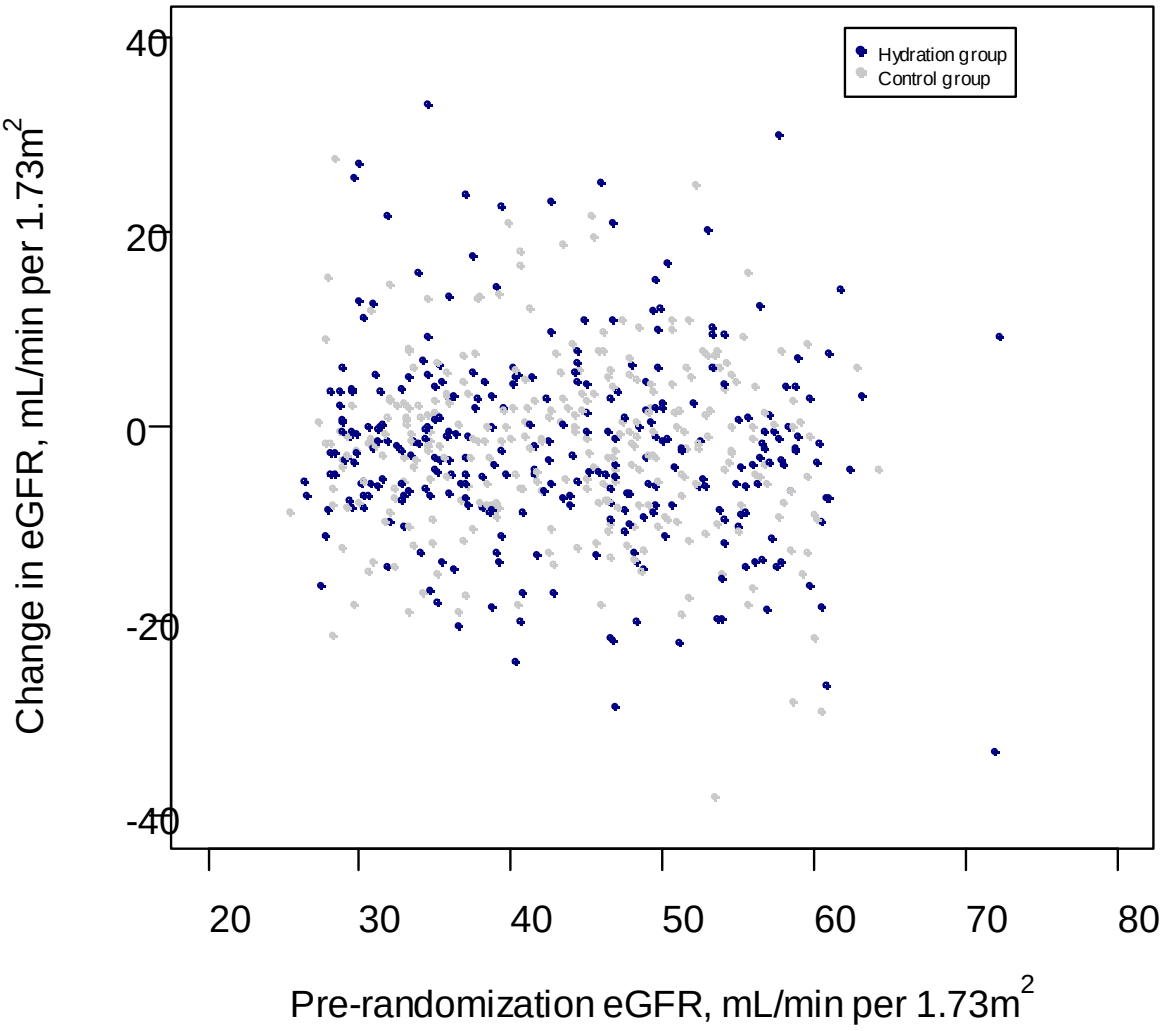
# Supplementary Online Content

Clark WF, Sontrop JM, Huang S-H et al. Effect of Coaching to Increase Water Intake on Kidney Function Decline in Adults With Chronic Kidney Disease: the CKD WIT Randomized Clinical Trial. *JAMA*. doi:10.1001/jama.2018.4930



This supplementary material has been provided by the authors to give readers additional information about their work.

**eFigure 1.** Scatterplot of the change in estimated glomerular filtration rate by baseline levels in the hydration and control groups



**eTable 1.** Justification of changes made to the original trial protocol

| Original protocol | Change | Justification |
|---|---|---|
| **Centers** | | |
| Page 4: Study centres: University Hospital and Victoria Hospital (London ON). | Added: Study centres: Nine chronic kidney disease clinics across Southwestern Ontario: London (3 centers), Oakville (2 centers), Windsor (2 centers), Guelph (1 center) and Hamilton (1 center). | Seven centers were added in order to increase the recruitment rate. |
| **Eligibility criteria** | | |
| Page 4 (inclusion criteria): Age 18–75 years | Changed: Age 18–80 years. | There was no safety concern with allowing patients age 76–80 years to participate. |
| Page 4 (exclusion criteria): Kidney transplant recipient (or on waiting list) | Received a kidney transplant in past 6 months | The original exclusion criterion was felt to be too restrictive, and there was no safety concern with allowing kidney transplant recipients to participate in the trial. |
| Page 4 | Added: chlorthalidone >50 mg/day, spironolactone >25 mg/day, ethacrynic acid <50 mg/day | These three diuretics were not included in the original list of diuretics, and were added to insure participant safety |
| **Data collection** | | |
| Page 5 and Table 3 | Added: Fluid intake survey (baseline and 3 months, 6 months, and 9 months after randomization) | This measure was added to aid in intervention adherence coaching and to track changes in fluid intake (in both groups) during the trial. |
| **Intervention** | | |
| Page 5 | Added: Participants in the hydration group were mailed 20 vouchers per month, each redeemable for 1.5 L of bottled water | This element was added to the protocol to encourage adherence to the intervention (the logistics of how to do this took longer than expected and so it was added to the protocol 5 months after randomization began). |

