Author's response to reviews

Title: Bronchial asthma is associated with increased risk of chronic kidney disease

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Author's response to reviews:

Dear Editor and Reviewers:

We appreciated your kind and professional opinions, which really improved the manuscript very much. We have tried our best to answer and reply all the recommendations and questions as the following. The revisions and corrections are all highlighted in the revised text.

Authors

For the Reviewer 1:

This study investigated the association between bronchial asthma and the risk of developing chronic kidney disease. The data were well analyzed and the results were interesting. Some suggestions as the followings:

Thanks for your kind suggestions to the editor and we hope the manuscript could be accepted for publication so that we could share the interesting results with world-wide medical colleagues.

Besides, we have also added as the highlighted phrase on page 10, paragraph 5 as:

To date, this is the first study to show that asthma patients are prone to developing CKD in comparison to non-asthma controls.

As well as a new paragraph, on page 11, as

In our study, the recruited subjects with asthma are in older age as 47.72±17.73 years. Several studies showed that asthma could develop at age after childhood, adolescence or young adult stage, and several genetic factors, air pollution or
obesity could be related to later onset of bronchial asthma.[37-39] One study of 504 asthmatic patients (303 males and 201 females) in Taiwan indicates that 29% developed asthma at age 25-44 years old, 21% developed asthma at age 45-65 years old, and 8% developed asthma beyond age of 64 [40]. The recent study indicates that the age of onset asthma is 45.4±10.4 years, which is also similar to our study of 47.72±17.73 years.[34]

With the reference of the following (which was published 3 days after our manuscript submission!)

34. Liu DW, Zhen XG, Liang Y, Jing XG, Zhang TS, Zhang GJ and Liu ZS. Persistent asthma increases the risk of chronic kidney disease: a retrospective cohort study of 2354 patients with asthma. Chinese Medical Journal 2013;126 (21) 4093

1. What are the control subjects? It should be cleared in the article.

Thanks for your suggestions and we have added the mentions about the control group:
Added in paragraph 2, on page 7, been highlighted:

The control cohort consists of the patients having no history of bronchial asthma or CKD from 2000 to 2010. These patients were randomly chosen by matching the gender and age of the study cohort with a ratio of 1:3. In addition, the middle date of the same month with that of the index date in the study cohort was assigned to the index date of the corresponding patient in the control cohort.

2. What is the criteria of CKD in this study? Is it the definition from KDIGO?

Thanks for your suggestions and we have added the mentions about the control group:
In paragraph 2, on page 6, been highlighted

In Taiwan, the diagnosis of CKD follows the criteria of “Kidney Disease: Improving Global Outcomes (KDIGO)”. CKD is defined as kidney damage as albumin-to-creatinine ratio >30 mg/g in two of three spot urine specimens or glomerular filtration rate (GFR) <60 mL/min/1.73 m2 for 3 months or more, irrespective of the cause.[16]

Reference:

3. For following-up patients, how long of the follow-up interval? This should be described in the study.
Thanks for your suggestions and we have added the mentions about the follow-up interval:

In paragraph 4, on page 7, been highlighted:

The follow-up interval of the subjects and controls for developing chronic kidney disease during is in a three-year follow-up period.

4. In P8, "Multiple logistic regression analyses were performed to estimate hazard ratio (HR) and 95% confidence intervals (CIs) of osteoporosis associated with CKD", should “osteoporosis” be "asthma” associated with CKD”?

Thanks for your suggestions and we have corrected the word:

In the 2nd paragraph of Statistical Analysis, on page 8

Multiple logistic regression analyses were performed to estimate hazard ratio (HR) and 95% confidence intervals (CIs) of bronchial asthma associated with CKD after controlling for age, sex, levels of urbanization and income. Statistical significance was set at p<0.05.

5. Besides age, sex, levels of urbanization and income, the adjust factors should including BMI or obesity in multiple logistic regression analyses to estimate hazard ratio (HR) and 95% confidence intervals (CIs) of asthma associated with CKD. As far as we know, obesity is closely related to CKD, also closely related to asthma.


Thanks for your suggestions and we have included obesity into the adjusted factors:

In the last paragraph on page 7, And all the data have adjusted accordingly both in the text and the tables (Table 1, Table 3, Table 4, Table 5), and the sites corrected were all highlighted though it seemed not to change the results:

The covariates considered included diabetes mellitus (ICD-9-CM 250, 357.2, 362.0x, and 366.41), hypertension (ICD-9-CM 362.11, 401.x-405.x, and 437.2), hyperlipidemia (ICD-9-CM 272.x), heart disease (ICD-9-CM 410-429 and A codes A270, A279-A281, and A289) and obesity (ICD codes: 278.00, 278.01, 278.02, 278.03).

In the 4th paragraph, on page 10 (the 2nd paragraph of Discussion)

Most researches report that patients with older age have increased risk of
developing CKD [25]. Moreover, patients with hypertension[3], heart disease[4], diabetes[5], hyperlipidemia[9] and obesity[26-28] also have high risk of CKD. However, after adjusting for sex, age, and these co-morbidities, subjects with asthma still have significant and independent high risk of CKD (HR: 1.13 [1.07-1.19], p<0.001).

