Author's response to reviews

Title: Impact of nephrolithiasis on kidney function

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Author's response to reviews: see over
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BMC Nephrology
BioMed Central
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Re: MS: 1199529082159519 - manuscript entitled “Impact of nephrolithiasis on renal function”, authored by Vaka K Sigurjonsdottir, Hrafnhildur L Runolfsdottir, Olafur S Indridason, Runolfur Palsson and Vidar O Edvardsson” (revised according to the STROBE guidelines).

To whom it may concern:

Enclosed is a revised version of the manuscript, entitled “Impact of nephrolithiasis on renal function”. As requested by the editors, the authors have carefully reviewed and edited the manuscript to ensure its compliance with the STROBE guidelines. All manuscript changes are highlighted with a yellow colour.

We greatly appreciate the opportunity to publish our work in BMC Nephrology.

Sincerely,

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Below you will find a point-by-point review of changes we have made to ensure compliance with the STROBE guidelines and we now believe that the manuscript adheres well to the latest version of these guidelines.

Methods

1. Participants (STROBE guideline item number 6).
   a. Give the rationale for the choice of cases and controls.
   **Authors’ reply:** The choice of cases has already been described in detail in the Method section and the text highlighted in yellow has been added to the manuscript, lines 117-118, to explain choices of control individuals: To compare kidney stone patients to the general population, a control group was drawn from a cohort of 1630 community dwelling subjects aged 29-87 years who participated in a cross-sectional study of bone health performed in Reykjavik in the years 2001-2003.

2. Data sources/measurement (item number 8).
   a. Describe comparability of assessment methods if there is more than one group.
   **Authors’ reply:** We used the same methods to assess kidney function and comorbid disease in cases and controls and to make that more clear the text highlighted in yellow has been added to the manuscript, lines 148-149: Information on comorbid conditions was obtained through medical history reported by the stone patients and the controls, review of their medical records and/or by searching for the appropriate ICD-9 and ICD-10 diagnostic codes for both cases and controls in the electronic patient information system at LUH.

3. Bias (item number 9).
   a. Describe any efforts to address potential sources of bias.
   **Authors’ reply:** Potential sources of bias are variables that may affect renal function and its estimation in all study participants and include a) changes in body composition (increase in BMI, overweight and obesity) occurring with time in the Icelandic population as in other Western societies and b) the potential drift in serum creatinine measurements with time which might adversely affect the comparison of kidney function between cases (serum creatinine measured in the years 2009-2013) and controls (serum creatinine measured in the years 2001-2003). All se-Cr measurements were, however, IDMS standardized.
      i. To address the potential bias introduced by changes in body composition with time we compared the BMI distribution of our study subjects to both the current Icelandic population and the control subjects.
      ii. To avoid overestimation of CKD in the cases we excluded patients with other known kidney disease, eGFR was calculated using the lowest available SCr values within the last year of observation and all SCr values had to be obtained at least 3 months after a documented clinical
stone event (Methods-Evaluation of renal function, lines 129-139). Moreover, cases and controls were age and sex matched to ensure that differences in these factors would not bias the eGFR calculations and comparisons between the groups.

iii. The text highlighted in yellow has been added to the manuscript, lines 123-125: Since body composition and SCr are affected by age and sex, both of which are included in eGFR calculations, cases and controls were matched for these factors. In addition, we also compared the distribution of BMI of our stone forming group to that of a group of 1271 subjects from the general Icelandic population using data from a nationwide study of nutrition conducted by the Icelandic Directorate of Health for the year 2011.

4. Statistical methods (item number 12):
   a. Describe any methods used to examine subgroups.
      Authors’ reply: The text highlighted in yellow has been added to the manuscript, lines 174-176: BMI, hypertension, diabetes and cardiovascular disease, which may affect the outcome variables. Same methods were used to compare a subgroup of patients with calcium stones to their corresponding control individuals.

Results
5. Participants (item number 13).
   a. (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. (b) Give reasons for non-participation at each stage.
      Authors’ reply: All the above information ((a) and (b)) is very clearly presented in the Methods section.

6. Main results (item number 16).
   a. Make clear which confounders were adjusted for and why they were included.
      Authors’ reply: The text highlighted in yellow has been added to the manuscript, lines 164-166: BMI, hypertension, diabetes and cardiovascular disease which may affect the outcome variables. Same methods were used to compare a subgroup of patients with calcium stones to their corresponding control subjects.

Discussion
7. Limitations (item number 19)
   a. Discuss both direction and magnitude of any potential bias.
      Authors’ reply: The text highlighted in yellow has been added to the “Strengths and limitations section” of the manuscript, lines 304-309: Other limitations include potential sources of bias related to ascertainment of variables known to affect kidney function and its estimation. However, by excluding stone
patients with other underlying kidney diseases and SCr values obtained during stone episodes and by using the lowest SCr available in the last year of observation for each patient, we believe we have avoided overestimation of CKD. To the contrary, the prevalence of CKD in kidney stone patients may have been underestimated.

8. Generalisability (item number 21)
   a. Discuss the generalisability (external validity) of the study results.
      Authors’ reply: The text highlighted in yellow has been added to the “Section on study strength”, lines 300-302: .. Finally, since the study participants were almost exclusively non-Hispanic Caucasians, our results are likely to be generalizable to the white population living in Europe and North America.

9. Other changes made by the authors.
   The text highlighted in yellow has been added to the manuscript, lines 136-137 (Methods-Evaluation of renal function): ... excluded, along with their corresponding controls, from the kidney function analysis.

   The following reference (a document in Icelandic published by the Icelandic Directorate of Health (a governmental agency which collects and publishes health statistics), on the institutions web-site) has been added at the end of line 128: “(available at www.landlaeknir.is).”