Peer Review File

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Reviewer A

Thank you for inviting me to review this paper. Generally, my comments are directed to shape the overall content of this paper. I presume the audience of this paper would not just be those involved in respiratory but also other clinical fields eg. primary care, public health etc. and from other different countries and settings. These are my suggestions to improve on the content.

Abstract:

1. Line 40 - Specify what other co-variates?

Reply: Thanks for your comments. We have modified the sentences regarding specific co-variates as follows; (page 2, line 41)

"but not to male sex, ever-smoking, obesity, or socioeconomic status."

Introduction:

2. Line 61 – Perhaps to specify findings from other studies, about risk factors in children and adult, rather than state in general.

Reply: Thanks for your valuable comments.

It is important to specify the risk factors for children and those for adults. We have added some sentence in introduction section (page 3, line 61-63)

"In children, multiple gene susceptibility, such as ORMLD3 and GSDML genes contributed to asthma; moreover, maternal diet and tobacco smoking are risk factors of asthma."

Methods:

3. Line 82 – I am interested to know how the younger children responded to this questionnaire as the population was stated 1-80 years old in the KNHANES survey

Reply: The KNHANES survey was conducted on a household bases and was analyzed based on the health survey questionnaire of the selected household. In the case of younger children, it had been responded by the representative of the household.
We have added some sentence in the method section (page 4, line 87-89)
“The KNHANES survey was conducted on a household basis and was analyzed based on the health survey questionnaires of the selected households.”

4. Line 84-85 – Suggest putting in data analysis section.
Reply: Thanks for your suggestion. We have included the section on page 4, line 87 as follows,

“Participants and data analysis”

In addition, we have revised the first sentence of this section as follows (page 4, line 86):

“A total of 92,442 participants (aged 1–80 years) were included. ”

5. Line 92-93 – Suggest a short description of what you mean by higher and lower half - good reference for the reader
Reply: Thanks for your suggestion. We modified the sentence in the methods section (page 5, line 100-104) as follows:

“In the original survey, household income levels were divided into four categories as follows: ‘lower’, ‘middle-lower’, ‘middle-upper’, and ‘upper’ quartiles. However, in this study, we classified household income into two categories for statistical analysis: ‘lower’ and ‘middle-lower’ quartiles were classified as ‘lower-half’, and the ‘middle-upper’, and ‘upper’ quartiles were classified as ‘higher-half’.”

Results:
6. Figure 2 - Suggest demonstrating in different colours – clearer
Reply: Thanks for your suggestion. We have modified the line color in Figure 2 to clarify the contents.

7. Line 195-200 – suggest putting the explanation of birth cohort analysis in data analysis section. What were the examples of birth bias that you have looked at?
Reply: This is a valuable point. We performed the birth cohort analysis to exclude the effects of environmental factors, which could potentially affect the prevalence of asthma. We have added this detail in the data analysis section (page 5, line 92-93) as followed:

"Additionally, we used birth cohort analysis to determine whether there was any causal relationship between the birth period and asthma."

Limitations:
8. Line 241-242 – suggest explaining a little more on the implications of self-reported survey on this study; eg. under/overdiagnosis, response bias, under/over reporting.
Reply: Thanks for your suggestions. In primary care, physician-diagnosed asthma could be overestimated or underestimated compared to asthma diagnosed based on laboratory and test results. Underestimation of asthma was associated with under-reporting of symptoms by patients. In contrast, among patients with physician-diagnosed asthma, studies have indicated that 30–35% of these patients do not actually have asthma, and this could lead to overestimation (ref : Am J Respir Crit Care Med Vol 198, Iss 8, pp 1012–1020, Oct 15, 2018). We revised some sentence in limitation section (page 13, line 276-281) as follows:

"Third, asthma defined as physician-diagnosed asthma in this study, could have been overestimated or underestimated compared to asthma diagnosed based on laboratory test results. Underestimation of asthma was associated with under-reporting of symptoms by patients. In contrast, among patients with physician-diagnosed asthma, studies have indicated that 30–35% of these patients do not actually have asthma, and this could lead to overestimation."

Discussion:
9. General comment - Any possible reasons that prevalence increased in the 20s band as compared to other bands? Eg. Diagnosis gets better? Young adults seek treatment

early?

Reply: Further analyses were conducted to find the possible reasons for the increase of prevalence of asthma in the 20s band. BMI was considered to be significantly related; however, it was not a significant factor in the multivariate analysis. In addition, young adults may be treated earlier due to their high level of awareness. However, this study was limited because there was no database until the time of treatment. Besides, the influence of Western lifestyles, such as dietary factors, may have been more evident in the young adult group, which could have contributed to the increase in the prevalence of asthma (ref : Nutr Rev. 2020 Nov 1;78(11):928-938.).

