of included studies. We will
54
55 196 exclude case reports, case series, case-control studies, and interventional studies. We will
56
57 197 exclude population-based studies with fewer than 73 total participants because estimates
58
59 198 from samples with less than 73 participants would produce 95% confidence intervals greater
60
199 than ± 0.05 when the anticipated minimum population proportion is estimated to be

1
2
3 200 0.05.[32] However, if we find studies on specific population subgroups (e.g., native
4
5 201 Americans) that have fewer than 73 total participants we will consider them for inclusion.
6

7 202 **Search methods for identification of studies**

9 203 Electronic Searches

11 204 Working with an information specialist, we will develop search strategies for Ovid Medline,
12
13 205 and Embase for population-based studies that report the prevalence and/or incidence of dry
14
15 206 eye. We will include studies involving persons with all ages from 1 January 2010 to the
16
17 207 current date with no language restrictions. The search strategy will include text word as well
18
19 208 as controlled vocabulary (e.g., medical subject headings, Emtree) terms for epidemiological
20
21 209 concepts, such as “epidemiology”, “prevalence”, “incidence”, and “burden of disease”,
22
23 210 combined with dry eye-related concepts, such as “dry eye syndromes” (see Supplementary
24
25 211 File 2).

27 212 Other Sources

29 213 We will hand-search references of included studies, dry eye epidemiology-related
30
31 214 systematic reviews, and clinical practice guidelines for additional studies. Conference
32
33 215 abstracts will be searched as part of our electronic search of Embase. We will search
34
35 216 literature provided by agencies including the World Health Organization. We will contact
36
37 217 study authors for complete data to calculate prevalence and/or incidence when required.
38

39 218 **Data collection and analysis**

41 219 Selection of studies

43 220 We will remove duplicate records and import the search results into Covidence®, a web-
44
45 221 based review management software.[33] Then, two investigators will independently screen
46
47 222 each title and abstract. Investigators will classify each record as 'yes' (relevant), 'maybe'
48
49 223 (possibly relevant) and 'no' (not relevant) for further full-text review. During title/abstract
50
51 224 screening, studies that meet the eligibility criteria for population, context, and condition will
52
53 225 be included for full text screening.

55 226 We will retrieve the full-text articles for records considered 'relevant' or 'possibly relevant'.
56
57 227 Then, two investigators will independently screen the full-text articles for eligibility and
58
59 228 classify articles as 'to be included' or 'to be excluded'. If there are questions regarding the
60

1
2
3 229 eligibility of a given study, we will contact its authors to obtain additional information. If the
4
5 230 authors do not respond to three emails within 4 weeks, we will use information available
6
7 231 from study reports to determine eligibility.
8

9 232 During the screening process, we will exclude but tag studies of non-US-based populations
10
11 233 that otherwise meet the eligibility criteria. This will prove useful should the population
12
13 234 eligibility criteria be broadened (i.e., Continental North American populations) due to
14
15 235 sparsity of US-based studies.

16
17 236 We will review studies in languages other than English that reach full text review based on
18
19 237 their title and abstract following translation by Google Translate when possible. We will
20
21 238 report reasons for exclusion of full texts in an 'Excluded Studies' table. We will classify
22
23 239 studies that meet eligibility criteria but have not yet been completed or have not published
24
25 240 full text reports within two years of completion as 'ongoing'. We will resolve discrepancies
26
27 241 regarding the classification of the studies by discussion and, where needed, adjudication by
28
29 242 a third investigator.

30 243 Data Extraction and Management

31
32 244 One investigator will extract all relevant study characteristics and other information from
33
34 245 included studies into a data collection form using a platform such as the Systematic Review
35
36 246 Data Repository Plus (SRDR+). An independent investigator will verify the information for
37
38 247 accuracy.[34] We will resolve discrepancies by consensus or, if consensus can't be reached,
39
40 248 by adjudication by a third investigator. Where available, we will extract the following data:
41
42 249 article information (first author's name, year of publication, country and region where the
43
44 250 study was conducted), study design, source population, study population, participant
45
46 251 inclusion and exclusion criteria, sampling method, sample size at baseline, index date, dates
47
48 252 of follow up, follow up period, region(s) where the participants were recruited, case
49
50 253 definition(s), participant characteristics (e.g., age, sex), prevalence, prevalence period,
51
52 254 cumulative incidence, incidence rate, and measures of precision. We will extract from each
53
54 255 study, all factors included in association analyses (e.g., age and sex are associated with
55
56 256 increased prevalence/incidence of dry eye). We will extract estimates (e.g., relative risk) and
57
58 257 their precisions for unadjusted and adjusted factors associated with disease. We will record
59
60 258 which covariates were included in the multivariable adjusted models of disease association.