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|---|---|---|
| **Measures and outcomes** | | |
| Page 6/page 10 | Added: The five-year risk of kidney failure (using the 4-variable Kidney Failure Risk Equation), 24-hour creatinine clearance, albuminuria (rather than albumin-to-creatinine ratio) | The investigators felt these secondary outcomes would be informative for evaluating the clinical effectiveness of intervention (and the data were already being collected). While we originally specified change in the albumin-to-creatinine ratio as a secondary outcome, change in total daily albumin (g/day) is a more appropriate measure when analyzing 24-hour urine samples. Given that neither the change in eGFR nor the change in albuminuria was statistically different between groups, we did not analyze the five-year risk of kidney failure for the final report because this equation is a function of eGFR and albuminuria. |
| Page 9/page 11 | Analysis of eGFR change (rate vs. difference in eGFR from baseline to 12 months after randomization) | We originally planned to compare the rate of change in eGFR between groups (using a mixed-effects model with a random intercept and a time-treatment group interaction); however, given concern about intervention time-lag effects, we opted to analyze change in eGFR as the 12-month minus baseline value. The results of both analyses were congruent, and the methods and results of the longitudinal mixed-effect analysis of change are presented in Appendix 3. |
| Page 7/page 9 | Defined change in health-related quality of life more specifically as the one-year change in patient-reported overall quality of health measured on a 10-point scale. | Item 22 from the RAND Kidney Disease Quality of Life Short Form. |
| **Methods to minimize bias** | | |
| Page 10: Minimize group contamination | Removed: To reduce the potential for communication between study groups, we will work with CKD clinic staff to ensure that participants in the intervention group do not share appointment times with participants in the control group (e.g. to limit the opportunity to discuss the study in the clinic waiting room. | This idea proved infeasible in practice. We also recognized that there was a low likelihood of participants from different groups discussing the intervention in clinic waiting rooms, and were confident in our measures to encourage and assess adherence to the allocated intervention. Finally, our trial was designed to assess effectiveness more so than efficacy. |

| | | |
|---|---|---|
| **Data Safety and Monitoring Board** | | |
| Page 11: The DSMB will review a descriptive summary of adverse and clinically important events at three-month intervals throughout the study | The DSMB received a descriptive summary of trial data and adverse events at three-to-nine–month intervals. | As the trial progressed with no safety concerns attributed to the intervention, the DSMB recommended that the frequency of reporting be extended. |
| **Statistical analysis** | | |
| Page 11 | Added: The following pre-specified covariates (measured at baseline) were adjusted for in the primary analysis: age (in years), sex, obesity (body mass index $\geq$30 kg/m$^2$), current smoker (yes/no), presence of diabetes, 24-hour urine albumin (mg/day) (log transformed), and use of any of the following medications: an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, diuretic, beta blocker, calcium channel blocker, or statin. | We refined our analytic plan while preparing our protocol for publication (Clark et al., CJKHD 2017:4), and pre-specified these variables as covariates to adjust for to improve the precision of our estimates. The results of the adjusted and unadjusted analyses were similar (-0.3 [p=.74] and -0.2 [p=.79]), respectively, reported in Table 3 and eTable 6). |
| Page 11 | Added: Supplementary analyses using alternative definitions of change in eGFR, including eGFR measured with cystatin C, and the between-group difference in *(i)* the annual percentage change defined as [(final eGFR-baseline eGFR)/baseline eGFR] and *(ii)* the proportion of participants with a one-year eGFR decline $\geq$20%. We also examined whether results were consistent in participants with and without macroalbuminuria at baseline. | These supplementary analyses were added while refining our analysis and protocol for publication. As indicated in our published protocol (Clark et al., CJKHD 2017:4), a p-value <0.05 would be interpreted as statistically significant only if there was concordance with the primary outcome. As reported in the main manuscript, the results of these supplementary analyses were concordant with the primary analysis, and all p-values were greater than 0.05. |

| | | |
|---|---|---|
| Page 11 | Added: We conducted a per-protocol analysis restricted to participants in the hydration group who maintained a 24-hour urine volume that was at least 0.5 L/day above their baseline value at 6-months and 12 months after randomization, and participants in the control group who maintained a 24-hour urine volume that was <0.5 L/day above their baseline value at each follow-up assessment; participants who missed an assessment or whose final urine sample was collected >16 months after randomization were excluded. | As described above, while preparing our protocol for publication (Clark et al., CJKHD 2017:4), we refined our analytic plan and added a more detailed description of the planned per protocol analysis. The per-protocol analysis was added to provide an estimate of the maximum potential benefit of increased hydration on eGFR. As reported in the main manuscript, the results of the per-protocol analyses were consistent with the primary intention-to-treat analysis (non-significant). |
| **Sample size and statistical power** | | |
| Page 12: Original planned enrollment: 700 patients (350 per group) over 18 months (to be followed for 12 months). | We enrolled 822 participants and randomized 631 to the intervention groups. After 3.1 years (37 months), we had complete 12-month follow-up measurements on 590 patients (295 per group). | As described on pages 9-10 of the manuscript, we originally powered our study to detect a between-group difference of at least 1 mL/min per 1.73 $m^2$ (assuming SD<5, two-sided alpha=0.05, power=0.8). The DSMB supported our decision to stop randomly allocating patients into the trial after 3.1 years, where complete 12-month follow-up measurements on 590 patients (295 per group) enabled us to detect a between-group difference of at least 2 mL/min per 1.73 $m^2$ in the mean change in eGFR over one year (with an observed SD of 9, two-sided alpha=0.05; power=0.8). |