We have added this sentence in the discussion section (page 11, line 234-238).

10. General comment - With regards to allergic rhinitis and atopic dermatitis – it is usually discussed as phenotypes of asthma, rather than as an association. You may want to discuss about asthma phenotypes.

Reply: Thank you for your valuable comments. There are several phenotypes of asthma, and the most common is allergic asthma (ref : J Allergy Clin Immunol Pract. 2020 Feb; 8(2): 429–440.). We revised some sentence in discussion section as followed;

“Furthermore, increased prevalence of asthma was related to allergic rhinitis and atopic dermatitis.” (page 9, line 186-187)

“Some phenotypes of asthma, defined as visible traits, were the outcome of a combination of inherited and environmental factors. Allergic asthma, which is the most common phenotype, occurs more often in people under 30 years of age” (page 12, line 258-260)

In addition, we have added this sentence in the limitations section as follows: (page 13, line 282-285):

“Fourth, the classification of asthma according to phenotype is important; however, in this study, test results, such as IgE and skin prick tests were limited. As we could not conduct the analysis of asthma phenotype, further research would be needed.”

11. Line 180-181 – Suggest discussing further the implication of knowing prevalence is increased in the 20s age band.

Reply: Thanks for your suggestions. We have added some sentences in the discussion section (page 9, line 191-194) as follows:

"The modifiable and treatable factors that increased the prevalence of asthma in the 20s age band were not clearly identified in this study. However, considering the economic and health burden of asthma, it is important to monitor its prevalence. Furthermore, it is necessary to divide and manage patients according to their age band."

12. Line 192-193 – What possible causes that could contribute to the differences in the US and Korea?

Reply: Thanks for your comments. It was unclear why the prevalence of asthma trends to increase in the elderly in the US. Improvement in methods that properly recognize asthma and a high proportion of people with obesity are possible causes (ref: Breathe (Sheff). 2016 Mar; 12(1): 18–28., Respir Med. 2018 Sep;142:29-35., J Allergy Clin Immunol Pract. 2018 May-Jun; 6(3): 764–773.).

13. Line 215-218 – Just wondering, whether smoking is highest in the 20s band as compared to other age band in your study? Although I understand, you compared asthma and non-asthma in your study.

Reply: In the 20s band, the proportion of ever-smoking was 42%, whereas it was 48.8% in the 30s band, 47.7% in the 40s band, 45.9% in the 50s band, 43.3% in the 60s band, and 38.8% in the 70s band (supplement figure 5). Additionally, according to our data base, in the 20s band, the proportion of participants who had ever smoked was 61.0% among male participants and 20.8% in female participants. Exposure to smoking might have affected the difference in the prevalence of asthma according to sex in the same age group.

14. Line 229-230 – Any reference?

Reply: Thank you for your comments. We have cited the reference in page 12, line 266.

Other comments:

15. Suggest you want to add the implication of findings on clinical practice and future research.

Reply: Thanks for your suggestion. As mentioned in the discussion section, this study emphasized the need for healthcare providers in charge of prevention to recognize and manage the prevalence of asthma according to age bands. We have added this sentence in discussion section (page 9, line 196-197) as followed ;

"This study emphasized the need for healthcare providers in charge of prevention to recognize and manage the prevalence of asthma according to age bands."

16. Please check some spelling errors.

Reply: Thank you for your comments. We have checked the manuscript and corrected the spelling errors. We have indicated revised sections in the manuscript in red font.

Reviewer B

Minor Revision

1. On average, there is a 30% over-diagnosis of asthma in patients who self-report physician diagnosis. please see Aarons et al.
https://www.atsjournals.org/doi/full/10.1164/rccm.201804-0682CI

Reply: Thank you for your comment. The use of a self-reported questionnaire is considered a limitation of this study, and this is an important point. We supplemented the contents by adding the following sentence to the limitations section (page 13, line 276-282).

"Third, this study was conducted based on self-reported questionnaire. Therefore, the prevalence of asthma may have been overestimated because it was defined as self-reported physician diagnosed asthma. Further research on the prevalence of asthma diagnosed based on laboratory test is required in the future."

Although there was a limitation, we considered this study was meaningful as a large-scale representative data in South Korea.