259 Assessment of Risk of Bias in Included Studies

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

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

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

284 Data Synthesis

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

1
2
3 289 environmental factors and screen time when data is available. We will document prevalence
4
5 290 and incidence of dry eye severity using previously defined classifications when reported in
6
7 291 the primary studies.[38,39] All data will be stratified by case definition whenever feasible.
8

9 292 Investigation of Heterogeneity

10
11 293 We will qualitatively investigate sources of heterogeneity of the data by assessing risk of
12
13 294 bias and other aspects of the design of each study (methodological heterogeneity) and
14
15 295 examining the characteristics of the populations (clinical heterogeneity) in each study,
16
17 296 including age, sex, case definition, and sociodemographic profiles. We will display the
18
19 297 estimates and their uncertainty from each study in forest plots (separately for prevalence
20
21 298 and incidence). We will quantitatively assess statistical heterogeneity by calculating the
22
23 299 amount of heterogeneity (τ^2) and the contribution of heterogeneity to the total variability
24
25 300 across studies (I^2).[40]

26 301 Meta-Analyses

27
28
29 302 When appropriate, we will conduct meta-analyses of prevalence and incidence estimates.
30
31 303 We will combine data if the study estimates have acceptable heterogeneity, both
32
33 304 qualitatively and quantitatively. If a study uses more than one case definition and reports
34
35 305 several prevalence and incidence estimates, we will stratify the estimates by case definition
36
37 306 and analyze them in separate subgroup meta-analyses. We will use our clinical expertise and
38
39 307 the literature to judge which case definitions are compatible for pooling in subgroup meta-
40
41 308 analyses. We will also consider stratifying meta-analyses by levels of risk of bias. We will
42
43 309 consider meta-analysis of measures of association for common risk factor covariates across
44
45 310 studies. Whether or not we conduct meta-analyses, we will qualitatively summarize the
46
47 311 findings across studies in a summary of findings table.

48 312 We will meta-analyse prevalence and cumulative incidence proportions using separate
49
50 313 random-intercept regression models with a logistic link function via the exact likelihood
51
52 314 method. We will combine incidence rate using a random-intercept regression model. Both
53
54 315 models and can be fitted in the Generalized Linear Mixed Model (GLMM) modules available
55
56 316 in many popular statistical packages such as SAS, R, and Stata.[41]
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3 317 Meta-regression
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5 318 If there are sufficient risk factor data within-sample (i.e., from the primary studies) and out-
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7 319 of-sample (e.g., from census-derived demographic data, governmental agency derived geo-
8
9 320 environmental data), we will consider conducting a Bayesian meta-regression with
10
11 321 integrative systems modelling using DisMod-MR software.[42] This will allow us to
12
13 322 extrapolate nationwide prevalence and incidence estimates captured in the primary studies
14
15 323 and stratify prevalence and incidence by factors such as age, sex, US region and geo-
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17 324 environmental factors.[42–44] Integrative systems modelling potentially addresses some of
18
19 325 the notable challenges faced in this meta-analysis including, (1) diverse case-definitions, (2)
20
21 326 variation in environmental and climatic exposures within the country, and (3) a lack of
22
23 327 standardised age stratification), which may improve compatibility for pooling of data. We
24
25 328 will consult with statisticians and integrative systems modelling experts to decide on the
26
27 329 most appropriate statistical approach.

28 330 **DISCUSSION**

29
30 331 Dry eye disease is a chronic symptomatic condition that is costly to society, reduces quality
31
32 332 of life and is among the leading reasons for presentation to eye care services worldwide. For
33
34 333 this reason, the World Health Organization has emphasized that dry eye must not be
35
36 334 overlooked when addressing global eye care needs.[45] With demographic ageing,[46]
37
38 335 lifestyle changes,[24] climate changes,[2,15,22] and the introduction of newer and more
39
40 336 costly therapies,[13] dry eye-related economic costs to the US society can be expected to
41
42 337 increase considerably. Hence, contemporaneous burden of disease estimates are necessary
43
44 338 to enable health policymakers and research funding bodies make decisions regarding public
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46 339 health interventions and adequate resource allocation.

