PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Prevalence and incidence of dry eye in the United States: a systematic review protocol
AUTHORS	McCann, Paul; Abraham, Alison; Gregory, Darren G.; Hauswirth, Scott; Ifantides, Cristos; Liu, Su-Hsun; Saldanha, Ian; Li, Tianjing

VERSION 1 – REVIEW

REVIEWER	Wolffsohn, JS Aston University, Ophthalmic Research Group, Life and Health Sciences
REVIEW RETURNED	06-Sep-2021

GENERAL COMMENTS	While BMJOPHTHOpen accepts protocols including those related to systematic reviews, this information needs to be included in a systematic review publication and therefore it is difficult to see the relevance of a protocol review. As highlighted, the definitions used in prevalence studies are not homogeneous so how will this review advance knowledge? Symptomology is missing from the definition of dry eye in the abstract. Personal pronouns such as “we” should be avoided in scientific writing Ln85-86 The TFOS definition of dry eye is the gold standard definition of dry eye and has been since 2007 with DEWS, updated in 2017 Ln333 note that this will only be relevant to clinicians, policy makers etc in the USA

REVIEWER	Woods, Jill University of Waterloo, CORE, Optometry
REVIEW RETURNED	20-Sep-2021

GENERAL COMMENTS	REVIEW: bmjopen-2021-056203 Very well written and very clear. A few comments only for consideration by the authors. Hauswirth, Ifantides & Liu have the word ‘Denver’ in the table of authors (University of Colorado Denver) but this word is not repeated in the manuscript’s author listing, page 4. Is this purposeful or an error? ABSTRACT Introduction, line 56 & 57: the description of dry eye here is not

	aligned with the description in the fiorst sentence on the Introduction. Suggest to replace inflammation of the ocular surface' with 'ocular symptoms', because DED can exist with no signs of anterior ocular inflammation, while symptoms are required for a diagnosis. Methods, line 63: suggest to add for clarity '… and cohort studies involving US based populations that report the prevalence …..'. INTRODUCTION Line102: Consider adding the following ' …an even larger societal and personal economic burden …'. LINE 118: There are better references to support the link between dry eye and screen time, and with contact lenses. Consider: □ Al-Mohtaseb et al. ClinOphthalmol 2021. 15:3811-20 □ Downie & Craig . Clin Exp Opt 2017, 100:438-458. □ Gomes et al. Ocul Surf 15(3),511-538. □ Gayton JL. Clinical Ophthalmol (Auck) 2009. 3(1),401-412

REVIEWER	Stapleton, Fiona The University of New South Wales, School of Optometry and Vision Science
REVIEW RETURNED	27-Sep-2021

GENERAL COMMENTS	Thank you for the opportunity to review this systematic review protocol. This is a well written and well considered manuscript. I have only minor comments. 1. The rationale is clearly presented and the proposed analysis and approach reasonable. 2. I suspect there will be limited studies to allow a formal meta-analysis by age and sex. It is not entirely clear if there is a fallback or alternative approach if this is the case. Similarly if data are not available disaggregated by age and sex. Is this where studies of electronic health records will be included or studies outside of north America? 3. As the authors state it is important to include youth as the majority of population based studies in youth have been conducted in Asia and there are limited US based studies. Controlling for digital device use as a risk factor will be challenging but important in this population. 4. On a point of clarification, the disease definitions in the TFOS Epidemiology Report, included signs (in studies where symptoms were not measured, not that symptoms were absent); signs and symptoms and symptoms (in studies where signs were not measured, not that symptoms were absent). 5. I am curious about the inclusion of health records as a surrogate sample for population incidence or prevalence - it may be simpler to exclude those from the grouping and report them separately. 6. Disease severity is not mentioned. From a perspective of the cost and impact of the disease and allocation of health resources, I would recommend that where possible prevalence is also reported by severity of dry eye disease. 7. Agree it is important to tag studies in other populations - if there are limited data from studies in north America, it may be helpful to look at eligible studies reporting rates in Caucasians, Asians, Blacks and hispanics in other populations, e.g data from the Lifelines cohort study in the Netherlands using the WHS criteria.