2. The overall prevalence in korea is still low compared to western countries. why?
Reply: This is an important point. The higher prevalence of asthma in Western countries may be due to the higher rates of obesity in these countries (ref : Ann Glob Health. 2019 Jan 22;85(1):2.). Additionally, the 'hygiene hypothesis' that frequent bacterial infection in childhood could lead to adverse association with allergic disease, might be related to the high prevalence of asthma in the Western countries (ref : Current Opinion in Allergy and Clinical Immunology: February 2013 - Volume 13 - Issue 1 - p 70-77).

We have added this sentence in the discussion section (page 10, line 203-206).

3. You can study variable that increase the risk of asthma, but you should also conduct why asthma diagnosis was reduced in the >70 age group. i think this will make the paper more interesting.
Reply: Thanks for your valuable comments. In a recently published paper, supporting evidences of the declining prevalence of asthma in the elderly was analyzed. (ref : Clinical and Experimental Pediatrics 2020;63(7):278-283.). In Korea, there were issues related to exposure to humidifier disinfectants until 2011, which might have contributed to the increase in the prevalence of asthma in elderly individuals who are more fragile. Furthermore, because of the influenza and Mycoplasma pandemic in 2010, the prevalence of asthma in the elderly might have increased at that time, and then gradually decreased afterwards. We considered that the pandemic and the level of pollution at certain periods have temporarily increased the prevalence of asthma in elderly individuals who are more vulnerable.

We have added these sentences in the discussion section (page 10, line 214-223)
4. Was spirometry performed in KNHANES?
Reply: In the KNHANES, spirometry was used to estimate lung function for individuals who were over the age of 40 years. This study was for all age groups; therefore, lung function tests were not performed.

5. Do you have information on symptoms? cough, shortness of breath, wheeze. it would be important to understand what symptoms these patients had and if they had any treatment.

Reply: There was information on wheeze, drug use in the past year, and symptom exacerbation in KNHANES. However, because the information was limited to some periods over a span of 3 years (from 2007 to 2009), information on symptoms and treatments could not be applied in this study.

6. What language was the study conducted in? Korean or English?

Reply: This study was conducted in Korean.

7. How were subjects recruited?

Reply: The target recruitment group for the National Health and Nutrition Survey comprises people living in Korea. The target of the survey was selected using a two-stage stratified colony sampling method in which the survey tools and households in the sampling frame for each year were the first and second extraction units, respectively. A total of 576 survey districts were extracted by layering based on the first stratification standard (city, town, town, and type of housing), the second stratification standard (residential area ratio), and the intrinsic stratification standard (householder education ratio). Households, which are the secondary extraction units, were extracted from appropriate households in the sample survey area using a systematic extraction method.

We have added some sentence regarding study design in the method section (page 4, line 77-81) as followed;

"The target recruitment group for the National Health and Nutrition Survey comprises people living in Korea. The target of the survey was selected using a two-stage stratified colony sampling method in which the survey tools and households in the sampling frame for each year were the first and second extraction units, respectively."

8. It is very unusual that male sex is a risk factor for asthma, because numerous studies has shown that asthma is more common in pre-pubescent males but after puberty, asthma is more common in female.

Reply: Thanks for your valuable comments. In our data, the proportion of obese male participants in the 20s band was higher than that of female participants (32.8% in male participants [95% CI 31.1–34.6] vs. 15.3% in female participants [14.1–16.5]) and there

were more ever-smoker (61.0% in male [95% CI 59.2–62.8] vs. 20.8% among female participants [19.3–22.3]). Although there was no significant association in the multivariable analysis, this difference could explain that the prevalence of asthma was higher in male participants.

9. Conditions such as allergic rhinitis and atopic dermatitis usually develop in childhood and so why do the authors think that AR and AD are risk factors in the 20's only. surely, these subjects had AR/AD since young age,

Reply: Thanks for your valuable comments. Generally, allergic rhinitis and atopic dermatitis were known to develop into childhood. However, in recent domestic data (ref: Clinical and Experimental Pediatrics 2020;63(7):278-283.), the prevalence of atopic dermatitis has decreased or remained stationary. In our data, the prevalence of atopic dermatitis in individuals who were under the age of 20 had declined from 16% in 2007 to 13.7% in 2018. However, although there is no significant difference in the prevalence of allergic rhinitis in the 20s band, the prevalence trend of atopic dermatitis increased from 5.9% in 2007 to 11.7% in 2018 (supplement figure 3), which could have contributed to the increase in the prevalence of asthma in the 20s band.

10. The grammar and English needs improving.

Reply: Thank you for your comments. We have checked for spelling errors have made relevant corrections to improve the grammar of the revised the manuscript. The changes are indicated in red font.