

## Peer Review File

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### Reviewer A

Comment 1: The systematic search may not have revealed all eligible studies available in the MedLine database as search terms like "adult" and "general population" were not included in the search strategy. E.g. important studies like J Allergy Clin Immunol Pract 2019;7:1783-1792 and Thorax 2022;77:223-230 were not included in the current review paper?

Reply 1: We thank the Reviewer for this kind suggestion. We have made the following modifications. In the Abstract and Main text, we have added “adult” and “general population” in the revised manuscript: “We searched Medline (PubMed interface) for relevant articles and their lists of references published in English using the key words of “chronic cough”, “chronic bronchitis”, “epidemiology”, “prevalence”, “risk factor”, “burden”, “quality of life”, “adult” and “general population””. (see Page 3, line 41-44; Page 7, line 98-101 and Page 40, table 1) respectively as the Reviewer suggested.

Additionally, we have quoted the two references (Çolak Y, et al. J Allergy Clin Immunol Pract. 2019;7(6):1783-1792.e8; Landt EM, et al. Thorax. 2022;77(3):223-230.) as the Reviewer suggested and made an extension in the revised version accordingly. In the part of Risk factors, we have added “Landt EM and colleagues reported there was a dose-response relationship between body mass index (BMI) and chronic cough, and chronic cough risk was two- to three-fold higher in obese individuals from the general population from the Copenhagen General Population Study, and this increased risk was partly mediated by GORD, low vegetable intake and occupational exposure (Landt EM, et al. Thorax. 2022;77(3):223-230)” (see Page 16-17, line 300-304). In the part of Disease burden of chronic cough, we have added “A similar finding was reported by Çolak Y and colleagues who investigated the role and impact of chronic cough in individuals with asthma from the general population, and found that those with chronic cough versus those without chronic cough in individuals with asthma had greater health care utilization (Çolak Y. J Allergy Clin Immunol Pract. 2019 Jul-Aug;7(6):1783-1792.e8.)” (see Page 22, line 429-433). “Çolak Y and colleagues also reported that among individuals with asthma, those with chronic cough versus those without had more often an FEV<sub>1</sub> %pred of less than 60% (14% vs 7%)” (see Page 24, line 465-467).

Comment 2: The present review should preferably follow the PRISMA guideline for systematic reviews ([https://www.prisma-statement.org/documents/PRISMA\\_2020\\_](https://www.prisma-statement.org/documents/PRISMA_2020_)

checklist.pdf).

Reply 2: In fact, the present review is a narrative review and not a systematic review. We have updated the narrative reviews checklist from the Journal of Thoracic Disease, and this has been submitted with the revised manuscript as Appendix 3.

Comment 3: Some of the included studies do not reflect the general population per se (e.g. ref. 28). Perhaps the authors could consider changing the wording "general population" to "population" throughout the manuscript?

Reply 3: We thank the Reviewer for this constructive suggestion. When we described the risk factors and disease burden of chronic cough in the present manuscript, we did quote several references from several non-general population, such as ref. 6 (Morice AH, et al. Eur Respir J. 2014;44(5):1149-1155.), ref. 36 (Zeiger RS, et al. J Allergy Clin Immunol Pract. 2020 May;8(5):1645-1657.e7.), ref. 38 (Kastelik JA, et al. Am J Respir Crit Care Med. 2002;166(7):961-964.), ref. 39 (Kelsall A, et al. Thorax. 2009;64(5):393-398.), however, the prevalence of chronic cough summarized in this manuscript were all from the survey conducted in the general population. In view of this, we prefer to keep the general population in the manuscript.

Comment 4: Abstract conclusion should preferably focus on novel findings from the reviewed literature. E.g. the urgent need for surveys using the standard definition of chronic cough so comparisons of prevalences and other findings across populations will become possible.

Reply 4: We thank the Reviewer for this kind suggestion. We have added a statement in the Abstract as the Reviewer suggested: "There is an urgent need to apply the standard definition of chronic cough in future research, so that comparisons of the prevalence and other findings across populations can be made." (see Page 4, line 59-61).