**eTable 2.** Summary of outcomes analyzed in the Chronic Kidney Disease Water Intake Trial (CKD WIT)

| Outcome | Between-group comparison | Pre-specified or post-hoc | Date specified | Specified in original protocol[a] | Specified in published protocol[b] | Reported in manuscript |
|---|---|---|---|---|---|---|
| **Primary outcome** | | | | | | |
| Estimated glomerular filtration rate (eGFR) | 1-year change[c] | Pre-specified | June 22, 2012 | Yes | Yes | Table 3; eAppendix 2 |
| ***Supplementary analyses of eGFR change*** | | | | | | |
| eGFR measured with cystatin C | 1-year change | Post-hoc | September 18, 2017 | No | No | eTable 6 |
| Mixed-effects analysis of change | 1-year change | Post-hoc | February 12, 2018 | No | No | eTable 7 |
| Percentage change in eGFR | 1-year change | Pre-specified | January 26, 2017 | No | Yes | Results |
| eGFR decline $\geq$5% [c,d] | Proportion | Pre-specified | June 22, 2012 | Yes | Yes | eTable 8[d] |
| eGFR decline $\geq$20% [c] | Proportion | Pre-specified | January 26, 2017 | No | Yes | eTable 8 |
| Per-protocol analysis[e] | 1-year change | Pre-specified | January 26, 2017 | No | Yes | Results |
| Subgroup analysis by macroalbuminuria | Interaction | Post-hoc | December 1, 2017 | No | No | eTable 9 |
| Subgroup analysis by diabetes | Interaction | Post-hoc | February 12, 2018 | No | No | eTable 10 |
| Subgroup analysis by eGFR $\geq$ or <45 | Interaction | Post-hoc | February 12, 2018 | No | No | eTable 11 |
| **Secondary outcomes** | | | | | | |
| Copeptin | 1-year change | Pre-specified | June 22, 2012 | Yes | Yes | Table 4 |
| Creatinine clearance | 1-year change | Pre-specified | November 10, 2016 | No | Yes | Table 4 |
| Albuminuria[c] | 1-year change | Pre-specified | June 22, 2012 | Yes | Yes | Table 4 |
| Health-related quality of life[c] | 1-year change | Pre-specified | June 22, 2012 | Yes | Yes | Table 4 |
| Estimated 5-year risk of kidney failure[f] | 1-year change | Pre-specified | February 7, 2017 | No | Yes | No[f] |
| **Other outcomes** | | | | | | |
| 24-hour urine osmolality | 1-year change | Post-hoc | June 19, 2017 | No | No | eTable 12 |
| 24-hour urine creatinine | 1-year change | Post-hoc | June 19, 2017 | No | No | eTable 12 |
| 24-hour urine urea | 1-year change | Post-hoc | June 19, 2017 | No | No | eTable 12 |
| 24-hour urine sodium | 1-year change | Post-hoc | June 19, 2017 | No | No | eTable 12 |
| 24-hour urine potassium | 1-year change | Post-hoc | June 19, 2017 | No | No | eTable 12 |
| Serum osmolality | 1-year change | Post-hoc | October 20, 2017 | No | No | eTable 13 |
| Serum creatinine | 1-year change | Post-hoc | October 20, 2017 | No | No | eTable 13 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Serum urea | 1-year change | Post-hoc | October 20, 2017 | No | No | eTable 13 |
| Blood pressure | 1-year change | Pre-specified | June 22, 2012 | Yes | Yes | eTable 14 |
| Weight | 1-year change | Post-hoc | September 18, 2017 | No | No | eTable 14 |
| Waist circumference | 1-year change | Pre-specified | October 22, 2012 | Yes | No[g] | eTable 14 |
| Body mass index | 1-year change | Pre-specified | June 22, 2012 | Yes | Yes | eTable 14 |
| HbA1c | 1-year change | Pre-specified | June 22, 2012 | Yes | Yes | No[h] |
| Dietary intake of protein | 6-month change | Post-hoc | October 20, 2017 | No | No | eTable 15 |
| Dietary intake of sodium | 6-month change | Post-hoc | October 20, 2017 | No | No | eTable 15 |
| **Safety** | | | | | | |
| Serum sodium | All time points | Pre-specified | June 22, 2012 | Yes | Yes | eTable 16 |

[a] Available in Supplement 1.

[b] The published protocol is available at: Clark WF, Huang S-H, Garg AX, et al. The Chronic Kidney Disease Water Intake Trial: Protocol of a Randomized Controlled Trial. *Can J Kidney Heal Dis.* 2017;4:205435811772510.

[c] Changes to the pre-specified measurement and/or analytic plan are described in eTable 1 in this Supplement.

[d] The proportion of participants within different categories of eGFR decline (including 5–20% and ≥20%) is shown in eTable 8; however, a separate comparison eGFR decline ≥5% was not reported (the proportion of participants in the hydration and control groups with an eGFR decline ≥5% was 52.2% and 46.8%, respectively; difference: 5.7% [95% CI: -0.2% to 13.7%]).

[e] Restricted to participants in the hydration group who maintained a 24-hour urine volume that was at least 0.5 L/day above their baseline value at 6-months and 12 months after randomization, and participants in the control group who maintained a 24-hour urine volume that was <0.5 L/day above their baseline assessment at each follow-up assessment.

