Author's response to reviews

Title: The Correlation between the bronchial hyperresponsiveness to methacholine and asthma like symptoms by GINA questionnaires for the diagnosis of asthma

The Correlation of Methacholine Bronchial Provocation Test and GINA Questionnaires to diagnose asthma

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Authors:

So Yeon Lim (Fiday63@hanmail.net)
YonJu Ryu (medyon@ewha.ac.kr)
Young Joo Jo (yjcho@ewha.ac.kr)
Eun Mi Chun (cem@ewha.ac.kr)

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Author's response to reviews: see over
Cover letter
The correlation between the bronchial hyperresponsiveness to methacholine and the validity of asthma like symptoms by GINA questionnaires for the diagnosis of asthma

Reply for Reviewer: Peter Wark
I appreciate sincere comments by reviewer and I answered for reviewer’s requests

Major limitations
Although our hospital is general hospital (university hospital), patients can visit by themselves without referred by primary physician for korean medical policy. Many subjects visited at this hospital without consulting of primary care after respiratory symptoms developed. Korea medical cost is relatively reasonable and many patients can chose proper hospital without economic and time limitations. Therefore, participants in this study were mixed pattern of primary care and secondary care population. I added comments regarding this issue in methods to clarify the pattern of populations if this study group.

Minor points
1) We enrolled participants who answered positive response at more than one question. Methacholine tests were performed only for subjects enrolled by positive answered questionnaire. Therefore, we did not enroll subjects with methacholine reactivity, but who answered no to the symptoms.

2) I changed discussion part by reviewer’s comment that this provides a gold standard as a questionnaire for diagnosis of asthma is an overstatement.

3) I described the definition of Youden index more precisely in discussion part with additional comment and reference. \( J = \text{maximum}\{\text{sensitivity}(c) + \text{specificity}(c)-1\}\), is generally used as the method of overall diagnostic effectiveness. The value close to 1 indicate that the biomarker’s effectiveness is relatively large.
Reply for Reviewer: Joerg Mattes

I appreciate sincere comments by reviewer and I answered for reviewer’s requests

1) Yes, I agree with reviewer’s comment that BHR is not an appropriate criteria to define asthma. Additionally, if this study was focused on only the association between BHR and symptoms, this study would add little novelty to previous work. Our study tried to investigate the validity of selected five items of GINA questionnaire which questions are more valuable to differentiate asthma in private clinic or epidemiologic study. It is helpful to select small number of proper questions to define asthma in clinical field due to limitations of time and cost. Present study aimed to confirm the more valuable questions among GINA questionnaire in private clinic or large scale epidemiologic study to have limitations of time and cost. I changed that the aim is to analyse the association between BHR and asthma like symptoms.

2) One of the limitation of present study was no healthy control group. This study was performed with no fund and healthy control group was not enrolled because of cost limitation for performing methacholine test and the ethics. Further study will be matched with control group to clarify our results. Most of the diagnoses in those 516 participants not classified as having asthma were URI, acute bronchitis because we excluded patients having emphysma, pneumonia, tuberculosis and interstitial lung diseases before enrolling criteria by radiologic examinations and pulmonary function tests. We enrolled subjects only asthma like symptoms with normal radiologic findings. This study was focused on differentiating valuable questions to define asthma in subjects with normal chest radiography and pulmonary function tests.

3) FEV₁ (%predicted) and FEV₁/FVC (%predicted) is slightly lower in asthmatics than non-asthmatics (93% vs 98%, 78% vs 82% respectively). Only subjects with a basal FEV₁ of more than 70% of the predictive value by spirometry were enrolled in present study. Therefore the PFT of asthmatics revealed similar value with non-asthmatics. Most of subjects had mild asthma like symptoms having normal value by spirometry.
4) We excluded subjects who already diagnosed asthma and no participants were on asthma treatments. We recommended subjects to stop any medications to influence the lung functions before pulmonary function tests. Most of medications were antihistamines and antitussives.

5) I revised the result part by reviewer’s comment that an AUC of 0.6 appears very modest by all standards that BHR in this cohort only predictive of an increased symptom score.

6) I revised the discussion to focus more on limitations including reviewer’s comments.

7) Our study focused on detecting the more valuable items among GINA questionnaire to apply in clinical field, especially private clinics, where have limitations to apply methacholine test to all patients because of cost and time. I added more comments to the discussion part about present study strength.: Especially, among five items, exercise-induced dyspnea, recurrent attacks of wheezing, and pollution induced dyspnea are more useful to differentiate asthmatics from non-asthmatics. Therefore, these three items may be adjusted to diagnose asthma more frequently than other questions.