	8. I appreciate there may be variations in the prevalence of dry eye by region, weather and pollution. How will these variations be handled in the analysis?

VERSION 1 – AUTHOR RESPONSE

We thank the Editor and Peer Reviewers for taking the time to consider this protocol and for their valuable comments and suggestions. In the table below we have addressed the comments with an author reply and have outlined any amendments. Please note than amendments column pertains to Main Document – 'marked copy' unless otherwise stated

Reviewer: 1	**Author reply**	**Amendment**
While BMJOPHTHOpen accepts protocols including those related to systematic reviews, this information needs to be included in a systematic review publication and therefore it is difficult to see the relevance of a protocol review.	Review protocols serve the purpose of pre-specifying the review process before the review is conducted and published. This step aims to prevent biased conduct of the review and holds the authors accountable to any deviations from the protocol. We do this to increase the methodological rigor of the systematic review.	No changes
As highlighted, the definitions used in prevalence studies are not homogeneous so how will this review advance knowledge?	Clinical and methodological diversity and statistical heterogeneity will be explored in depth to ascertain reasons for variability in the prevalence/incidence of dry eye in this review. Heterogenous disease definitions are only one aspect of clinical heterogeneity which this review will explore. Systematic exploration of clinical, methodological, and statistical heterogeneity has not been conducted in previous reports of dry eye epidemiology in the US population and the TFOS epidemiology report did not conduct critical steps of the systematic review process (e.g., risk of bias assessment) when it reviewed descriptive epidemiology of dry eye.	

	We will advance knowledge by pooling compatible results from across studies with varied definitions for dry eye to increase precision of estimates and by systematically exploring risk of bias and heterogeneity in the current literature. This will provide insight into the quality of current literature and highlight methodological considerations for future studies that estimate dry eye epidemiology. Such a systematic review is not currently available for US populations.	
Symptomology is missing from the definition of dry eye in the abstract.	Symptomology added to definition of dry eye in the abstract	Line 56 – 58: Dry eye is a multifactorial chronic condition characterized by tear film insufficiency and instability, and ocular symptoms including foreign body sensation, itching, irritation, soreness, and visual disturbance.
Personal pronouns such as "we" should be avoided in scientific writing	We used consistent active voice rather than passive voice as it is recommended (https://www.bmj.com/about-bmj/resources-authors/house-style). If it is a major editorial problem, we will make necessary changes	No changes
Ln85-86 The TFOS definition of dry eye is the gold standard definition of dry eye and has been since 2007 with DEWS, updated in 2017	Agreed – amendment made – 'definition of' changed to 'diagnostic test for'	Line 96 - 97: Because there is no gold standard diagnostic test for DED, the term "dry eye" is used to describe various presentations of ocular discomfort and tear film abnormalities.
Ln333 note that this will only be relevant to clinicians, policy makers etc in the USA	Agreed - the target population for the systematic review is the US population. The findings may be generalizable to similar population contexts	Line 369 – 373: Despite potential limitations, the information gathered from this study is likely to be widely used in the United States and in comparable settings by patients, physicians, health policymakers, researchers,

