Author's response to reviews

Title: Uric acid is a risk factor for ischemic stroke and all-cause mortality in the general population. A gender specific analysis from The Tromso Study.

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Author's response to reviews:

To the editors Tromsø November 12th 2013
BMC Cardiovascular Disorders

Dear editors,

Thank you for the review of our research article “Uric Acid is a risk factor for ischemic stroke and all-cause mortality in the general population. A gender specific analysis from The Tromsø Study.” (Manuscript ID 354604231 9957307)

Authors: Storhaug HM, Norvik JV, Toft I, Eriksen BO, Løchen ML, Zykova SN, Solbu MD, White S, Chadban S, Jenssen T.

In the present paper, we address the predictive value of uric acid for development of cardiovascular disease. The role of hyperuricemia regarding cardiovascular disease is debated, since serum uric acid is reported to be a risk factor for cardiovascular disease in some studies, but not in others. The key problem regarding this inconsistency is, that previous studies were unable to correct for important confounding variables such as drug intake and renal dysfunction.

In the Tromsø Studies, we have data on all these covariates. Gender differences may also influence the results. We find that one SD increment in uric acid is a strong, independent risk factor for stroke in men. Uric acid was also associated with all-cause mortality in both genders. Associations with myocardial infarction
did not persist after adjustments for lipid profile.

The study consisted of 2696 men and 3004 women from the general population, with a observation time of 12 years for CVD endpoints and 15 years for all-cause mortality. Our study should be a valuable addition to the scientific literature, and contribute to the topic whether hyperuricemia plays a causative role in the development of cardiovascular disease or not.

We have now made the changes suggested by the reviewers, and are re-submitting the revised manuscript. All authors have agreed with the present version of the paper, and to the re-submission to BMC Cardiovascular Disorders.

We hope that the article now will be acceptable for publication in your on-line journal.

Below, please find a point-by-point description of the changes we have made according to the reviewers comments.

Yours Sincerely

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Comments and point-by-point description of changes made according to the reviewers suggestions.

Referee 1:

1. Regarding the suggestion to address more thoroughly the fact that serum uric acid was not associated with myocardial infarction in multivariable analyses:

We agree that exclusion of high-risk persons such as persons with diabetes or established cardiovascular disease at baseline, could be the reason why we did not find significant associations in any gender. We therefore reanalyzed the data, with persons with diabetes or previous CVD included. This did not change our findings. Results of these subanalyses are now reported in the “Result Section” (page 10, lines 4-7). And the finding are discussed in the “Discussion” section (page 12, lines 16-18). We have also added 2 lines at the bottom of page 12, where we point at factors that may have influenced the difference between our and others observations regarding uric acid and future myocardial infarction.

2. Referee 1 suggests that Cox regression analyses should be done not only using tertiles of uric acid, but also after stratification according to normal and unnormal uric acid level:

We have stratified by high uric acid or not (cut off levels > 400 µmol/L for women and >480 µmol/L for men), and done gender-specific, multivariable Cox regression analyses, with the dichotomy variable “abnormal high uric acid (yes/no)” as predictor variable. The association with myocardial infarction,
ischemic stroke and all-cause mortality did not differ from what we observed using uric acid tertiles. This is shortly mentioned in the “Result Section” (page 10, lines 8-12) and in the “Discussion Section” (page 19-20).

Minor essential Revisions:
The small errors in “Population Section”, table 1 and in the footnote in table 2 have been corrected.

Referee 2:

1. In women, uric acid was associated with all-cause mortality, but not with ischemic stroke and myocardial infarction. The referee suggests that we could speculate about the causes of death in women.

Unfortunately, we do not have access to the “causes of death registry”, so it is hard to guess the causes of death. We found no association between uric acid and “having a cancer diagnosis” at baseline, or “having got a cancer diagnosis” at the follow-up study in 2007/08 (The 6th Tromsø Study where 2863 participants from the 4th Tromsø Study were reexamined).

Since the manuscript should not be too long, we have left out a discussion about potential causes of death in women.

2. Explanation why the association between serum uric acid and ischemic stroke reached significance in men, but not in women.

We agree that gender-differences in vascular biology may contribute to our findings, and have now included a paragraph where the importance of differences in aortic stiffness and pulse wave reflection are discussed (Discussion Section; page 11, lines 8-15)