PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	The Chronic Kidney Disease Water Intake Trial (WIT): Results from the Pilot Study
AUTHORS	Clark, William; Sontrop, Jessica; Huang, Shih-Han; Gallo, Kerri; Moist, Louise; House, Andrew; Weir, Matthew; Garg, Amit

VERSION 1 - REVIEW

REVIEWER	McMahon, Emma University of Queensland, School of Human Movement Studies
REVIEW RETURNED	19-Sep-2013

THE STUDY	The present paper reports on a pilot study of a planned trial exploring the effect of water intake in CKD patients. The pilot trial aims to measure feasibility and safety of increasing water intake as well as measuring changes in renal function markers. Overall the planned trial is a useful and warranted in CKD, and the pilot trial aims to answer important questions re: the feasibility and safety of the larger planned trial. The current paper is lacking details about study methods and is greatly lacking in key discussion points. Specific notes and suggestions are outlined below: Methods: - Please ensure all outcomes are described. e.g. how was blood pressure measured. - Statistical methods for subgroup analyses or relationships between outcomes not described. - Confusion as to how many urine samples were measured indicates 3 every two weeks in discussion but no reference to this frequency earlier.
RESULTS & CONCLUSIONS	Discussion: - The three aims of the discussion are not adequately met: Further discussion re: interpretation and generalisability of the results as well as study limitations is needed. - Comparison to other studies should be expanded upon – several references to previous research are made in the intro. How do the present results compare to these? Are there any studies suggesting increasing water intake is not feasible? - The third aim to “compare between-group changes in kidney function, physical health, and health-related quality of life” is not discussed in terms of interpretation of results or comparison to other studies. - Dietary changes measured but not discussed Many limitations not discussed – ie limitations of measurement technique (e.g. what are the limitations of a 3 day diet record for measuring dietary intake – why was dietary history (which is normally gold standard) not used), how likely is it that one 24 hour

	urine captured fluid intake? Was lack of statistically significant differences in safety / kidney function markers due to a lack of power? - Discussion needs to be reordered somewhat as is does not flow – plans for future study should be moved to the end prior to conclusion. All limitations in one section.
GENERAL COMMENTS	The present paper reports on a pilot study of a planned trial exploring the effect of water intake in CKD patients. The pilot trial aims to measure feasibility and safety of increasing water intake as well as measuring changes in renal function markers. Overall the planned trial is a useful and warranted in CKD, and the pilot trial aims to answer important questions re: the feasibility and safety of the larger planned trial. The current paper is lacking details about study methods and in key discussion points. Specific notes and suggestions are outlined below: Methods: - Please ensure all outcomes are described. e.g. how was blood pressure measured. - Statistical methods for subgroup analyses or relationships between outcomes not described. - Confusion as to how many urine samples were measured indicates 3 every two weeks in discussion but no reference to this frequency earlier. Results: - Baseline differences between groups: unsure if this was analysed statistically as statistical methods not described, and significant differences are not noted in table. - Dietary sodium intake of 259 with SD 275 and 201 SD 161 – suspect this is not normally distributed due to very large SDs. Discussion: - Further discussion re: interpretation and generalisability of the results as well as study limitations is needed. - Comparison to other studies should be expanded upon – several references to previous research are made in the intro. How do the present results compare to these? Are there any studies suggesting increasing water intake is not feasible? - The third aim to “compare between-group changes in kidney function, physical health, and health-related quality of life” is not discussed in terms of interpretation of results or comparison to other studies. - Dietary changes measured but not discussed Many limitations not discussed – ie limitations of measurement technique (e.g. what are the limitations of a 3 day diet record for measuring dietary intake – why was dietary history (which is normally gold stanrd) not used), how likely is it that one 24 hour urine captured fluid intake? Was lack of statistically significant differences in safety / kidney function markers due to a lack of power? - Discussion needs to be reordered somewhat as is does not flow – plans for future study should be moved to the end prior to conclusion. All limitations in one section. Other - Page 8, Line 46. 'affects thirst and urination' requires a reference - Page 14, line 33, Electrolytes, osmolality and parameters of kidney function remained within expected ranges for patients with CKD – this sentence needs references

	- Page 15, line 57, this sentence does not make sense. Clarification needed. - Were there body weight changes? - Title of paper does not include 'randomised' as indicated in checklist.

