Author's response to reviews

Title: Low urine pH and acid excretion do not predict bone fractures or the loss of bone mineral density: a prospective cohort study

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Author's response to reviews: see over
We appreciate the opportunity to respond to the reviewers’ helpful comments and have addressed their comments and concerns below.

A. Response to Reviewer: Dr. Fariba Roughead

Thank-you for your review of our manuscript and your insightful comments. Please see our responses below:

Major Compulsory Revisions

1. Add emphasis on the weakness of first-morning void versus longer collection times: Good point, we have further emphasized the limitations of our use of second morning void urine samples.

B. Response to Reviewer: Dr. Jean-Phillipe Bonjour

Thank-you for your review of our manuscript and your helpful comments. Please see our responses below:

Suggestions for consideration

1. P.2 Abstract/Methods: Agreed. We have clarified our abstract methods.
2. **P.5, 2nd Para:** We included the source of the organic acid estimate, as well as the formula.

3. **P.6, 1st Para:** We have clarified in the text on page 6 how we used indicator variables to retain the sample size.

4. **Table 1.** Thank you for catching this error. It is now corrected.

5. **P.6, Results:** We agree. It has been corrected in the text. We have omitted the dotplot.

6. **P.6 3rd Para:** We added in the fact that 89% (41 of 46) of the confirmed fragility fractures occurred among those aged 50 or greater.

7. **P. 7 and Table 5:** Although several of the potential confounding variables were related to the outcomes of interest, there was no association between either urine pH or urine acid excretion and the outcomes of interest whether the models were fully, partially, or not controlled for the confounding variables.

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C. **Response to Reviewer: Dr. Jane Kerstetter**

We thank you for your review of our manuscript and your insightful comments. Please see our responses below:

**Major Concerns**

1. **A positive control or validation of diet:** Since people are encouraged to measure their urine pH to assess their risk of osteoporosis as well as their general health status, we felt that assessing the validity of this claim was warranted. Thus the primary objective of this study was to determine whether low urine pH in fasting morning urine predicts fragility fractures and five-year change of bone mineral density. We had the information to carry out this objective. Unfortunately comprehensive dietary data was not collected at baseline in this study, so it is not possible to validate the urine variables to dietary intake in this study. We did conduct a sub-study to assess stability of within-patient urine acid excretion diet as an indirect indicator of diet-stability in the 5-year period: Fenton TR, et al. Low 5-year stability of within-patient ion excretion and urine pH in fasting-morning-urine specimens. Nutr Res. 2009; 29(5): 320-6.

2. We agree with you that changes in urine with storage could alter urine pH. Mineral oil or other urine preservative measures were not used because the urine specimens were processed and stored rapidly after voiding. A detailed description of specimen handling was previously published by the CaMos group (Kreiger N et al. The Canadian Multicenter Osteoporosis Study (CaMos): background, rationale, methods. Can J Aging 2002;18:376–387). Pre-analytic changes to urine pH attributed to evaporation of CO2 (and with some specimens NH3) are avoided by handling within 2 hours (this is also mentioned by Oster et al. Nephron 50: 320, as you cited), and were not likely to result in misrepresentation of the measurements.

3. Thank you for pointing out that the avoidance of misclassification is not the term we are describing.

**Minor**

1. **Table 2:** Good point. We have reported the urine concentrations per mmol of creatinine to control for concentration and hydration status.
Discretionary

1. Background: Regarding our introduction, to the abstract and the paper, we have chosen to focus this paper on the marketing that is promoted to lay audiences since we anticipate that this paper may be of interest to lay readers. The open-access nature of this journal will likely facilitate access to the paper by lay readers interested in this topic.

2. Same as #2 above.

3. Methods: We have clarified that the measurements were made in fasting morning urine. Although several researchers have associated the food-based potential renal acid load with net acid excretion in 24-hour urine (eg Remer 1994), we do not know how equivalent this fasting morning urine estimated acid excretion is to net acid excretion. We were unable to measure net acid excretion (titratable acidity + ammonium – bicarbonate) in the stored samples since both ammonium and bicarbonate are volatile (as ammonia and carbon dioxide), and likely to have been lost since collection.

4. Discussion: Of the 15 references we quote regarding the hypothesis, 5 refer to pharmacologic manipulation, 9 refer to diet manipulation, and one included both types of interventions. We will be pleased to alter or remove the critical appraisal of reference 13 if the Editors believe that this is necessary.

5. Table 1: Yes, vitamin D status was measured as serum 25(OH) Vitamin D, and this has been clarified in the Table.

Sincerely,

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