[f] As noted in eTable 1, the equation for the 5-year risk of kidney failure is a function of eGFR and albuminuria; since neither of these variables were statistically different between groups, we did not analyze the five-year risk of kidney failure.

[g] Waist circumference was mistakenly omitted from the published protocol.

[h] This outcome will be the focus of a second manuscript.

**eTable 3.** Eligibility criteria for the Chronic Kidney Disease Water Intake Trial (CKD WIT)[a]

| **Inclusion criteria** |
|---|
| • Age between 18 and 80 years.<br>• Able to provide informed consent and willing to complete follow-up visits.<br>• Estimated glomerular filtration rate between 30 and 60 ml/min/1.73m$^2$.<br>• Trace protein or greater (Albustix) or urine albumin/creatinine ratio $\geq$2.8 mg/mmol (if female) or $\geq$2.0 mg/mmol (if male) from a random spot urine sample.<br>• Ability to read and speak English. |
| **Exclusion criteria** |
| • Self-reported fluid intake $\geq$10 cups/day or 24-hour urine volume $\geq$3L.<br>• Enrolled in another randomized controlled trial that could influence the intervention, outcomes, or data collection of this trial (or previously enrolled in this trial).<br>• Received one or more dialysis treatments in the past month.<br>• Received a kidney transplant in past six months.<br>• Pregnant or breastfeeding.<br>• History of kidney stones in the past five years.<br>• Less than two years' life expectancy.<br>• Serum sodium <130 mEq/L without suitable explanation.<br>• Serum calcium >2.6 mmol/L without suitable explanation.<br>• Currently taking hydrochlorothiazide >25 mg/day, indapamide >2.5 mg/day, furosemide >40 mg/day, metolazone >2.5 mg/day, chlorthalidone >50 mgday, spironolactone >25 mg/day, ethacrynic acid <50 mg/day.<br>• Currently taking lithium.<br>• Currently under fluid restriction (<1.5 L a day) for kidney disease, heart failure, or liver disease, and meets any of the following criteria (*i*) end-stage disease (heart left ventricular ejection fraction <40%, New York Heart Association class 3 or 4, or end-stage cirrhosis) or *(ii*) any hospitalization for heart failure, ascites, and/or anasarca.<br>• Significant gastrointestinal disease (e.g. inflammatory bowel disease or Crohn's disease) |

[a] From Clark WF, Huang S-H, Garg AX, et al. The Chronic Kidney Disease Water Intake Trial: Protocol of a Randomized Controlled Trial. *Can J Kidney Heal Dis.* 2017;4:205435811772510.

**eTable 4.** Hydration intervention by age and sex[a]

| | | Target water intake | | | |
|---|---|---|---|---|---|
| **Sex** | **Weight** | **Daily total (L/day)** | **Breakfast** | **Lunch** | **Dinner** |
| Female | < 70 kg | 1.0 | 250 ml (1 cup) | 500 ml (2 cups) | 250 ml (1 cup) |
| | ≥ 70 kg | 1.25 | 250 ml (1 cup) | 500 ml (2 cups) | 500 ml (2 cups) |
| Male | < 70 kg | 1.25 | 250 ml (1 cup) | 500 ml (2 cups) | 500 ml (2 cups) |
| | ≥ 70 kg | 1.5 | 500 ml (2 cups) | 500 ml (2 cups) | 500 ml (2 cups) |

[a] From Clark WF, Huang S-H, Garg AX, et al. The Chronic Kidney Disease Water Intake Trial: Protocol of a Randomized Controlled Trial. *Can J Kidney Heal Dis.* 2017;4:205435811772510.

**eTable 5.** Schedule of study visits and measures[a]

| | Baseline (pre-randomization) | Follow-up[b] | | | | | |
|---|---|---|---|---|---|---|---|
| | | 3 weeks | 3 months | 6 months | 9 months | 12 months | 18–24 months |
| SURVEY | | | | | | | |
| Demographics | + | | | | | | |
| Diet (3-day diet record) | +[c] | | | + | | | |
| Health history | + | | | + | | + | |
| Health-related quality of life | + | | | + | | + | |
| Fluid intake survey | + | | + | + | + | | |
| CLINICAL | | | | | | | |
| Height (cm) | + | | | | | | |
| Weight (kg) | + | | | | +[d] | | |
| Waist circumference (cm) | + | | | | +[d] | | |
| Blood pressure (mm Hg) | + | | | | +[d] | | |
| Medications | + | | | | +[d] | | |
| BLOOD | | | | | | | |
| Blood sample | + | + | + | + | + | + | |
| Serum creatinine (umol/L) | + | + | + | + | + | + | +[e] |
| Serum sodium (mmol/L) | + | + | + | + | + | + | |
| Urea (mmol/L) | + | | | + | | + | |
| Osmolality (mosm/kg) | + | | | + | | + | |
| Copeptin (pmol/L) | + | | | | +[d] | | |
| Hematocrit (L/L) | + | | | + | | + | |
| Cystatin C (mg/L) | + | | | | +[d] | | |
| HbA1c (%) | + | | | + | | + | |
| URINE | | | | | | | |
| 24-hour urine sample (L) | + | | | + | | + | +[e] |
| Urine creatinine (mmol/d) | + | | | + | | + | +[e] |
| Urine sodium (mmol/d) | + | | | + | | + | |
| Urine potassium (mmol/d) | + | | | + | | + | |
| Urea (mmol/d) | + | | | + | | + | |
| Osmolality (mosm/kg) | + | | | + | | + | |
| Albumin (mg/day) | + | | | + | | + | |
| Creatinine clearance (ml/min/1.73m$^2$) | + | | | + | | + | +[e] |
| Random spot urine sample | + | | | | | | |
| Specific gravity (g) | + | | | | | | |
| Osmolality (mosm/kg) | + | | | | | | |

[a] Adapted from Clark WF, Huang S-H, Garg AX, et al. The Chronic Kidney Disease Water Intake Trial: Protocol of a Randomized Controlled Trial. *Can J Kidney Heal Dis.* 2017;4:205435811772510.