REVIEWER	Johnson, Richard University of Colorado, Medicine
REVIEW RETURNED	19-Sep-2013

GENERAL COMMENTS	This is an interesting proposal, and the study seems well done. I have several concerns 1. Do the authors feel there are enough cases to assure the safety of the study? It seems like there are relatively few n. 2. I would have liked to see a reduction in urine osmolarity with increasing water intake . Is this a power issue? 3. 24 hour urine collections are usually checked for accuracy by measuring the urinary creatinine content. Most individuals will excrete a constant amount of creatinine in a 24 hour period when at steady state. Thus, if urinary creat/d is measured in individuals, it would be nice to show that serial collections had the same total amount, plus/minus 10 percent

VERSION 1 – AUTHOR RESPONSE

Reviewer: Emma McMahon, Research Dietitian, Princess Alexandra Hospital, Australia

The present paper reports on a pilot study of a planned trial exploring the effect of water intake in CKD patients. The pilot trial aims to measure feasibility and safety of increasing water intake as well as measuring changes in renal function markers.
Overall the planned trial is a useful and warranted in CKD, and the pilot trial aims to answer important questions re: the feasibility and safety of the larger planned trial. The current paper is lacking details about study methods and is greatly lacking in key discussion points.

Specific notes and suggestions are outlined below:

Methods:
- Please ensure all outcomes are described. e.g. how was blood pressure measured.

RESPONSE: The revised manuscript now includes information on all outcomes (pages 10-11 of revised manuscript).

- Statistical methods for subgroup analyses or relationships between outcomes not described.

RESPONSE: No subgroup analyses were performed, and this is now stated on page 12 of the methods.

- Confusion as to how many urine samples were measured indicates 3 every two weeks in discussion but no reference to this frequency earlier.

RESPONSE: We apologize for the confusion. In total, participants were asked to collect three 24-hour urine samples: one sample every two weeks. This has been clarified in the revised manuscript (page 16 of the discussion).

Discussion:
- The three aims of the discussion are not adequately met: Further discussion re: interpretation and generalisability of the results as well as study limitations is needed.

RESPONSE: Interpretation and generalisability of the results as well as study limitations are now described more clearly in the discussion of the revised mansucript (pages 15-17).

- Comparison to other studies should be expanded upon – several references to previous research are made in the intro. How do the present results compare to these? Are there any studies suggesting increasing water intake is not feasible?

RESPONSE: Yes, we describe several observational studies in the introduction which suggest a beneficial effect of increased hydration on the kidney. However, to our knowledge, there are no previous clinical trials of increased water intake in adults with chronic kidney disease. We have clarified this in the revised discussion. Clinical trials of increased fluid intake in other patient groups (eg overweight adults, elderly men, and patients with polycystic kidney disease or kidney stones,) demonstrate no adverse effects. These studies instructed participants to increase water intake by up to 2.0 L/day. In particular, Spigt et al. conducted several studies of healthy elderly males and showed that an increased fluid intake of 1 L/day, on average, was safe in terms of serum sodium, GFR and quality of life (n=142) and can be sustained over a 6-month period. (25-27). As well, in a subset of 44 elderly males, a 2 L/day increase in fluid intake for 2 months was associated with an improvement in lower bladder function (27).

- The third aim to “compare between-group changes in kidney function, physical health, and health-related quality of life” is not discussed in terms of interpretation of results or comparison to other studies.

RESPONSE: Greater discussion of these variables has now been added to the revised manuscript (pages 14-16). Electrolytes, osmolality and parameters of kidney function remained within expected ranges for patients with CKD. We did not expect nor see any changes in kidney function since this pilot was not designed nor powered to test this hypothesis, which is the focus of our much larger randomized control trial. Overall health, physical health, social functioning, sleep and appetite quality remained similar in the hydration and control groups. Similar to Spigt’s study (26), participants in the hydration group experienced a significant increase in nocturia; however, this was not associated with any measurable changes in health-related quality of life.

- Dietary changes measured but not discussed
Many limitations not discussed – ie limitations of measurement technique (e.g. what are the limitations of a 3 day diet record for measuring dietary intake – why was dietary history (which is normally gold standard) not used), how likely is it that one 24 hour urine captured fluid intake? Was lack of statistically significant differences in safety / kidney function markers due to a lack of power?

RESPONSE: We acknowledge that a 24-hour urine collection may not accurately capture average long-term fluid intake; however, because our primary outcome required participants to collect several 24-hour urine collections in a short period of time, we did not wish to increase respondent burden by requiring a detailed dietary history as well. Nonetheless, we observed a strong correlation (r=0.84) between self-reported fluid intake from a 3-day diet record and 24-hour urine output. Dietary intake from the 3-day food record was collected in consultation with a renal dietician as part of the standard of care given to patients at the LHSC CKD clinic. We have described this issue more clearly in the limitations section of the discussion (pages 16-17).