Reference:

For the Reviewer 2:
The authors have examined the association between asthma and chronic kidney disease in a population cohort from Taiwan.
There are several major issues that require attention from the authors
Thanks for your kind suggestions for revisions and we hope the corrected manuscript could be accepted for publication so that we could share the interesting results with world-wide medical colleagues.

1. How asthma diagnosis was made?

Thanks for your question, and we have added the mentions about making asthma diagnosis in Taiwan:

On page 6, paragraph 1:
The diagnosis of bronchial asthma bases on characteristic clinical history such as intermittent breathlessness, wheezing, troublesome night time cough and chest tightness, aided by lung function tests in some cases,[17, 18] which is similar to criteria of the Global Initiative for Asthma (GINA) guidelines.[19, 20]

Besides, we have mentioned that the patients of bronchial asthma were collected from ICD-9-CM: 493 (page 7), and the internal mechanism of to verify the diagnosis “The Bureau of National Health Insurance randomly reviews the charts of 1 per 100 ambulatory and 1 per 20 in-patient claim cases to verify the accuracy of the diagnosis[15].” (page 6)

References:
17. Yeh KW, Chiang LC, Chen SH, Huang JL: Survey of the clinical practice of physicians in the management of asthma in Taiwan. Asian Pacific journal of allergy and immunology / launched by the Allergy and Immunology Society of


2. Cigarette smoking data was not provided or included in the analysis and is a likely important factor in both asthma, and other risk factors such as heart disease and even CKD itself

Thanks for your question, and we have added the mentions about this limitation and we regret we could not find the records of NHIRD:

In the 1st paragraph, on page 13

Furthermore, no information about cigarette smoking, which is a risk factor of CKD,[42] is available in the NHIRD database. However, we have adjusted other metabolic risk factors such as diabetes mellitus, hypertension, hyperlipidemia, and obesity.

Reference:


3 Patient BMI or obesity was not included as a risk factor or data provided

Thanks for your suggestions and we have included obesity into the adjusted factors:

In the last paragraph on page 7, And all the data have adjusted accordingly both in the text and the tables (Table 1, Table 3, Table 4, Table 5), and the sites corrected were all highlighted though it seemed not to change the results:

The covariates considered included diabetes mellitus (ICD-9-CM 250, 357.2, 362.0x, and 366.41), hypertension (ICD-9-CM 362.11, 401.x-405.x, and 437.2), hyperlipidemia (ICD-9-CM 272.x), heart disease (ICD-9-CM 410-429 and A codes A270, A279-A281, and A289) and obesity (ICD codes: 278.00, 278.01, 278.02, 278.03).
In the 4th paragraph, on page 10 (the 2nd paragraph of Discussion)

Most researches report that patients with older age have increased risk of developing CKD [25]. Moreover, patients with hypertension[3], heart disease[4], diabetes[5], hyperlipidemia[9] and obesity[26-28] also have high risk of CKD. However, after adjusting for sex, age, and these co-morbidities, subjects with asthma still have significant and independent high risk of CKD (HR: 1.13 [1.07-1.19], p<0.001).

References:

4. The age of the patients suggests asthma diagnosis at an older age which means they may have another airway disease such as COPD and limited details on diagnosis was provided.

Thanks for your suggestions; we have discussed this issue as the following on page 11-12, in a new paragraph:

In our study, the recruited subjects with asthma are in older age as 47.72±17.73 years. Several studies showed that asthma could develop at age after childhood, adolescence or young adult stage, and several genetic factors, air pollution or obesity could be related to later onset of bronchial asthma.[37-39] One study of 504 asthmatic patients (303 males and 201 females) in Taiwan indicates that 29% developed asthma at age 25-44 years old, 21% developed asthma at age 45-65 years old, and 8% developed asthma beyond age of 64 [40]. The recent study indicates that the age of onset asthma is 45.4±10.4 years, which is also similar to our study of 47.72±17.73 years.[34]

References:

The abstract background provides no rationale for doing the study - why is it important to clarify this association

Thanks for your suggestions; we have added in the Abstract Background as the first sentence, on page 3:

Bronchial asthma also influences other chronic diseases such as coronary heart disease, diabetes mellitus, and hypertension, but the impact of asthma on other vital organs such as chronic kidney disease are not yet verified.

The discussion contains no reference to other studies in the research area or evidence to support the findings in this paper.

Thanks for your suggestions; we have added a new paragraph for discussion about this issue, on page 11:

One study from a retrospective cohort of 2354 asthma patients found 9.6% incidence of CKD in a six-year period follow-up, without non-asthma controls, in which the group of persistent asthma have independent higher risk of CKD than non-persistent group, and patients with three traits together of long history of asthma > 20 years, not well-controlled asthma and persistent stage of asthma have significant risk as high as OR=3.39 (95% CI 1.36–8.73), compared to patients without these traits. Our study found an association between asthma and later CKD in larger cohort including asthma subjects (n=35086) and non-asthma controls (N=105258) in a three-year period of follow-up. Steroid and other medication treatment might decrease the risk of CKD associated with asthma. The value of well-controlled asthma not only important to preserve the respiratory function, but also in other organs is similar between two studies.

(Besides, we have also added as the highlighted phrase on page 10, paragraph 5 as:
To date, this is the first study to show that asthma patients are prone to developing CKD in comparison to non-asthma controls.)

Reference: