

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Association between asthma and dry eye disease: A meta-analysis based on observational studies
<b>AUTHORS</b>	huang, qun; Zheng, Yanlin; zhang, chuantao; wang, wanjie; liao, tingting; xiao, xili; wang, jing; wang, juan

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Genschmer, Kristopher The University of Alabama at Birmingham
<b>REVIEW RETURNED</b>	12-Nov-2020

<b>GENERAL COMMENTS</b>	This manuscript analyzed the relationship between patients with Asthma also being affected by DED. The authors did a retrospective analysis of various asthma and DED studies and found a correlation between individuals with asthma also having DED. The limitations of lack of causality were well defined. This is an interesting analysis, and would provide guidance for both clinicians and further research into the link between asthma and other inflammatory diseases such as DED.
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<b>REVIEWER</b>	Rodriguez-Garcia, Alejandro Tecnologico de Monterrey, Institute of Ophthalmology and Visual Sciences
<b>REVIEW RETURNED</b>	15-Nov-2020

<b>GENERAL COMMENTS</b>	<p>The authors performed a neat systematic review and meta-analysis on eligible reports regarding the relationship between dry eye disease (DED) and asthma.</p> <p>The subject is relevant and the manuscript original.</p> <p>The methodology used for a systematic review and meta-analysis is appropriate.</p> <p>The flaws and limitations regarding the results of the analysis concern the observational and methodological nature of the studies included in the meta-analysis only.</p> <p>I have some minor observations to the authors:</p> <ol style="list-style-type: none"><li>1. In the introduction section, the prevalence range of DED (5-50%) given by the authors refers to symptoms with or without signs of DED. It would be appropriate to add that the prevalence is much higher (up to 75%) when only signs are considered for the diagnosis.</li><li>2. Regarding the prevalence of asthma, perhaps the authors should mention that this varies depending on if the disease is diagnosed by a medical doctor, by clinical/treated asthma, by</li></ol>
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	<p>symptoms like wheezing (8.6%), and depending on the country (To T, Stanojevic S, Moores G, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. BMC Public Health 2012; 12, 204. doi.org/10.1186/1471-2458-12-204). This subject is relevant for the meta-analysis since the studies included varied in the way asthma was diagnosed (Table 1).</p> <p>3. In the discussion section, the authors should mention that in at least 50% of the observational studies included for analysis, the DED diagnosis relied on survey instruments (questionnaires), and not on a clinical basis. This is relevant, since dry eye questionnaires are a useful tool for characterizing the type and severity of dry eye, and also for evaluating the effectiveness of therapeutic interventions, but as mentioned before, the clinical diagnosis, which relies on detecting signs of dry eye and the analysis of tear film abnormalities is essential for confirming the diagnosis. This methodological fact could modify the prevalence rate of DED disease in the asthma patients analyzed by such studies.</p> <p>4. Finally, in the first paragraph of the discussion section: "...and this significant correlation could be observed in different ethnicities expect for Arabians" there is a misspelling, instead of "expect", it should be "except".</p>
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<b>REVIEWER</b>	Rossi, Gemma Fondazione IRCCS Policlinico San Matteo
<b>REVIEW RETURNED</b>	02-Dec-2020

<b>GENERAL COMMENTS</b>	<p>I congratulate you on the work you have done The topic is interesting and the research has been done well. If possible, add some more comments on environmental factors and the impact of asthma therapy (some etiopathogenetic comments) on dry eye</p>
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<b>REVIEWER</b>	Yoo, Tae Keun Aerospace Medical Center
<b>REVIEW RETURNED</b>	17-Feb-2021

<b>GENERAL COMMENTS</b>	<p>This study is a meta-analysis study of the relationship between asthma and dry eye and is worth reporting. However, there are some parts that are not clear, so re-evaluation is needed after revision.</p> <p>The relationship with the following paper, in which the same authors participated, should be clarified: "Association between asthma with dry eye disease: A protocol for systematic review and meta-analysis, Medicine, 99(41), 2020" For this reviewer, this kind of publication is strange.</p> <p>Methods Please, specify why some papers were removed. (such as Comorbidities of dry eye disease: a nationwide population-based study, Acta Ophthalmol.2012; 90: 663–668)</p> <p>Result</p>
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The papers in the Table 1 cannot be found in the references. For example, I cannot find the name of "Abdulaziz" in the references. Due to this reason, it is difficult to evaluate this study. The methods of included researches in Table 1 should be clearly specified. Cross-sectional studies, cohort studies, case-control studies or epidemiological studies?

