PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	DISEASES WITH ORAL MANIFESTATIONS AMONG ADULT ASTHMATICS IN FINLAND - A POPULATION-BASED MATCHED COHORT STUDY
AUTHORS	Lemmetyinen, Riikka; Karjalainen, Jussi; But, Anna; Renkonen, Risto; Pekkanen, Juha; Haukka, Jari; Toppila-Salmi, Sanna

VERSION 1 – REVIEW

REVIEWER	Choi, Hyo Geun Hallym University
REVIEW RETURNED	18-Jun-2021

GENERAL COMMENTS	This study evaluated the risk of oral disease in asthma adult using the data of Finland national registry. The author conclude that asthma is the risk factors of oral disease. Is this study confirmed the oral health status in the start point of study? Is this study evaluated the effects of medication for asthma? If possible, the medication history of asthma should be considered in that it might affect the oral health status directly. For example, steroid inhaler is the direct cause of fungal infection. Therefore, the effects of asthma itself, and the effects of asthma medication should be described differently. In this study, the reviewer could not know the author have considered this. I have the question for the diagnostic accuracy of oral disease. Did you have any data? How did you include this oral disease? Did you include the herpes zoster who have diagnostic code B02 only single time? Diagnosis using the only ICD-10 codes might not be accurate. It should be supported their history of other treatment such as medication history. The discussion need more pathophysiologic explanation between asthma and oral disease. It could be possible steroid inhaler, oral steroid medication, allergic mechanism. This explanation is not sufficient in the current status. Additionally, as stated above, I suggest to divide the explanation as direct effects of asthma itself, and medication effects.

REVIEWER	Faustino-Silva, Daniel Demétrio Grupo Hospitalar Conceição
REVIEW RETURNED	24-Jun-2021

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript. The theme is very relevant and in general the study has good qualities Suggestions and recommendations: Title: Include country and type of study. Introduction: The theoretical framework on oral health and asthma needs to be updated. There are many new articles published, including recent systematic reviews. Do the same in the discussion. Hypothesis: correct for major ORAL diseases in asthmatics. Tables: title should be as complete as possible describing place and year of collection of information. It is necessary to clarify whether the patients were assisted by dentists in the services where the data were collected. Also, have records of dental diseases such as caries and periodontitis been diagnosed by dentists or physicians? These points need to be better discussed as important biases. Conclusions: It is important to highlight the importance of monitoring asthmatic patients by dentists who are part of the healthcare team.

VERSION 1 – AUTHOR RESPONSE

Point by point responses
Reviewer: 1

Dr. Hyo Geun Choi, Hallym University

Comments to the Author:

This study evaluated the risk of oral disease in asthma adult using the data of Finland national registry. The author conclude that asthma is the risk factors of oral disease.

Is this study confirmed the oral health status in the start point of study?
Response: No, unfortunately not. This study includes a questionnaire (collected in 1997) and register data from 1997 to 2014. Clinical examination was not part of the study design. We have discussed this as a limitation in Discussion section p 17.

Is this study evaluated the effects of medication for asthma? If possible, the medication history of asthma should be considered in that it might affect the oral health status directly. For example, steroid inhaler is the direct cause of fungal infection.
Therefore, the effects of asthma itself, and the effects of asthma medication should be described differently.
In this study, the reviewer could not know the author have considered this.
Response: Thank you very much for this excellent comment. We acknowledge that asthma medication may affect oral health. We have evaluated this by using data of patient-reported use of inhaled corticosteroids (ICS) at the time when questionnaire was performed in 1997. 71 % of asthmatics reported using regular ICS and 76% used any inhaled asthma medication at baseline. (Results section, page 11)

It is true that medication may have effect on e.g. fungal infection. However, analyzing them is not straight forward, because we have information only of baseline medications. Also, only a few fungal diagnoses were recorded in this study. In order to analyze association between medication and our

end-points we should use current medication, not baseline one. In addition, we are planning to make more detailed analyses of medication in separate paper. Thus, in our opinion including in detail analyses of medications is not in scope of our current manuscript.

I have the question for the diagnostic accuracy of oral disease. Did you have any data?
How did you include this oral disease?
Response: We assume that you refer to the Table 2, where matched and adjusted hazard rates have been calculated for different disease groups. “Any oral disease” means that all the following disease groups (herpes zoster, malign neoplasms, benign neoplasms, dental diseases, and dermatological diseases, diagnose codes are described more accurately in the “Outcomes”) are combined. The hazard ratio shows that the risk of having any oral disease (of the listed diseases) is 1.41-fold among people with asthma. We acknowledge that this may be misleading and have clarified this in the Results Section page 11.

Did you include the herpes zoster who have diagnostic code B02 only single time?
Diagnosis using the only ICD-10 codes might not be accurate. It should be supported their history of other treatment such as medication history.
Response: Each diagnose, including herpes zoster, was recorded only once. In Finland, only physicians or dentists use the ICD-10 codes to register the clinical diagnose in patient records. Therefore, we consider it to be quite accurate, even without the medication history. We have speculated this in Discussion section pages 15–16.