Comment 5: In addition to a systematic search of MedLine for eligible papers, the authors may consider searching the reference lists of the papers included in their study - and adding this methodology to their Methods section in the manuscript.

Reply 5: We have checked again the lists of references included in the eligible papers searched from MedLine. We have added this methodology to the Abstract methods and Methods section in the revised manuscript: "We searched Medline (PubMed interface) for relevant articles and their lists of references published in English using the key words of "chronic cough", "chronic bronchitis", "epidemiology", "prevalence", "risk factor", "burden", "quality of life", "adult" and "general population" (see Page 3, line

41-44 and Page 7, line 98-101).

Comment 6: Change subheading from "Discussion" to "Results"?

Reply 6: We thank the Reviewer for this kind suggestion. In the present study, we select subheading “Discussion”, which has been used in some previous narrative reviews published in JTD journal (e.g. Youssefnia A, et al. J Thorac Dis. 2022;14(9):3575-3597; Hirahara N, et al. J Thorac Dis. 2022;14(9):3606-3612.). Therefore, we would like to keep the subheading as it is.

## **Reviewer B**

### **Major**

Comment 1: Title, P1, line 1. Although a significant part of this article is devoted to risk factors, the risk factors are omitted from the title. Therefore, this reviewer recommends adding “risk factors” to the title as well. For example, “Worldwide prevalence and burden of chronic cough in the general population: a narrative review” → “Worldwide prevalence, risk factors and burden of chronic cough in the general population: a narrative review”

Reply 1: We thank the Reviewer for this kind suggestion. We have revised the title as the reviewer suggested: “Worldwide prevalence, risk factors and burden of chronic cough in the general population: a narrative review” (see Page 1, line 1-2).

Comment 2: Discussion. It is confusing because there is no distinction between the headings and the subheadings of the discussion part. Therefore, please indicate the subheadings included in the “Risk factors” and “Disease burden of chronic cough” using different font size, bold writing, indentation or other methods from the headings. For example, Risk factors, Ethnicity.

Reply 2: We have updated the format of the headings and the subheadings of the discussion part in the revised version. We hope that the revised format is more readable.

Comment 3: Discussion, P5-7. Researchers present different prevalence according to sex, smoking history, and age group in the text. To improve the delivery power and make understanding easier, I suggest presenting these data as a table, where possible, with the p-value of the difference between groups.

Reply 3: We thank the Reviewer for this kind suggestion. A Table has been added in the revised manuscript which describes the prevalence of chronic cough according to sex, age, and smoking with p-values (see Page 43, table 3). And we have added a brief

description: “More details about the prevalence of chronic cough according to sex, age, and smoking status are shown in Table 3” in the revised manuscript. (see Page 8, line 116-117)

Comment 4: Discussion, P12, line 221-226. The authors provide evidence from only one study in China that BMI and chronic cough are not associated. However, if Asian-style diet, which are opposed to Western diet, are the reason for this, it would be reasonable to present data on the relationship between BMI and chronic cough conducted in other Asian countries.

In addition, it would be a better discussion if other possible reasons that could explain this phenomenon besides antioxidants were presented. For example, in addition to BMI, if there is a study on the relationship between body composition of fat and chronic cough, more advanced discussion will be possible.

Reply 4: We thank the Reviewer for this kind suggestion. We have modified the discussion in the revised version as the Reviewer suggested: “and these results were consistent with another study conducted in Korea. Using the data from the 2019 KNHANES study, Kim and colleagues reported there was no significant relationship between BMI and the occurrence of chronic cough using a multivariate analysis (Kim TH. BMC Pulm Med. 2022 Nov 16;22(1):419 ). These inconsistent findings between Eastern and Western populations may be attributed partly by the higher proportion of vegetables in Eastern diet compared to the Western diet, because vegetables and fruits are the major food sources of antioxidants which are helpful to protect the lung from oxidative stress and independently associated with less symptoms of cough with phlegm. A recent study also showed that against the background of abdominal obesity, the risk of chronic cough with phlegm increased with the serum levels of some adipokines such as lipocalin-2 and glucose-dependent insulintropic polypeptide (GIP) and tumor necrosis factor-alpha (TNF- $\alpha$ ) (Khudiakova AD. Biomolecules. 2022;12(10):1502.). We therefore cannot exclude the potential link between the various fat components and chronic cough, which needs to be further studied in the future (see Page 17, line 306-319).