The funnel plot needs 95% CI.

#### Discussion

Air pollution is a very strong factor that link the factors. The authors should comprehensively review the literature about the association between these factors. Allergen also influence both diseases, so the discussion should be revised to confirm the results.

Most patients with allergic marches, such as asthma, have allergic conjunctivitis. This conjunctivitis may be related to symptoms of dryness and may confuse diagnosis. The authors should discuss about this issue.

### VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Kristopher Genschmer, The University of Alabama at Birmingham

Comments to the Author:

This manuscript analyzed the relationship between patients with Asthma also being affected by DED. The authors did a retrospective analysis of various asthma and DED studies and found a correlation between individuals with asthma also having DED. The limitations of lack of causality were well defined. This is an interesting analysis, and would provide guidance for both clinicians and further research into the link between asthma and other inflammatory diseases such as DED.

Reply: Thank you so much for the comments!

Reviewer: 2

Dr. Alejandro Rodriguez-Garcia, Tecnologico de Monterrey

Comments to the Author:

The authors performed a neat systematic review and meta-analysis on eligible reports regarding the relationship between dry eye disease (DED) and asthma.

The subject is relevant and the manuscript original.

The methodology used for a systematic review and meta-analysis is appropriate.

The flaws and limitations regarding the results of the analysis concern the observational and methodological nature of the studies included in the meta-analysis only.

I have some minor observations to the authors:

1. In the introduction section, the prevalence range of DED (5-50%) given by the authors refers to symptoms with or without signs of DED. It would be appropriate to add that the prevalence is much higher (up to 75%) when only signs are considered for the diagnosis.

Reply: We gratefully thanks for the precious time the reviewer spent making constructive remarks. We have added a detailed description of the prevalence of DED in the revised introduction section in a red font as follows:

"The prevalence is driven mainly by the classification of DED, with the prevalence of signs much higher

(up to 75%) compared to symptoms [8]”

2. Regarding the prevalence of asthma, perhaps the authors should mention that this varies depending on if the disease is diagnosed by a medical doctor, by clinical/treated asthma, by symptoms like wheezing (8.6%), and depending on the country (To T, Stanojevic S, Moores G, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. BMC Public Health 2012; 12, 204. doi.org/10.1186/1471-2458-12-204). This subject is relevant for the meta-analysis since the studies included varied in the way asthma was diagnosed (Table 1).

Reply: we have added a detailed description of the prevalence of asthma in the revised introduction section in a red font as follows:

“Asthma is one of the most common chronic immunological diseases in humans, affecting 1%–18% of the population in different countries.[14] Specifically, the prevalence of asthma varies depending on whether the disease is diagnosed by a medical doctor (4.3%), clinical/treated asthma (4.5%), or symptoms such as wheezing (8.6%), and varies by up to 21 times in different countries.[15]”

3. In the discussion section, the authors should mention that in at least 50% of the observational studies included for analysis, the DED diagnosis relied on survey instruments (questionnaires), and not on a clinical basis. This is relevant, since dry eye questionnaires are a useful tool for characterizing the type and severity of dry eye, and also for evaluating the effectiveness of therapeutic interventions, but as mentioned before, the clinical diagnosis, which relies on detecting signs of dry eye and the analysis of tear film abnormalities is essential for confirming the diagnosis. This methodological fact could modify the prevalence rate of DED disease in the asthma patients analyzed by such studies.