We do not think that the absence of statistically significant differences in safety / kidney function markers is due to a lack of power. Although our sample size is small, between-group differences on these markers were minimal and not clinically significant.

- Discussion needs to be reordered somewhat as is does not flow – plans for future study should be moved to the end prior to conclusion. All limitations in one section.

RESPONSE: Thank you, we have re-ordered the discussion section as suggested. All limitations are now described in one section and information on our future trial now comes at the end, before the conclusion.

Other
- Page 8, Line 46. 'affects thirst and urination' requires a reference

RESPONSE: Thank you we have added the following reference: Baylis et al. Water Disturbances in Patients Treated with Oral Lithium Carbonate Ann Intern Med. 1978;88(5):607-609.

- Page 14, line 33, Electrolytes, osmolality and parameters of kidney function remained within expected ranges for patients with CKD – this sentence needs references

RESPONSE: Thank you, we have added the following reference: Documenta Geigy Scientific Tables, Seventh Edition; Edited by K Diem & C. Lentner:523,531-36, 557 Published CIBA-GEIGY Ltd, Basle, Switzerland, Reprinted 1973

- Page 15, line 57, this sentence does not make sense. Clarification needed.

RESPONSE: Thank you, we have clarified this in the revised manuscript.

- Were there body weight changes?

RESPONSE: No, there were no changes in body weight over the six-week period of this trial. Body mass index was similar between hydration and control groups at baseline (31 and 30 kg/m2, respectively) and was 30 kg/m2 in each group at the six-week follow-up (p=0.28 for between-group change). This information has been added to page 13.

- Title of paper does not include ‘randomised’ as indicated in checklist.

RESPONSE: ‘Randomized controlled trial’ now appears in the title.

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Reviewer: Johnson, Richard
University of Colorado, Medicine

no competing interests

This is an interesting proposal, and the study seems well done. I have several concerns
1. Do the authors feel there are enough cases to assure the safety of the study? It seems like there are relatively few n.

RESPONSE: Although our sample size is small, the between-group differences on safety markers and parameters of kidney function were minimal and not clinically significant. In particular, serum sodium remained above 130 mmol/L for all participants at all follow-up points and was similar between groups at all comparison points. At the final follow-up the average sodium concentration was 138 mmol/L in both groups.

2. I would have liked to see a reduction in urine osmolarity with increasing water intake . Is this a power issue?

RESPONSE: Urine osmolality did decrease to a greater extent in the hydration group compared with the control group (by 19% vs. 5%, respectively); however, the difference was not statistically significant. We think this is partly a power issue (urine osmolality has a high standard deviation and so a larger sample would be needed to achieve statistical significance), as well, urine osmolality is affected by other factors such as diet, sex and ethnicity. Although other studies have demonstrated that acute water loading can significantly reduce urine osmolality (for example, Barash et al. CJASN 2010;5:693); these studies evaluated hydration regimens that were higher than ours (eg 3 L/day

compared with 1-1.5 L/day in our study). We have added this information to page 16 of the discussion.

3. 24 hour urine collections are usually checked for accuracy by measuring the urinary creatinine content. Most individuals will excrete a constant amount of creatinine in a 24 hour period when at steady state. Thus, if urinary creat/d is measured in individuals, it would be nice to show that serial collections had the same total amount, plus/minus 10 percent

RESPONSE: We have added this information to the revised manuscript (Table 4). Urine creatinine (mmol/d) remained within 10% of baseline values in both the hydration (+3.8%) and the control groups (-6.4%).

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Reviewer: Benjamin Kearns,
Research Associate,
The University of Sheffield,
England.

No competing interests.

CONSORT checklist provided - appears fine.

Conclusion discusses increases in intake by up to 1.5 L/d - it would be better to quote the average between-group change of 0.9 or the average within-group change of 0.7

RESPONSE: We originally used 1.5 L/day because we coached participants in the hydration group to increase their water intake by up to 1.5 L/day; however, to avoid confusion we now use the between-group change of 0.7 L/day in the conclusion of the abstract and main body.

This is a well-written whose findings will be of use and interest to those with similar research interests. However, the article would improve from some additional explanations and details to aid readers who are unfamiliar with the subject area.

Below I have made a series of suggestions for the authors to consider.

General Points.

Within the 'Key messages' and 'Abstract', the authors mention increasing "intake by 1.0 to 1.5 litres per day" – this may give the erroneous impression that the target intake level is 1.5 (and so imply that base-case levels are 0.5 litres per day). Re-wording, for example to increase "intake by between 1.0 and 1.5 litres per day", is advised.

RESPONSE: We have re-worded as suggested.

Sometimes the abbreviation "L/d" is used, sometimes "L/day" – please be consistent throughout.