		and custodians to obtain and allocate funds and other resources to target the prevention and treatment of dry eye.
Reviewer: 2		
Hauswirth, Ifantides & Liu have the word 'Denver' in the table of authors (University of Colorado Denver) but this word is not repeated in the manuscript's author listing, page 4. Is this purposeful or an error?	Consistent affiliations added	Consistent affiliations added
ABSTRACT Introduction, line 56 & 57: the description of dry eye here is not aligned with the description in the fiorst sentence on the Introduction. Suggest to replace inflammation of the ocular surface' with 'ocular symptoms', because DED can exist with no signs of anterior ocular inflammation, while symptoms are required for a diagnosis. Methods, line 63: suggest to add for clarity '… and cohort studies involving US based populations that report the prevalence …..'.	Suggestions added	Line 56 – 58: Dry eye is a multifactorial chronic condition characterized by tear film insufficiency and instability, and ocular symptoms including foreign body sensation, itching, irritation, soreness, and visual disturbance. Line 62 – 65: 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.
INTRODUCTION Line102: Consider adding the following ' …an even larger societal and personal economic burden …'. LINE 118: There are better references to support the link between dry eye and screen time, and with contact lenses. Consider: Al-Mohtaseb et al.	Suggestions added	Line 113 – 114: With introduction of newer and more costly therapies, an even larger societal and personal economic burden of dry eye can be expected.

ClinOphthalmol 2021. 15:3811-20 Downie & Craig . Clin Exp Opt 2017, 100:438-458. Gomes et al. Ocul Surf 15(3),511-538. Gayton JL. Clinical Ophthalmol (Auck) 2009. 3(1),401-412		
Reviewer: 3		
I suspect there will be limited studies to allow a formal meta-analysis by age and sex. It is not entirely clear if there is a fallback or alternative approach if this is the case. Similarly if data are not available disaggregated by age and sex. Is this where studies of electronic health records will be included or studies outside of north America?	In our meta-analyses section, we did not specify meta-analysis to be stratified by age and sex. We will stratify meta-analysis by case definition and/or by risk of bias assessment. In the qualitative data-synthesis (i.e., in structured tables) we will document risk factors for dry eye reported by each study such as age and sex and we will report the effect estimates. We have removed mention of stratification by various factors in the secondary objectives as this may be interpreted as stratification of the meta-analysis. If there is sufficient information available, we will conduct Bayesian meta-regression to explore associations between prevalence/incidence estimates and age, sex, or other risk factors. Electronic health records (i.e., ICD-10 code definitions of dry eye) are eligible for inclusion. We have made this more explicit and removed any wording that introduced doubt	Line 156 – 158: 1. Estimate the effect of disease definition, age group, sex, US region, and geo-environmental factors on prevalence and incidence of dry eye in the US by using meta-regression methods. Line 190 – 194 added: Our source populations will be from studies conducted within the US and studies conducted outside the US are not eligible. However, the target population may be broadened to Continental North American populations if there is a sparsity of US-based studies (i.e., less than two US-based studies) although this is not expected. Line 339 – 351: Meta-regression If there are sufficient risk factor data within-sample (i.e., from the primary studies) and out-of-sample (e.g., from census-derived demographic data, governmental agency derived geo-environmental data), we will consider conducting a Bayesian meta-

	regarding this point. Studies outside of US are not eligible for the study. We will consider studies in Continental North America if there are less than 2 US-based studies. Disaggregation by age and sex is not a consideration for broadening eligibility criteria to Continental North American populations, only lack of studies	regression with integrative systems modelling using DisMod-MR software. This will allow us to estimate prevalence and incidence estimates not captured in the primary studies and stratify prevalence and incidence by factors such as age, sex, US region and geo-environmental factors. 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.
As the authors state it is important to include youth as the majority of population based studies in youth have been conducted in Asia and there are limited US based studies. Controlling for digital device use as a risk factor will be challenging but important in this population.	Now specified in the data synthesis – but reporting in our review will not explicitly be limited to youth	Line 301 – 304: We will also present all reported potential risk factors for dry eye including their definitions (e.g., age grouping) and effect estimates for each potential risk factor, including specific risk factors such as geo-environmental factors and screen time when data is available.
On a point of clarification, the disease definitions in the TFOS Epidemiology Report, included signs (in studies where symptoms were not measured, not that symptoms were absent); signs and symptoms and symptoms (in studies where signs were not measured, not that symptoms	Clarifications made	Line 198 – 205: In the TFOS report, case definitions of DED included: (1) Women's Health Study (WHS) criteria (i.e., self-reported physician diagnosis and/or self-reported 'constant' or 'often' symptoms), (2) dry eye symptoms when signs were not measured (e.g., measured by the Ocular