Comment 5: Discussion, P18. There is no mention of direct or indirect cost in the “Disease burden of chronic cough”. Therefore, it will be more valuable data if the burden of disease is investigated in terms of objective cost.

Reply 5: We thank the Reviewer for this kind suggestion. In the Discussion Section, we have added a statement about the direct or indirect disease burden of chronic cough in the revised version as the Reviewer suggested: “Chronic cough is believed to have a high disease burden both directly (economic burden, healthcare resource utilization)

and indirectly (comorbidities and concomitant symptoms, lung function, impact on life quality)” (see Page 21, line 394-396). After that, we specially added a paragraph to state the economic burden caused by chronic cough: “Health costs resulting from having chronic cough has been evaluated both in high income and low income countries. A case-control study based on the data from the PharMetrics Integrated Database in the US reported that chronic cough patients with phlegm had high total costs for 12 months prior to diagnosis and 24 months post-diagnosis. The heaviest economic burden for chronic cough patients with phlegm compared to those without occurred during the 6 months post-diagnosis (US\$12,781 vs US\$3,862) (Blanchette CM, et al. Int J Chron Obstruct Pulmon Dis. 2011;6:73-81. Published 2011 Jan 13. doi:10.2147/COPD.S15882). Sichali JM and colleagues based on the general population in Malawi reported that the mean care-seeking cost per patient with chronic cough was US\$3.90 in a 12-month period, and it was 2.3 times the average per capita expenditure on health of US\$1.69. The largest costs for the patient with chronic cough were due to transport (US\$1.4), followed by drugs (US\$1.3) (Sichali JM, et al. PLoS One. 2019;14(12):e0225712. Published 2019 Dec 31. doi:10.1371/journal.pone.0225712).” (see Page 21, line 398-408) In the section of Healthcare resource utilization, we have also added “Similarly, a case-control study based on the data from the PharMetrics Integrated Database in US found that chronic cough patients with phlegm had 5.6 times more hospitalizations and 3.1 times more emergency department/urgent care visits” (see Page 22, line 420-422).

### **Minor**

Comment 1: Discussion, P5, line 72. “the LEAD cohort” → Since it is the study name mentioned for the first time in the text, it is better to present the full name rather than using an abbreviation.

Reply 1: As the Reviewer suggested, we have added the full name “Lung, hEart, sociAl, boDy (LEAD)” (see Page 8, line 119-120).

Comment 2: Discussion, P10, line 176. The headings “occupation” and “occupational exposure” are not considered to be different. Accordingly, it is thought that the headings should be integrated into one of “occupation” or “occupational exposure”.

Reply 2: We have updated the headings as “occupational exposure” in the revised manuscript (see Page 14, line 245).

Comment 3: P11, line 206. “the SALIA cohort” → Since it is the study name mentioned for the first time in the text, it is better to present the full name rather than using an abbreviation.

Reply 3: We have added the full name “Study on the influence of Air pollution on Lung function, Inflammation and Aging (SALIA)” (see Page 15-16, line 281-282).

Comment 4: Discussion, P16, line 319. “FEV1%pred” → Since it is the study name mentioned for the first time in the text, it is better to present the full name rather than using an abbreviation.

Reply 4: We have added the full name “FEV<sub>1</sub> %predicted” (see Page 24, line 463).

Comment 5: Discussion, P18, line 352. “the KPSC Research” → Since it is the study name mentioned for the first time in the text, it is better to present the full name rather than using an abbreviation.

Reply 5: We have added the full name “Kaiser Permanente Southern California (KPSC)” (see Page 21, line 410).

Comment 6: English proofreading is required.

Reply 6: The resubmitted manuscript has been edited and proofread by a professional English-language editor.