47 340 Our systematic review and meta-analysis will overcome some of the limitations in previous
48
49 341 reviews of dry eye epidemiology reports as we will use contemporaneous data and
50
51 342 comprehensive methods to enhance transparency and reproducibility. However, we do
52
53 343 anticipate challenges and limitations in our study. An important limitation will be the
54
55 344 anticipated high levels of heterogeneity in prevalence and incidence estimates. But this will
56
57 345 provide the opportunity to explore and report the reasons for heterogeneity such as clinical
58
59 346 and methodological variations. Another limitation is that we will search only published
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347 literature and we acknowledge the potential of publication bias. Despite potential

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2
3 348 limitations, the information gathered from this study is likely to be widely used in the United
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5 349 States and in comparable settings by patients, physicians, health policymakers, researchers,
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7 350 and custodians to obtain and allocate funds and other resources to target the prevention
8
9 351 and treatment of dry eye.

10
11 352 **ETHICS AND DISSEMINATION**

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13 353 This review does not require the approval of an Ethics Committee because it will use
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15 354 previously published studies. We will publish our results in a peer-reviewed journal and
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17 355 present at relevant conferences.
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3 356 **AUTHOR STATEMENT:**
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5 357 Paul McCann: Concept, design, drafting, final submission
6

7
8 358 Alison Abraham: Statistical and methodological design, drafting
9

10 359 Darren Gregory: Design, drafting
11

12 360 Scott Hauswirth: Design, drafting
13

14 361 Cristos Ifantides: Design, drafting
15

16 362 Su-Hsun Liu: Methodological design, drafting
17

18 363 Ian J. Saldanha: Methodological design, drafting, final submission
19

20 364 Tianjing Li: Concept, design, drafting, final submission, guarantor
21

22 365 **CONFLICTS OF INTEREST:** None to declare.
23

24 366 **FUNDING:** This work was supported by National Eye Institute, National Institutes of Health,
25
26 367 grant number UG1EY020522. The funding body had no role in developing the protocol.
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3 498 **DATA STATEMENT:** Data will be made available upon reasonable request.
4

5 499 **ACKNOWLEDGEMENTS:** We would like to acknowledge the contribution of Kristen Desanto,
6
7 500 our information specialist, who assisted us with developing the search strategy for
8
9 501 electronic databases. We would also like to acknowledge and thank Dr Abraham Flaxman
10
11 502 (University of Washington) for reviewing and consulting on our proposed meta-regression
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13 503 methods.
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1 Supplementary File 1

2

3 **PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis**
 4 **Protocols) 2015 checklist: recommended items to address in a systematic review**
 5 **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.

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3 35 YLD*.tw,kf.
4 36 YLL*.tw,kf.
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9 39 38 NOT (exp animals/ NOT exp humans/)
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Embase (via Elsevier)

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13 #1 'dry eye'/exp
14 #2 'dry eye syndrome'/exp
15 #3 'evaporative dry eye disease'/exp
16 #4 'keratoconjunctivitis sicca'/exp
17 #5 'xerophthalmia'/exp
18 #6 'meibomian gland'/exp
19 #7 (dry* NEAR/3 eye*):ab,ti,kw
20 #8 ((keratoconjunctivitis or kerato-conjunctivitis) NEAR/1 sicca):ab,ti,kw
21 #9 xerophthalmi*:ab,ti,kw
22 #10 'meibomian gland dysfunction':ab,ti,kw
23 #11 'Sjogren syndrome'/exp
24 #12 ((Sjogren* or Sjogren*) NEAR/1 (syndrom* or disease*)):ab,ti,kw
25 #13 (#11 OR #12) AND ('eye'/exp OR eye* OR ocular* OR ophthalm*)
26 #14 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #13
27 #15 'epidemiology'/exp
28 #16 epidemiology:lnk
29 #17 'burden of disease':ab,ti,kw
30 #18 DALY*:ab,ti,kw
31 #19 'death rate*':ab,ti,kw
32 #20 'Disability Adjusted Life Years':ab,ti,kw
33 #21 'disease burden':ab,ti,kw
34 #22 endemic*:ab,ti,kw
35 #23 epidemic*:ab,ti,kw
36 #24 epidemiolog*:ab,ti,kw
37 #25 frequency:ab,ti,kw
38 #26 incidence*:ab,ti,kw
39 #27 morbidities:ab,ti,kw
40 #28 morbidity:ab,ti,kw
41 #29 occurrence:ab,ti,kw
42 #30 outbreak*:ab,ti,kw
43 #31 prevalence:ab,ti,kw
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3 #32 surveillance:ab,ti,kw
4 #33 'survival rate*':ab,ti,kw
5 #34 'years lived with disability':ab,ti,kw
6 #35 'years of life lost':ab,ti,kw
7 #36 YLD*:ab,ti,kw
8 #37 YLL*:ab,ti,kw
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10 #38 #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR
11 #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37
12 #39 #14 AND #38
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14 #41 #40 AND [2010-2021]/py
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