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

Authors:

So Yeon Lim (Firday63@hanmail.net)
YonJu Ryu (medyon@ewha.ac.kr)
Young Joo Jo (yjcho@ewha.ac.kr)
Eun Mi Chun (cem@ewha.ac.kr)

Version: 5 Date: 5 September 2014

Author's response to reviews: see over
Reviewer's report

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.

Version: 3 Date: 26 May 2014
Reviewer: Peter Wark

Reviewer's report:

This is an interesting manuscript that uses the 5 GINA asthma questions to determine the presence of asthma, as defined by bronchial responsiveness induced by methacholine. This is a large sample and this adds considerable validity to the findings. The manuscript makes an important contribution to the field addressing what questions can be used to define asthma. There are some major limitations however that need to be addressed. Importantly it needs to be clarified as to the nature of the population. They are stated as subjects referred to a large university hospital with possible asthma. If so then this is not a sample representative of primary care, but rather secondary care. While still valid the applicability of these findings are potentially different. If they have been referred then this in itself is a selected population and the sensitivity and specificity for an unselected primary care population would be different. This is an important point and requires clarification.

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

Participants were mixed populations referred from other primary physicians and visited to pulmonary department by themselves without consultations.
Minor points

1. In the methods it is stated that those with symptoms and methacholine reactivity were diagnosed with asthma. Clarify if those with methacholine reactivity, but who answered no to the symptoms were defined.

We enrolled participants who answered positive responses for more than one question. Methacholine tests were performed only for subjects who answered positive to respiratory questionnaire. Therefore, we did not enroll subjects with methacholine reactivity, but who answered no to the symptoms.

2. The statement in the discussion that this provides a gold standard as a questionnaire for diagnosis of asthma is an overstatement and should be revised.

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

: acceptable screening method

3. Page 12 of the discussion the Youden index is mentioned. This needs to be defined, and will not be understood by the majority of readers.

I added the definition of Youden index more precisely in discussion part.

: Youden index, $(J) = \text{maximum} \{\text{sensitivity( c )+ specificity( c )-1}\}$, is generally used as the method of overall diagnostic effectiveness. The value close to 1 indicate that the biomarker’s effectiveness is relatively large

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
Reviewer's report

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.

Version: 3  Date: 13 July 2014  
Reviewer: Joerg Mattes

Reviewer's report:

Major:
1) Asthma is defined as bronchial hyperresponsiveness (BHR) to methacholine in this study but as the authors rightly point out on several occasions, this is NOT an appropriate criteria to define asthma. Thus the manuscript would need to be rewritten with the aim to analyse the association between BHR and symptoms. However the results of such study would add little novelty to previous work unless BHR and symptoms would also be able to be correlated with the participants' diagnosis, eg asthma, COPD etc.

: Yes, I agree with reviewer’s comment that BHR is not an appropriate criteria to define asthma. I changed the objective of abstract as following:

_The aim of this study was to analyze the association between hyperresponsiveness to methacholine and the validity of five items of the asthma like questionnaire recommended by the Global Initiative for Asthma (GINA)._

Additionally, if this study was focused on only the association between BHR and symptoms, this study would add little novelty to previous works. Present study tried to investigate the validity of selected five items of GINA questionnaire which questions are more valuable to define asthma in private clinic or epidemiologic study. Our study may be helpful to select small number of the proper questions to define asthma in clinical field due to limitations of time and cost. The new point of present study aimed to find the more valuable questions among GINA questionnaire in
private clinic or large scale epidemiologic study to have limitations of time and cost.

2) One major issue is that there is no healthy control group making it very difficult to argue that it is possible to calculate sensitivity and specificity of a symptom questionnaire to detect specific disease. This is complicated by the lack of clarity in terms of what the diagnosis is of those participants who have not been diagnosed with BHR (asthma) as per their definition. Many important differential diagnoses (e.g. COPD) have actually been excluded as per study design (how many have been excluded and why?). So what are the diagnoses in those 516 participants not classified as having asthma yet having significant enough symptoms to be referred to outpatient department for respiratory symptoms?

: One of the limitation of present study was no healthy control group. This study was performed without funds and healthy control group was not enrolled because of cost and ethic limitations for performing methacholine test. Further study will be matched with control group to clarify our results with fund. Most of the diagnoses in those 516 participants not classified as having asthma were URI, acute bronchitis because we excluded patients having COPD, pneumonia, tuberculosis and interstitial lung diseases before enrolling criteria by radiologic examinations. 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. I added comments in method part about diagnoses not classified as having asthma

: The subjects having other lung diseases including pneumonia, emphysema, tuberculosis, interstitial lung disease were exclude by radiologic examinations.

3) There is no difference in FEV1% and FEV1/FVC% between "asthmatics" and "non-asthmatics"

: 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 values with non-asthmatics. Most of subjects had mild asthma like symptoms having normal value by
basal spirometry.

4) What were the effects of any treatment the participants were on? How many were on asthma treatments? Were bronchodilators withheld before pulmonary function testing?
   : We enrolled who had never been diagnosed asthma by physicians in other clinics or hospitals. Therefore, there were no effects by other treatments including bronchodilators.

5) An AUC of 0.6 appears very modest by all standards, highlighting that BHR in this cohort only modestly predictive of an increased symptom score
   : I added the comments regarding AUC in the results according to reviewer’s advice.
   
   An AUC OF 0.6 appears that BHR in this cohort means modestly predictive of an increased symptom score for the asthma group.

6) The discussion needs to focus more on the limitations of the study (see above) 7) The demographic data needs to have more information (medications, diagnoses, etc) as well as define what aspects are novel about this study and what it adds
   : I added the limitations in the parts of discussion.

First, one major limitation is that there was no healthy control group. This problem probably make it somewhat difficult to argue that it is possible to calculate sensitivity and specificity of a symptom questionnaire to detect specific disease.

The part for demographic data including medications, diagnoses were described in the methods. Most of participants took common antitussive or antibiotics before visiting to our hospital. Diagnoses were mainly URI or acute or chronic bronchitis. I added the comments the novel aspects of this study in discussion part.

: 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.

Level of interest: An article of limited interest

Quality of written English: Needs some language corrections before being
published

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**
I declare that I have no competing interests