were absent).		Surface Disease Index), (3) dry eye clinical signs when symptoms were not measured (e.g., tear break up time), (4) a combination of dry eye signs and symptoms (distinct from WHS criteria), and (5) Meibomian gland dysfunction.[16] We will also include dry eye definitions based on relevant International Classification of Disease codes.
I am curious about the inclusion of health records as a surrogate sample for population incidence or prevalence - it may be simpler to exclude those from the grouping and report them separately.	The use of health records as a source population may well produce a representative sample of the US population (especially in large databases across states) so we will not group and report them separately based on being health records. Representativeness will be examined as part of risk of bias assessment. Grouping of reporting / meta-analysis will be informed by heterogeneity between the studies. Case definitions in health records are commonly based on ICD10 codes therefore prevalence and incidence will be stratified on this basis.	No changes
Disease severity is not mentioned. From a perspective of the cost and impact of the disease and allocation of health resources, I would recommend that where possible prevalence is also reported by severity of dry eye disease.	Agreed	Line 304 – 305: We will document prevalence and incidence of dry eye severity using previously defined classifications when reported in the primary studies.
Agree it is important to tag studies in other populations - if there are limited data from studies in north America, it may be helpful to look at eligible studies reporting rates in Caucasians, Asians, Blacks	Thank you for your suggestions and highlighting relevant literature. We do plan to report race/ethnicity-specific estimates if there are relevant group-specific data available. However, whilst reporting rates in Caucasians, Asians, Blacks	No changes

and hispanics in other populations, e.g data from the Lifelines cohort study in the Netherlands using the WHS criteria.	and hispanics in other populations (e.g., in the Netherlands) is important, the current review aims to synthesize evidence based on US studies, rather than study populations outside of the US. Because the US has distinct climatic and environmental factors we believe this would limit the generalizability of prevalence/incidence estimates in Europe subpopulations to the US population. Our contingency if there are limited data from studies in the US is to widen our target population to Continental North America.	
I appreciate there may be variations in the prevalence of dry eye by region, weather and pollution. How will these variations be handled in the analysis?	They will be reported in the qualitative synthesis in structured tables when reported by the primary studies. The amount of variation (heterogeneity) will be quantified as I-squared statistics in meta-analysis and the range of its possible values deemed as considerable heterogeneity, for example, 75% to 100%, will prompt us to consider the choice of random-effects models other than fixed-effects models. Whether and how much geographical regions, weather conditions, and air quality of the study sites contributed to the observed variations across studies, will also be explored and accounted for by Bayesian meta-regression methods if sufficient data are available.	Line 301 – 304: We will also present all reported potential risk factors for dry eye including their definitions (e.g., age grouping) and effect estimates for each potential risk factor, including specific risk factors such as geo-environmental factors and screen time when data is available. Line 336 – 348: If there are sufficient risk factor data within-sample (i.e., from the primary studies) and out-of-sample (e.g., from census-derived demographic data, governmental agency derived geo-environmental data), we will consider conducting a Bayesian meta-regression with integrative systems modelling using DisMod-MR software. This will allow us to estimate prevalence and incidence estimates not captured in the primary studies and stratify prevalence and incidence by factors such as age, sex, US region and geo-environmental factors. 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.
Additional changes	We have removed the meta-analysis formula and retained a narrative description with relevant references cited	
	We have added to the discussion regarding the potential for publication bias as a limitation of the review	

VERSION 2 – REVIEW

REVIEWER	Stapleton, Fiona The University of New South Wales, School of Optometry and Vision Science
REVIEW RETURNED	05-Nov-2021

GENERAL COMMENTS	Thank you for the opportunity to review the revised manuscript. In my opinion the revised manuscript is suitable for publication and the reviewers comments have been appropriately addressed.