[b] Time from randomization.

[c] Participants received the 3-day diet record to complete at the time of randomization.

[d] While local labs are able to measure and process blood and urine samples, they do not measure weight, blood pressure, cystatin C, or copeptin; these measures were obtained at the participants' follow-up kidney care clinic visit (approximately 6–7 months after randomization).

[e] Post-trial data (18–24 months after randomization) will be obtained from participants' medical charts where possible to reduce respondent burden.

**eTable 6.** Post-hoc analyses of the unadjusted one-year change in eGFR using the CKD-EPI creatinine and cystatin C equations[a,b]

| | Intervention group | | | |
|---|---|---|---|---|
| | **Hydration** | **Control** | **Between-group Difference[c] (95% CI)** | ***P Value*[c]** |
| | n=291 | n=299 | | |
| **eGFR, mL/min per 1.73 m$^2$** | | | | |
| Pre-randomization | 43.2 (10.2) | 43.4 (9.1) | | |
| 12 months | 41.1 (13.3) | 41.5 (12.3) | | |
| Change | -2.1 (9.8) | -1.9 (8.8) | -0.2 (-1.7 to 1.3) | .79 |
| **Cystatin C–eGFR, mL/min per 1.73 m$^2$** | | | | |
| Pre-randomization | 46.9 (19.9) | 47.9 (18.6) | | |
| 12 months | 42.3 (18.5) | 43.5 (17.9) | | |
| Change | -4.5 (16.5) | -4.4 (18.8) | -0.2 (-3.8 to 3.4) | .93 |

Abbreviations: CI, confidence interval; CKD EPI, Chronic Kidney Disease Epidemiology; eGFR, estimated glomerular filtration rate.

[a] Calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine and cystatin C equations.[22]

[b] Means and standard deviations are reported unless otherwise indicated. Change was calculated as the 12-month value minus the pre-randomization value; restricted to participants who provided follow-up data within 8–16 months of randomization (excluding 12 participants who died during the 12-month trial period [5 in the hydration group and 7 in the control group]). All analyses followed the intention-to-treat principle.

[c] Between-group differences in change were analyzed using the independent-samples t test.

**eTable 7.** Post-hoc analyses of the adjusted one-year change in eGFR using a mixed-effects model[a]

| | Intervention group | | | |
|---|---|---|---|---|
| | **Hydration** | **Control** | **Adjusted between-group Difference in change[b] (95% CI)** | ***P Value*[b]** |
| | n=291 | n=299 | | |
| **eGFR, mL/min per 1.73 m$^2$** | | | | |
| Pre-randomization | 43.2 (10.2) | 43.4 (9.1) | | |
| 12 months | 41.1 (13.3) | 41.5 (12.3) | | |
| Change | -2.1 (9.8) | -1.9 (8.8) | -0.3 (-1.8 to 1.2) | .71 |

Abbreviations: CI, confidence interval; CKD EPI, Chronic Kidney Disease Epidemiology; eGFR, estimated glomerular filtration rate.

[a] Means and standard deviations are reported unless otherwise indicated. Change was calculated as the 12-month value minus the pre-randomization value; restricted to participants who provided follow-up data within 8–16 months of randomization (excluding 12 participants who died during the 12-month trial period [5 in the hydration group and 7 in the control group]). All analyses followed the intention-to-treat principle.

[b] The adjusted between-group difference in change in eGFR was analyzed using a mixed-effects model with a random intercept to account for center, adjusted for age (in years), sex, obesity (body mass index $\geq$30 kg/m$^2$), current smoker, presence of diabetes, albumin (mg/day) (log transformed), and use of the following medications: an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, diuretic, beta blocker, calcium channel blocker, and statin.

**eTable 8.** Percentage change in eGFR[a]

| | Intervention group | | |
|---|---|---|---|
| | **Hydration** | **Control** | ***P Value***[b] |
| | n=291 | n=299 | |
| **Percentage change in eGFR**[a] | | | |
| Increasing (≥5%) | 81 (27.8%) | 85 (28.4%) | .39 |
| Stable (-5% to 5%) | 58 (19.9%) | 75 (25.1%) | |
| Moderate decline (-5% to -20%) | 89 (30.6%) | 77 (25.8%) | |
| Rapid decline (≥20% decline) | 63 (21.6%) | 62 (20.7%) | |

Abbreviations: eGFR, estimated glomerular filtration rate.

[a] Percentage change in eGFR was calculated as [(final eGFR-baseline eGFR)/baseline eGFR]; restricted to participants who provided follow-up data within 8–16 months of randomization (excluding 12 participants who died during the 12-month trial period [5 in the hydration group and 7 in the control group]). Analysis followed the intention-to-treat principle.

[b] The between-group difference in categories of eGFR change was compared using the chi square test.

**eTable 9.** Post-hoc subgroup analysis of the one-year change in eGFR in by macroalbuminuria at baseline

| | **Change in eGFR[a] (ml/min/1.73 $m^2$)** | | | |
|---|---|---|---|---|
| | **Hydration** | **Control** | **Between-group difference[b]** | |
| | **Mean (SD)** | **Mean (D)** | **Mean 95% (CI)** | ***P Value*** |
| **Baseline albumin** | | | | |
| <300 mg/day (n=394) | -0.4 (9.6) | -0.1 (8.3) | -0.3 (-2.1 to 1.6) | .62 |
| ≥300 mg/day (n=198) | -4.9 (10.2) | -5.4 (9.2) | 0.6 (-2.3 to 3.4) | |

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; SD, standard deviation.