Reply: We appreciate the comments and have added the argument in the revised discussion section in a red font as follows:

“It can not be ignored that dry eye questionnaires are not only a useful tool for characterizing the type and severity of dry eye, but also for evaluating the effectiveness of therapeutic interventions. Therefore, in at least 50% of the observational studies included in this meta-analysis, the diagnosis of DED was based on survey instruments (questionnaires) rather than on clinical basis.”

4. Finally, in the first paragraph of the discussion section: “...and this significant correlation could be observed in different ethnicities expect for Arabians” there is a misspelling, instead of “expect”, it should be “except”.

Reply: We are sorry for this typo, this misspelling has been fixed in our revised manuscript.

Reviewer: 3

Dr. Gemma Rossi, Fondazione IRCCS Policlinico San Matteo

Comments to the Author:

I congratulate you on the work you have done

The topic is interesting and the research has been done well.

If possible, add some more comments on environmental factors and the impact of asthma therapy (some etiopathogenetic comments) on dry eye.

Reply: We gratefully appreciate for your careful review and have added some more comments on environmental factors and the impact of asthma therapy on dry eye as follows:

“In addition, in terms of treatment, some studies found that patients receiving asthma-related treatments (including leukotriene receptor antagonists, antihistamines, and inhaled corticosteroids) have a higher risk of DED, among which antihistamines were the most frequently reported. Antihistamines are widely used to relieve allergic symptoms. However, it should not be ignored that antihistamines have a muscarinic effect on the surrounding muscarinic receptors, thereby reducing the production of tears by reducing mucin output from the goblet cells [39]. Therefore, the use of antihistamines to treat allergic diseases,

including asthma, induces or exacerbates the signs and symptoms of DED.[40-42] Several studies have reported that antihistamines may be associated with DED,[43-44]”

“With the emergence of many risk factors for DED, environmental conditions are associated with the occurrence and persistence of the disease. [46] One study showed that exposure to adverse environmental conditions, especially bioaerosols and air pollution, has a serious negative impact on DED symptoms.[47] This finding is largely consistent with other literature because elevated levels of air pollutants and microorganisms have been related to adverse health outcomes, including asthma and immune disorders.[48-49] Since our eyes are directly exposed to the air, the composition and characteristics of the air will undoubtedly change the anterior corneal tear film and affect the corneal nerve function.[50] Air pollution is the indicator most often associated with DED.[51-52] In addition, exposures to other pollutants have been found to be in association to symptoms and signs of DED. For example, changes in ground-level ozone concentrations are closely related to changes in DED parameters, including tear secretion and Ocular Surface Disease Index scores.[53] Both air pollutants and microbial contamination may contribute to the worsening of DED symptoms, possibly because both are associated with inflammation and oxidative stress. In animal studies, topical use of PM2.5 on mouse corneas has resulted in ocular surface damage similar to that of human dry eyes.[54-55] Humidity is also an interesting risk factor, because both low and high humidity have been shown to be related to DED.[56-57] This may be because high humidity is conducive to the growth and survival of microorganisms in the air, while low humidity leads to aqueous loss.[57] ”

Reviewer: 4

Dr. Tae Keun Yoo, Aerospace Medical Center

Comments to the Author:

This study is a meta-analysis study of the relationship between asthma and dry eye and is worth reporting. However, there are some parts that are not clear, so re-evaluation is needed after revision.

1. The relationship with the following paper, in which the same authors participated, should be clarified: “Association between asthma with dry eye disease: A protocol for systematic review and meta-analysis, *Medicine*, 99(41), 2020” For this reviewer, this kind of publication is strange.

Reply: Firstly, we gratefully thanks for the precious time the reviewer spent making constructive remarks. “Association between asthma with dry eye disease: A protocol for systematic review and meta-analysis, *Medicine*, 99(41), 2020” is only the protocol of our meta-analysis. Publishing the protocol was intended to reduce potential biases associated with data mining, thereby helping to generate reliable evidence.

