Author's response to reviews

Title: Does decreasing serum uric acid level prevent hypertension? -- A nested randomised controlled trial in cohort study: Rationale, methods and baseline characteristics of study cohort

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Author's response to reviews: see over
Author’s response to reviews

Title: Does decreasing serum uric acid level prevent hypertension? --A nested RCT in cohort study: Rationale, methods and baseline characteristics of study cohort

Authors:
Yuan Wang (gw_928@163.com)

Version: 3 Date: 23 June 2013

Reviewer’s report

Title: Does decreasing serum uric acid level prevent hypertension? --A nested RCT in cohort study: Rationale, methods and baseline characteristics of study cohort

Version:2 Date:26 February 2013

Reviewer: Francesca Viazzi

Reviewer’s report:

In the present study protocol, authors propose to randomize to either a health educational package group or a control group 2495 hyperuricemic subjects in order to investigate whether reduction of serum uric acid levels decreases the risk of hypertension during a 5 year follow-up. Unfortunately, the manuscript is poorly written and needs extensive editing of the English form. Albeit the argument is very interesting, there are several major issues that should be addressed before the manuscript can be considered for publication.

Major Compulsory Revisions

Comment 1: In the methods section Hyperuricemia is defined as a serum uric acid value above 6.0 mg/dl for males and above 7.0 mg/dl for females. Authors should specify the reason for these cut-off values which, certainly, are not in line with the literature. In fact, since serum uric acid is normally higher in men than in women, hyperuricemia is typically defined for higher serum uric acid levels in males. This is a critical issue, since the independent association
between hyperuricemia and pre-hypertension in females but not in males reported by Authors in the manuscript could simply be due to the selection of females patients with a more severe hyperuricemia.

Response: We are sorry for our carelessness. The right definition was “Hyperuricemia is defined as a serum uric acid value above 6.0 mg/dl for females or above 7.0 mg/dl for males". This definition was generally accepted in China.

Comment 2. The protocol does not provide sufficient information about dietary intervention and lifestyle recommendations the authors are going to propose to the participants.

Response: Each subjects will be given an inform letter including tailored recommendations with taking the dietary habit of participants into account after evaluation of a food and fluid intake sheet recalled by subjects. Generally, three modules were included: Risk of hyperuricemia, dietary recommendations with lists of restricted and recommended food according to the subject’s recall, and lifestyle modification recommendations. The intervention and lifestyle recommendation was individualized.

The following text was added: Participants were asked to finish questionnaires about their dietary habits and lifestyle. After evaluating participants’ dietary habits and lifestyle, trained nutritionist will make tailored recommendations for each participant. An inform letter including tailored recommendations will be sent subjects after a face to face health-related advisory services. Generally, three modules were included: Risk of hyperuricemia, dietary recommendations with lists of restricted and recommended food according to the subject’s recall, and lifestyle modification recommendations.

Comment 3. Moreover, a detailed description of tools used to evaluate compliance to recommendation is not provided. This reviewer believe that measuring urinary 24 hour sodium excretion might give important information about the state of the volume and the adherence to diet.

Response: We thank the reviewer for the valuable advice. However during out pilot trial, this measurement failed to be carried out. Most of subjects didn’t do it, and among those who do, many perform the collection incorrectly.
Many subjects complained that the measurement of 24-hour urine sodium excretion is cumbersome and inconvenient. We have to give up this measurement instead subjects were asked to finish a questionnaire included the information about diet which will be evaluated by a trained nutritionist.

**Comment 4:** Table 2 lack any data about renal function. Again, this is instrumental to analyze and discuss in a constructive way the findings of this RCT.

**Response:** Renal function tests were carried out annually during their health examination. The renal function tests include creatine and BUN.

The following text was added in method section: Renal function was assessed by testing creatine and BUN.

**Comment 5:** It is not clear to me how the Authors are going to handle those patients who may possibly start to assume uric acid lowering treatment because symptomatic for hyperuricemia during the study follow-up.

**Response:** Medical history of the last year will be collected during annually health examination. Subjects will be asked whether he or she had uric acid lowering treatment in the last year which will be considered during analysis.

The following text was added in discussion section: A potential bias would be in the uric-acid lowering treatment for patients with symptoms of hyperuricemia. Subjects will be asked whether he or she had uric-acid lowering treatment in the last year, and if so this will be considered as a covariate during analysis.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Not suitable for publication unless extensively edited

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
I have no competing interests to declare
Reviewer's report

Title: Does decreasing serum uric acid level prevent hypertension? --A nested RCT in cohort study: Rationale, methods and baseline characteristics of study cohort

Version:2  Date:29 March 2013

Reviewer: Sunil V Badve

Reviewer's report:

Song and colleagues describe rationale and methods of a cohort study and a nested RCT.

1. The manuscript requires extensive corrections of English grammar and spellings. The text is presented in past, present and future tense on several occasions. It is quite confusing, especially where all tense occur in the same paragraph.

   We are sorry for the poor grammar of the original draft. The revision version had been edited by Professional Editing Service SPI global

   http://www.prof-editing.com/index.php

2. The selection method for the cohort study needs to be described in detail. It appears that the selection process is biased towards those people whose employers have long term annual check-up contracts with the research centre. This raises a selection bias and will affect external validity of the study to other populations.

   We agree with the reviewer that there might be selection bias. The subjects were employers who have long term annual check-up contracts with our center. It should be cautious when one tries to use the results in other population. The following text was added in discussion: The subjects in this study were employed by an employer who had a long-term contract with the Health Management Centre. One should be cautious when generalizing the research results to other populations.