[a] Change in eGFR was calculated as the 12-month value minus the pre-randomization value; restricted to participants who provided follow-up data within 8–16 months of randomization (excluding 12 participants who died during the 12-month trial period [5 in the hydration group and 7 in the control group]).

[b] Differences in eGFR change within sub-groups of participants with and without macroalbuminuria were analyzed using linear regression with an interaction term. Unadjusted regression models were used.

**eTable 10.** Post-hoc subgroup analysis of the one-year change in eGFR in participants with and without diabetes at baseline

| | Change in eGFR[a] (mL/min/1.73 $m^2$) | | | |
|---|---|---|---|---|
| | **Hydration n=291** | **Control n=299** | **Between-group difference[b]** | |
| | **Mean (SD)** | **Mean (SD)** | **Mean (95% CI)** | ***P Value*** |
| **Diabetes** | | | | |
| No (n=307) | -1.4 (8.5) | -1.5 (8.8) | 0.0 (-1.9 to 2.0) | .83 |
| Yes (n=283) | -2.7 (10.9) | -2.4 (8.8) | -0.3 (-2.6 to 2.0) | |

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; SD, standard deviation.

[a] Change in eGFR was calculated as the 12-month value minus the pre-randomization value; restricted to participants who provided follow-up data within 8–16 months of randomization (excluding 12 participants who died during the 12-month trial period [5 in the hydration group and 7 in the control group]).

[b] Differences in eGFR change within sub-groups of participants with diabetes at baseline were analyzed using linear regression with an interaction term. Unadjusted regression models were used.

**eTable 11.** Post-hoc subgroup analysis of one-year change in eGFR in participants with a baseline eGFR above or below 45 mL/min per 1.73m$^2$

| | Change in eGFR[a] (mL/min/1.73 m$^2$) | | | |
|---|---|---|---|---|
| | Hydration n=291 | Control n=299 | Between-group difference[b] | |
| | Mean (SD) | Mean (SD) | Mean (95% CI) | *P Value* |
| **Baseline eGFR** | | | | |
| ≥45 mL/min per 1.73m$^2$ (n=267) | -3.3 (10.4) | -2.5 (9.4) | -0.9 (-3.2 to 1.5) | .48 |
| <45 mL/min per 1.73m$^2$ (n=323) | -1.1 (9.3) | -1.4 (8.2) | 0.2 (-1.7 to 2.1) | |

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; SD, standard deviation.

[a] Change in eGFR was calculated as the 12-month value minus the pre-randomization value; restricted to participants who provided follow-up data within 8–16 months of randomization (excluding 12 participants who died during the 12-month trial period [5 in the hydration group and 7 in the control group]).

[b] Differences in eGFR change within eGFR sub-groups were analyzed using linear regression with an interaction term. Unadjusted regression models were used.

**eTable 12.** Post-hoc analyses of the one-year change in 24-hour urine osmolality, creatinine, urea, sodium, and potassium[a]

| | Intervention group | | | |
|---|---|---|---|---|
| | **Hydration** | **Control** | **Mean difference[b] (95% CI)** | ***P Value*[b]** |
| | n=291 | n=299 | | |
| **Urine osmolality, mOsm/kg** | | | | |
| Pre-randomization | 450.8 (138.4) | 456.1 (131.6) | | |
| 12 months | 372.6 (128.1) | 449.0 (128.9) | | |
| Change | -84.4 (119.1) | -8.8 (127.2) | -75.6 (-98.2 to -53.0) | <.001 |
| **Urine creatinine, mmol/day** | | | | |
| Pre-randomization | 11.9 (4.3) | 12.1 (3.7) | | |
| 12 months | 12.4 (4.5) | 11.8 (3.8) | | |
| Change | 0.5 (3.2) | -0.4 (2.8) | 0.8 (0.3 to 1.4) | .003 |
| **Urine urea, mmol/day** | | | | |
| Pre-randomization | 341.6 (128.5) | 352.4 (125.1) | | |
| 12 months | 362.9 (141.8) | 346.3 (122.8) | | |
| Change | 12.7 (112.6) | -12.6 (108.9) | 25.4 (5.1 to 45.6) | .01 |
| **Urine sodium, mmol/day** | | | | |
| Pre-randomization | 145.2 (61.1) | 150.4 (62.4) | | |
| 12 months | 162.4 (65.6) | 145.0 (61.1) | | |
| Change | 15.5 (64.3) | -6.5 (64.6) | 21.9 (10.3 to 33.6) | <.001 |
| **Urine potassium, mmol/day** | | | | |
| Pre-randomization | 63.7 (26.4) | 64.8 (23.4) | | |
| 12 months | 65.5 (26.8) | 63.8 (25.3) | | |
| Change | 0.5 (24.3) | -2.2 (22.8) | 2.8 (-1.6 to 7.1) | .22 |

Abbreviations: CI, confidence interval;

[a] Means and standard deviations are reported. Change was calculated as the 12-month value minus the pre-randomization value; restricted to participants who provided follow-up data within 8–16 months of randomization (excluding 12 participants who died during the 12-month trial period [5 in the hydration group and 7 in the control group]). All analyses followed the intention-to-treat principle.

[b] Between-group differences in change were analyzed using the independent-samples t test.