The discussion need more pathophysiologic explanation between asthma and oral disease. It could be possible steroid inhaler, oral steroid medication, allergic mechanism. This explanation is not sufficient in the current status. Additionally, as stated above, I suggest to divide the explanation as direct effects of asthma itself, and medication effects.
Response: Thank you very much for this comment. We have now addressed this issue more sufficiently in the Introduction section (p.5-6) of the manuscript.

Reviewer: 1
Competing interests of Reviewer: I have no conflicts of interests.

Reviewer: 2

Dr. Daniel Demétrio Faustino-Silva, Grupo Hospitalar Conceição

Comments to the Author:

Thank you for the opportunity to review this manuscript.

The theme is very relevant and in general the study has good qualities
Suggestions and recommendations:
Title: Include country and type of study.
Response: Thank you for this excellent suggestion. The title has now been modified as requested “Diseases with oral manifestations among adult asthmatics in Finland – a population-based matched cohort study”

Introduction:

The theoretical framework on oral health and asthma needs to be updated. There are many new articles published, including recent systematic reviews. Do the same in the discussion.
Response: Thank you for this important remark. We have now updated the literature review and added the following references:

24 Ghapanchi J, Rezazadeh F, Kamali F, et al. Oral manifestations of asthmatic patients. J Pakistan Med Assoc 2015;65:1226–7.https://jpma.org.pk/PdfDownload/7531 (accessed 25 Aug 2021).
25 Gani F, Caminati M, Bellavia F, et al. Oral health in asthmatic patients: a review Asthma and its therapy may impact on oral health. Clin Mol Allergy 2020;18:22. doi:10.1186/s12948-020-00137-2
26 Wee JH, Park MW, Min C, et al. Poor oral health is associated with asthma, allergic rhinitis, and atopic dermatitis in Korean adolescents: A cross-sectional study. Medicine (Baltimore) 2020;99:e21534. doi:10.1097/MD.0000000000021534
27 Gaeckle NT, Pragman AA, Pendleton KM, et al. The Oral-Lung Axis: The Impact of Oral Health on Lung Health. Published Online First: 2020. doi:10.4187/respcare.07332
28 Ryberg M, Möller C, Ericson T. Saliva composition and caries development in asthmatic patients treated with beta 2-adrenoceptor agonists: a 4-year follow-up study. Scand J Dent Res 1991;99:212–8. doi:10.1111/J.1600-0722.1991.TB01887.X
29 Hyyppä T. Gingival IgE and histamine concentrations in patients with asthma and in patients with periodontitis. J Clin Periodontol 1984;11:132–7. doi:10.1111/J.1600-051X.1984.TB00841.X
30 Peters U, Dixon A, Forno E. Obesity and Asthma. J Allergy Clin Immunol 2018;141:1169. doi:10.1016/J.JACI.2018.02.004
35 Marra F, Parhar K, Huang B, et al. Risk Factors for Herpes Zoster Infection: A Meta-Analysis. Open Forum Infect Dis 2020;7. doi:10.1093/OFID/OFAA005

Hypothesis: correct for major ORAL diseases in asthmatics.
Response: We have now corrected this as requested (p 6). Thank you.

Tables: title should be as complete as possible describing place and year of collection of information.
Response: This is an excellent point, thank you very much. We have now updated the table labels to be more precise (pages 9,12,13).

It is necessary to clarify whether the patients were assisted by dentists in the services where the data were collected. Also, have records of dental diseases such as caries and periodontitis been diagnosed by dentists or physicians? These points need to be better discussed as important biases.
Response: This data includes self-reported questionnaire data and register data. ICD-10 codes are used in Finland by physicians or dentists. It is not possible to find out is the diagnose made by a dentist or a physician but physicians in Finland do not diagnose dental or periodontal diseases unless they have a double degree (many oral and maxillofacial surgeons are both dentists and physicians). Also, this data does not include primary care data, such as routine oral examinations made by dentists, only diseases treated in specialized care. We have clarified this now in the Discussion section (p 16–17). Thank you.

Conclusions: It is important to highlight the importance of monitoring asthmatic patients by dentists who are part of the healthcare team.
Response: We agree and have added this important point to the Conclusions section (p 19). Thank you.

Reviewer: 2
Competing interests of Reviewer: None.

VERSION 2 – REVIEW

REVIEWER	Choi, Hyo Geun Hallym University
REVIEW RETURNED	05-Oct-2021

GENERAL COMMENTS	The author responded correctly. I have no more comments. Thank you for your good work.

REVIEWER	Faustino-Silva, Daniel Demétrio Grupo Hospitalar Conceição
REVIEW RETURNED	06-Oct-2021

GENERAL COMMENTS	The authors made the requested corrections.