3. The practice of financial compensation to the participants raises ethical concerns.
We prepared small gifts as a form of financial compensation for subjects after they finished the questionnaire. This practice was approved by the ethical committee in Tianjin Medical University. “Participants will be offered financial compensation for their time lost as a result of the study “was deleted. The following text was added in discussion: Small gifts were given as financial compensation for the time lost in completing the questionnaires for this study.

4. In the nested RCT, the methods of random sequence generation and allocation concealment are not described. The following text was added in study design description: Participants were randomized by a computer-generated number, which was concealed in sequentially numbered, sealed, and opaque envelopes, and kept by a trained nutritionist who delivered the intervention.

5. There are no details of the contents and medium of the ‘education package’.
   In this study education package was individualized. Participants were asked to finish questionnaires about their dietary habits and lifestyle. After evaluating participants’ dietary habits and lifestyle, trained nutritionist will make tailored recommendations for each participant. An inform letter including tailored recommendations will send to subjects after a face to face health-related advisory services. The following text was added: Participants were asked to answer questionnaires about their dietary habits and lifestyle. After evaluating the participants’ dietary habits and lifestyle, a trained nutritionist will make tailored recommendations for each participant. An information letter that included the tailored recommendations was sent to the subjects after the face-to-face health-related advisory service. Generally, three modules were included: risk of hyperuricemia, dietary recommendations with lists of restricted and recommended food according to the subject’s recollection, and lifestyle modification recommendations.

6. From the discussion section, it appears that the ‘education package’ will target not only uric acid reduction, but also obesity, alcohol reduction, and multiple components of lifestyle modification. Each of these factors is a known
risk factor for hypertension. Obviously, in spite of being a RCT, the final result of the nested RCT will be heavily confounded by several hypertension risk factors that can be modified by the intervention (in this case- educational package).

We agree with the reviewer. Many risk factors were associated with both high serum uric acid and blood pressure. The researchers were most interested in whether lowering uric acid was associated with blood pressure. The education package may result both uric acid and blood pressure lowering. In intervention group (PHI), there will be two subgroups divided according to whether the uric acid was controlled or not. The comparison of hypertension occurrence between subgroups aimed to illustrate whether decreasing serum uric acid level prevent hypertension. The following text was added in discussion: In addition, a comparison of transition rate of hypertension will be performed between the controlled hyperuricemia group and the uncontrolled hyperuricemia group.

7. The entire paragraph of the sample size calculation requires some work. The authors need to describe their assumptions, evidence behind these assumptions, effect size, etc. Should the RCT group be PH and not NH? What does the 'each group' of 289 designate? Four cohort groups or 2 arms of the RCT? How was the sample size of 1455 calculated? Please pay attention to grammar.

Sample size calculation for the primary endpoint is made under the assumption that during the 5-year observational period about 30% of subjects in intervention group and 20% of subjects in control group develop hypertension. The detectable risk increase is compatible with 80% power and significance of 0.05 is 10%. We are sorry that the assumption was made rather arbitrarily. We refer to the publication of Doctor Feig which the relative risks of hypertension were 1.2 to 3.5, most around 1.5 for high uric acid. A relative risk of 1.5 was adopted in this study. In addition, 1455 was changed to 1445 with 289 for each group. Again we are sorry for the poor grammar and we asked an editing service for correcting.
8. Are the definitions of hyperuricemia for male and female interchanged?
We are sorry for our carelessness. The right definition was “Hyperuricemia is defined as a serum uric acid value above 6.0 mg/dl for females or above 7.0 mg/dl for males”.

9. How the use of uric acid lowering medications (such as allopurinol) will be handled?
Subjects will be asked whether he or she had uric acid lowering treatment in the last year that will be considered during final analysis. The following text was added in discussion section: A potential bias would be in the uric-acid lowering treatment for patients with symptoms of hyperuricemia. Subjects will be asked whether he or she had uric-acid lowering treatment in the last year, and if so this will be considered as a covariate during analysis.

10. The sentence in the discussion section 'The findings about factors associated with .... in compliant participant' doesn't make sense. I am not sure what the investigators mean by that.
We are sorry for the confusion. We corrected this sentence. Factors associated with non-adherence in this study will be investigated according to the information filled in the questionnaire. Measures could be developed to ensure the implement of intervention.

11. It is not clear whether the baseline characteristics described in this article are of those individuals that are eligible to participate or have already participated in the cohort study and the nested RCT.
The baseline characteristics described in this article are of those individuals that are eligible to participate. Individuals aged from 35-75 were asked if he or she would please to participate in their coming annual health check-ups. The baseline characteristics will be described after all participants enrolled. The
Individuals aged from 35-75 were asked if he or she would participate in their scheduled annual health check-ups.

12. I could not find the registration number of the RCT.
The study has registered at Chinese Clinical Trial Registry (Registration No. ChiCTR-TRC-12002925).

Minor Essential Revisions
1. Page numbers are not inserted.
Page numbers had been inserted.
2. Abbreviations are not described for Table 1.
Abbreviations had been described for Table 1.
3. Units of blood investigations are not described in Table 2.
Units of blood investigations were added.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Not suitable for publication unless extensively edited

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
I declare that I have no competing financial interests. I am one of the chief investigators of the CKD-FIX Study (Registration number ACTRN12611000791932).