**eTable 13:** Post-hoc analyses of the one-year change in serum osmolality, creatinine, and urea[a]

| | Intervention group | | | |
|---|---|---|---|---|
| | **Hydration** | **Control** | **Between-group difference[b] (95% CI)** | ***P Value*[b]** |
| | n=291 | n=299 | | |
| **Serum osmolality, mOsm/kg** | | | | |
| Pre-randomization | 300.2 (7.1) | 301.2 (8.4) | | |
| 12 months | 300.8 (7.5) | 302.6 (8.0) | | |
| Change | 0.4 (7.3) | 1.3 (8.0) | -0.9 (-2.2 to 0.5) | .20 |
| **Serum creatinine, mg/dL** | | | | |
| Pre-randomization | 1.6 (0.3) | 1.6 (0.3) | | |
| 12 months | 1.7 (0.6) | 1.7 (0.7) | | |
| Change | 0.1 (0.4) | 0.1 (0.5) | -0.0 (-0.1 to 0.1) | .87 |
| **Serum urea, mg/dL** | | | | |
| Pre-randomization | 28.8 (9.1) | 28.7 (10.3) | | |
| 12 months | 30.9 (11.2) | 31.2 (13.2) | | |
| Change | 2.0 (9.1) | 2.4 (10.4) | -0.4 (-2.0 to 1.2) | .61 |

Abbreviations: CI, confidence interval.

SI conversion factors: To convert serum creatinine to µmol/L, multiply by 88.4; osmolality to mOsml/L, multiply by 1; urea to mmol/L, multiply by 0.357.

[a] Means and standard deviations are reported. Change was calculated as the 12-month value minus the pre-randomization value; restricted to participants who provided follow-up data within 8–16 months of randomization (excluding 12 participants who died during the 12-month trial period [5 in the hydration group and 7 in the control group]). All analyses followed the intention-to-treat principle.

[b] Between-group differences in change were analyzed using the independent-samples t test.

**eTable 14.** One-year change in blood pressure, weight, waist circumference, and body mass index

| | Intervention group | | | |
|---|---|---|---|---|
| | **Hydration** | **Control** | **Between-group difference[b] (95% CI)** | ***P Value*[b]** |
| | n=291 | n=299 | | |
| **Systolic blood pressure, mmHg** | | | | |
| Pre-randomization | 141 (19) | 137 (17) | | |
| 12 months | 136 (17) | 132 (16) | | |
| Change | -5 (19) | -5 (21) | -0.5 (-4 to 3) | .78 |
| **Diastolic blood pressure, mmHg** | | | | |
| Pre-randomization | 79 (10) | 78 (11) | | |
| 12 months | 77 (11) | 77 (11) | | |
| Change | -2 (11) | -1 (12) | -1 (-3 to 1) | .43 |
| **Mean arterial pressure, mmHg** | | | | |
| Pre-randomization | 100 (11) | 97 (11) | | |
| 12 months | 96 (11) | 95 (10) | | |
| Change | -3 (12) | -2 (13) | -1 (-3 to 1) | .52 |
| **Weight, kg** | | | | |
| Pre-randomization | 86 (18) | 88 (20) | | |
| 12 months | 86 (18) | 87 (20) | | |
| Change | -0.5 (4) | -0.6 (5) | 0.1 (-1 to 1) | .76 |
| **Waist circumference, cm** | | | | |
| Pre-randomization | 104 (16) | 105 (18) | | |
| 12 months | 102 (18) | 102 (17) | | |
| Change | -3 (15) | -3 (13) | 0.7 (-2 to 3.5) | .63 |
| **Body mass index, kg/m$^2$** | | | | |
| Pre-randomization | 30 (6) | 30 (6) | | |
| 12 months | 30 (6) | 30 (6) | | |
| Change | -0.1 (1) | -0.2 (2) | 0.0 (-0.2 to 0.3) | .81 |

Abbreviations: CI, confidence interval.

[a] Means and standard deviations are reported. Change was calculated as the 12-month value minus the pre-randomization value; restricted to participants who provided follow-up data within 16 months of randomization (excluding 12 participants who died during the 12-month trial period [5 in the hydration group and 7 in the control group]). All analyses followed the intention-to-treat principle.

[b] Between-group differences in change were analyzed using the independent-samples t test.

**eTable 15.** Post-hoc analysis of self-reported dietary intake of sodium and protein[a]

| | Intervention group | | | |
|---|---|---|---|---|
| | **Hydration** | **Control** | **Between-group difference[b,c] (95% CI)** | ***P Value*[c]** |
| | n=291 | n=299 | | |
| **Sodium intake, mmol/day** | | | | |
| At randomization | 118 (43) | 117 (40) | | |
| 6-months | 97 (52) | 99 (47) | | |
| Change | -21 (56) | -17 (50) | -4 (-15 to 7) | .45 |
| **Protein intake, g/kg/day** | | | | |
| At randomization | 1.0 (0.3) | 1.0 (0.3) | | |
| 6-months | 1.0 (0.3) | 1.0 (0.3) | | |
| Change | 0.0 (0.3) | -0.0 (0.3) | 0.0 (-0.0 to 0.1) | .49 |

Abbreviations: CI, confidence interval.

[a] Participants completed a 3-day diet record at the time of randomization and again at 6 months after randomization, which they mailed back to the study center in a pre-addressed postage-paid envelope. The diet records were analyzed by The Food Processor (ESHA: Elizabeth Stewart Hands and Associates Research 2016 version 11.2).

[b] Means and standard deviations are reported. Change was calculated as the 6-month value minus the pre-randomization value; restricted to participants who provided follow-up data within 16 months of randomization (excluding 12 participants who died during the 12-month trial period [5 in the hydration group and 7 in the control group]). All analyses followed the intention-to-treat principle.