RESPONSE: Thank you; we have corrected this in the revised manuscript.

Background.

Page 7, line 15: "Increased water intake suppresses plasma vasopressin" – the authors may want to expand on why this is important.

RESPONSE: Thank you, we have added the following information to the introduction:

Increased water intake suppresses plasma vasopressin (6,11), which is an anti-diuretic hormone that regulates thirst and water conservation in mammals. While essential for water regulation, vasopressin

has vaso-constrictive effects and there is evidence that increased plasma levels can have negative effects on renal hemodynamics, blood pressure, and ventricular function (12-18).

Methods.

The authors mention in the background section that they are looking at stage 3 CKD. They mention in the methods section that they use the range of eGFR between 30 to 60 as an inclusion criteria. It would be good if the authors explicitly mention that this eGFR range is how they define stage 3 CKD. Some further details on how they have defined CKD would also be useful, for example was only one eGFR value used? (If so, this should be mentioned as a limitation of the study).

RESPONSE: Thank you for this suggestion. Stage 3 chronic kidney disease was defined based on the presence of both reduced kidney function and proteinuria. Patients provide a blood sample and their glomerular filtration rate was estimated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). Serum creatinine was measured from blood samples and analyzed using the isotope dilution/mass spectroscopy-traceable enzymatic method. We used the most recent estimated glomerular filtration rate (eGFR) and defined CKD as at least one eGFR between 30–60 ml/min/1.73m2, as well as the presence of albuminuria [albumin/creatinine >2.8 mg/mmol (if female) or >2.0 mg/mmol if male) from a spot urine sample or trace protein (albustix)].

We have made this change in the abstract and methods.

Page 9, lines 48 to 55: it is unclear why some participants in the control group were advised to decrease their fluid intake, and what impact this had on the results.

RESPONSE: Because it was not possible to blind participants in this pilot trial (nor in the main trial), both groups were fully informed of the main trial's hypothesis/research question: does increased hydration reduce progression of CKD. To test this hypothesis, participants needed to be randomized to 1) maintenance of their usual intake or 2) increased hydration (by between 1 to 1.5 L per day). To test our hypothesis and maintain ethically informed consent and attempt to reduce regression to the mean, which is well described by Spigt et al. (24), we actively coached participants in the hydration group to increase hydration. To counteract any potential contamination of our control group being informed about our hypothesis and its potential benefit, we coached controls to not increase their hydration beyond normal intake or thirst. The fact that the control group demonstrated a slight reduction in urinary output suggests our coaching may have reduced the potential contaminating effect of informed consent. We have added this to the discussion (page 17).

Page 11, statistical analysis: please state the software that was used to carry-out the analyses. If non-standard methods were used for generating confidence intervals, please state these too.

RESPONSE: Standard methods were used for generating confidence intervals. Data were analyzed using IBM SPSS Statistics 19. This has been added to the section on statistical analysis

Page 11, statistical analysis: please state the type of correlation coefficient that is presented in Figure 3. Please also include this information with Figure 3.

RESPONSE: Bivariate correlations were estimated using the Pearson product-moment correlation coefficient (r). We have added this information to the figure and section on statistical analysis.

Discussion.

The authors could discuss if the between-group differences were likely to be exaggerated due to some of the control group being advised to decrease their fluid intake.

RESPONSE: I have already addressed in prior section and will include in discussion. We believe the small reduction in urine volume by our control group has counteracted the contaminating effect of our ethical informed consent process and allows a real not exaggerated comparison of increased hydration in this coached CKD population.

The authors discuss their future planned trial. The authors could use the results from this pilot in a power analyses for their planned trial.

RESPONSE: We have used the results from the pilot study to inform the design of the main trial with respect to feasibility, safety, and recruitment rate. However, our primary outcome in the main trial is the decline in eGFR over one year. Therefore, to conduct a power analysis for the main trial, we referred to other observational studies of CKD patients that measured average eGFR decline and reported the standard deviation of this decline.

Page 15: The 'comparison with other studies' paragraph does not flow well. The authors may want to consider re-writing or breaking-up some of the sentences. In addition "Spigt et al. have", not "Spigt et al. has".

RESPONSE: Thank you, we have re-written this section to improve readability and flow.

Conclusion.

It is unclear where the value of 1.5 L/d comes from. It would be better to quote the average between-group change of 0.9 or the average within-group change of 0.7. (This occurs in the abstract as well).

RESPONSE: We originally used 1.5 L/day because we coached participants in the hydration group to increase their water intake by up to 1.5 L/day; however, to avoid confusion we now use the between-group change of 0.7 L/day in the conclusion of the abstract and main body.