2. Methods: Please, specify why some papers were removed. (such as Comorbidities of dry eye disease: a nationwide population-based study, *Acta Ophthalmol.*2012: 90: 663–668)

Reply: This paper (Comorbidities of dry eye disease: a nationwide population-based study, *Acta Ophthalmol.*2012: 90: 663–668) met the inclusion criteria of this study and was included in this meta-analysis, as shown in Reference 35.

3. Result: The papers in the Table 1 cannot be found in the references. For example, I cannot find the name of "Abdulaziz" in the references. Due to this reason, it is difficult to evaluate this study. The methods of included researches in Table 1 should be clearly specified. Cross-sectional studies, cohort studies, case-control studies or epidemiological studies?

Reply: We are sorry for the mistake, we somehow used the author's first name to represent this study, which has been corrected in our revised manuscript. The figures and tables were also corrected accordingly. Furthermore, we added the study design in Table 1 according to your suggestion.

The funnel plot needs 95%CI.

Reply: Thank you for your suggestion. We remade the funnel plot with 95%CI, but this figure was generated using Stata software because when using Revman for meta-analysis, the lines for 95%CI could only be made under the fixed effect model.

4. Discussion: Air pollution is a very strong factor that link the factors. The authors should comprehensively review the literature about the association between these factors. Allergen also influence both diseases, so the discussion should be revised to confirm the results.

Reply: We gratefully appreciate for your careful review and have added some more comments on Air pollution on dry eye. As follows :

“With the emergence of many risk factors for DED, environmental conditions are associated with the occurrence and persistence of the disease. [46] One study showed that exposure to adverse environmental conditions, especially bioaerosols and air pollution, has a serious negative impact on DED symptoms.[47] This finding is largely consistent with other literature because elevated levels of air pollutants and microorganisms have been related to adverse health outcomes, including asthma and immune disorders.[48-49] Since our eyes are directly exposed to the air, the composition and characteristics of the air will undoubtedly change the anterior corneal tear film and affect the corneal nerve function.[50] Air pollution is the indicator most often associated with DED.[51-52] In addition, exposures to other pollutants have been found to be in association to symptoms and signs of DED. For example, changes in ground-level ozone concentrations are closely related to changes in DED parameters, including tear secretion and Ocular Surface Disease Index scores.[53] Both air pollutants and microbial contamination may contribute to the worsening of DED symptoms, possibly because both are associated with inflammation and oxidative stress. In animal studies, topical use of PM2.5 on mouse corneas has resulted in ocular surface damage similar to that of human dry eyes.[54-55]”

Most patients with allergic marches, such as asthma, have allergic conjunctivitis. This conjunctivitis may be related to symptoms of dryness and may confuse diagnosis. The authors should discuss about this issue.

Reply: We have discussed the association of asthma patients with allergic conjunctivitis and dry eye syndrome, as shown below:

“In addition, most patients with allergic diseases, such as asthma, have allergic conjunctivitis. It is estimated that as many as 20% of adults and 44% of children with asthma have symptoms of allergic conjunctivitis.[64] Allergic conjunctivitis itself can induce or aggravate dry eye by reducing the density of goblet cells and conjunctival mucin and destabilize the tear film.[65-66] In addition, DED and allergic conjunctivitis have certain similarities in signs and symptoms.[67-68] Therefore, we cannot rule out the possibility that some allergic conjunctivitis in this population may be misdiagnosed as dry eye, and the results should be interpreted cautiously.”

I would like to convey my heartfelt thanks again to you for your constructive comments!

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Yoo, Tae Keun Aerospace Medical Center
<b>REVIEW RETURNED</b>	28-May-2021

**GENERAL COMMENTS**

The manuscript has been improved significantly. It also includes an indepth review about the association between dry eye syndrome and asthma.  
Ref. 21 should be revised before publication.

**VERSION 2 – AUTHOR RESPONSE**

Reviewer: 4

Comment: The manuscript has been improved significantly. It also includes an indepth review about the association between dry eye syndrome and asthma.

Ref. 21 should be revised before publication.

Response: Thank you very much for your careful review and approval. We are very sorry for our incorrect writing and we have corrected Ref. 21.