[c] Between-group differences in change were analyzed using the independent-samples t test.

**eTable 16.** One-year change in serum sodium

| | Intervention group | |
|---|---|---|
| **Serum sodium, mEq/L** | **Hydration** | **Control** |
| | n=291 | n=299 |
| **Pre-randomization** | | |
| Mean (SD) | 139 (3) | 139 (3) |
| Min/max | 131/146 | 129/146 |
| **3 weeks** | | |
| Mean (SD) | 139 (3) | 140 (3) |
| Min/max | 130/146 | 130/149 |
| **3 months** | | |
| Mean (SD) | 139 (3) | 140 (3) |
| Min/max | 129/147 | 130/147 |
| **6 months** | | |
| Mean (SD) | 139 (3) | 140 (3) |
| Min/max | 130/147 | 128/146 |
| **9 months** | | |
| Mean (SD) | 139 (3) | 140 (3) |
| Min/max | 123/147 | 130/147 |
| **12 months** | | |
| Mean (SD) | 139 (3) | 140 (3) |
| Min/max | 130/146 | 130/147 |
| **12-month change**[a] | | |
| Mean (SD) | 0.3 (3) | 0.8 (3) |
| Min/max | -9/8 | -7/8 |
| Between-group difference[b] (95% CI) | -0.5 (-1.0 to -0.04) | |
| *P Value*[b] | .04 | |

Abbreviations: CI, confidence interval; Min, minimum; Max, maximum; SD, standard deviation.

SI conversion factors: To convert sodium to mmol/L, multiply by 1.

[a] Change: 12-month value – pre-randomization value; for this calculation, missing 12-month values were imputed with 9-month values for 36 participants in the hydration group and 28 participants in the control group. Participants who died within 12 months of randomization were excluded (5 in the hydration group and 7 in the control group) as were those whose final blood sample was submitted >16 months after randomization.

[b] The between-group difference in change was calculated using the independent-samples t test.

**eAppendix 1**: Methods of handling missing data in the Chronic Kidney Disease Water Intake Trial (CKD WIT)

Missing baseline data occurred for <0.2% of categorical covariates (if missing, the condition was considered absent) and 6% for 24-hour urine albumin (imputed using fully conditionally specified models[1] as described below). Participants who died within one year of follow-up were excluded from the primary and secondary outcome analyses (12 of 631 participants [1.9%]). Less than 5% of survivors were missing a 12-month post-randomization eGFR ($\pm$4 months); missing eGFR data was imputed using fully conditionally specified models[1] with the following baseline variables: treatment group, center, age (in years), sex, presence of obesity (body mass index $\geq$30 kg/m$^2$), current smoker (yes/no), presence of diabetes, 24-hour urine albumin (mg/day) (log-transformed), and use of any of the following medications: an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, diuretic, beta blocker, calcium channel blocker, and statin (yes/no). Estimated GFR values at the 3-month and 6-month study time points were also included in the imputation. Twenty datasets were imputed. We assumed that data were missing at random, and that the data were from a multivariate normal distribution. We conducted several sensitivity analyses to examine whether conclusions were sensitive to assumptions about the missing-data mechanism; these analyses included a complete-case unadjusted analysis, simple imputation, and imputation that did not include the treatment group.[2,3] SAS PROC MIANALYZE was used to combine results from imputed datasets.[4] The type I error rate was set at 0.05.

**eAppendix 2:** Longitudinal analysis of eGFR data in the Chronic Kidney Disease Water Intake Trial (CKD WIT)

## Methods

We conducted a longitudinal data analysis of eGFR data, estimating the mean change in eGFR for each 1-month increase in time, for both groups. To do this, we used a mixed-effects model with a random intercept. The outcome was eGFR measured at one of four time points. The fixed-effects regression coefficients were time (0, 3, 6, and 12 months), and a time-treatment group interaction term. The time coefficient describes the mean change in eGFR for a one-month increase in time for participants who were randomized to the hydration group. The time-treatment group interaction term represents the additional change in eGFR for the control group (i.e. the sum of the two coefficients represents the mean change in eGFR for a one-month increase in time for participants randomized to the control group). The random intercept was used to account for within-subject correlation. For this analysis, 3- month eGFR was defined as the eGFR measured closest to 3 months (between 1.5 and 4.5 months after randomization), 6-month eGFR was defined as the eGFR measured closest to 6 months (between 4.5 and 8 months after randomization), and 12-month eGFR was defined as the eGFR measured closest to 12 months (between 8 and 16 months after randomization).

We tested whether the coefficient for the time-treatment group interaction term was equal to zero, which would indicate that the change in eGFR over time was equal between the groups. If this term was significantly different from zero, we will report the mean change in eGFR for a one-month increase in time for both groups separately. If the time-treatment interaction coefficient was not significantly different from zero at the $\alpha=0.05$ level, we will fit the same mixed-effects regression model, but omitting the interaction term. From this model, we will test the null hypothesis that the mean change in eGFR is equal to zero at the $\alpha=0.05$ level, for both treatment groups simultaneously.

## Results

The estimate for the coefficient of the time-treatment group interaction term is 0.02 (95% CI -0.07, 0.12), $P=.62$, comparing the control group to the hydration group. This indicates that there is not sufficient evidence to suggest that the change in eGFR over time is different between treatment groups.

When we fit a model without a time-treatment group interaction term, the coefficient estimate for time was -0.16 (95% CI -0.21, -0.11), $P<.001$. This indicates that the change in eGFR over time was significantly different from zero, in the negative (decreasing) direction.

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