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Original Article

# Fluid and nutrient intake and risk of chronic kidney disease

GIOVANNI FM STRIPPOLI,[1,2,3] JONATHAN C CRAIG,[1,2] ELENA ROCHTCHINA,[4] VICTORIA M FLOOD,[4] JIE JIN WANG[4] and PAUL MITCHELL[4]

[1]Centre for Kidney Research, NHMRC Centre for Clinical Research Excellence in Renal Medicine, Cochrane Renal Group, The Children's Hospital at Westmead, [2]School of Public Health and [4]Department of Ophthalmology (Centre for Vision Research, Westmead Millennium Institute, Westmead Hospital), University of Sydney, Sydney, New South Wales, Australia and [3]Diaverum Medical Scientific Office, Via Solarino, Bari, Italy

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**Correspondence:**
Assoc Professor Giovanni FM Strippoli, Cochrane Renal Group, NHMRC Centre for Clinical Research Excellence in Renal Medicine, The University of Sydney, Sydney, NSW 2145, Australia. Email: strippoli@negrisud.it

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## SUMMARY AT A GLANCE

It is unclear whether increasing fluid intake will slow the progression of chronic kidney disease. In this issue, Strippoli and co-workers examine this important question using the Blue Mountains observational cohort consisting of more than 2500 patients in Western Sydney. The results show that subjects who drank more than 3.2 L per day had a lower risk of chronic kidney disease (OR 0.5, 95%CI 0.32–0.77).

## ABSTRACT:

*Aim:* **We evaluated the association between fluid and nutrient intake and chronic kidney disease (CKD).**

*Methods:* **Two cross-sectional population-based studies. Validated nutrition food frequency questionnaires (FFQ) administered to people >50 years, identified in a door-to-door census of a well-defined suburban area. Based upon nutrition tables we calculated intakes of over 40 nutrients (factors) and total daily energy intake. Primary outcome was CKD. Fluid (total content of fluid and drinks assessed in the FFQ) and nutrient intake was stratified in quintiles and association with CKD analysed by logistic regression, expressed as unadjusted and adjusted odds ratios, with testing for linear trend.**

*Results:* **The proportion of participants who completed the FFQ and had glomerular filtration rate (GFR) measures was 2744/3654 (75.0%) for the first and 2476/3508 (70.6%) for the second survey. CKD was present in 12.4–23.5% men and 14.9–28.7% women (mean ages 66.4–65.4 years), respectively. Participants who had the highest quintile of fluid intake (3.2 L/day) had a significantly lower risk of CKD (odds ratio 0.5, 95%CI 0.32 to 0.77, *P* for trend = 0.003). These findings were consistent across both study periods, both equations to calculate GFR and both GFR thresholds.**

*Conclusion:* **Higher intakes of fluid appear to protect against CKD. CKD may be preventable at a population level with low-cost increased fluid intake.**

The number of people affected by chronic kidney disease (CKD) and end-stage kidney disease is substantial and increasing. Population-based surveys have documented a 5–8% prevalence of CKD or around 3.5 million people in the USA alone.[1] Most people with CKD have moderate CKD (defined as a glomerular filtration rate (GFR) <60 mL/min per 1.73 $m^2$), but about 10% have severe CKD (GFR <10 mL/min per 1.73 $m^2$) and require renal replacement therapy.[2] The number of new patients with end-stage kidney disease treated by renal replacement therapy (dialysis or transplantation) has increased at an average of 7% per year over the past 10 years.[3] Currently, about 1.1 million patients are on renal replacement therapy worldwide, a number that will exceed two million over the next 10 years.[4] Medicare expenditure for renal replacement therapy over the next 10 years will be about $28 billion.[5] CKD is also associated with substantially increased risk for cardiovascular disease morbidity and mortality, independent of traditional cardiovascular risk factors such as diabetes, hypertension, lipoprotein levels and tobacco use.[6]

Preventing CKD is therefore a major public health challenge worldwide. Although the causes are largely unknown, hypertension, diabetes, smoking, hyperlipidaemia, age and socioeconomic disadvantage are established risk factors and have been known for some time. Interventions to reduce most of these risk factors, however, have not resulted in the expected reduction of the incidence of CKD.[7,8]

Several studies have recently explored the role of modifiable risk factors in preventing cardiovascular and chronic degenerative diseases. The intake of certain nutrient categories and anti-oxidants has been associated with reduced risk of cardiovascular diseases, cancer and other degenerative diseases but no study has yet examined the impact of these modifiable factors on the risk of developing CKD.[9–16] There is also an accepted truism in the general community that fluid consumption is good for the kidney but this has never been formally examined.[17–19]

In this study, two surveys of the same geographically defined group of older people conducted at a 5 years interval were used to determine whether there was a cross-sectional association between fluids and nutrient intake and the prevalence of CKD.

## METHODS

### Subjects and design

We performed two surveys based on a door-to-door census of all subjects aged 49 years living in two postcode areas in the Blue Mountains region, west of Sydney, Australia. This geographically well-defined area was chosen as it has a stable and relatively homogeneous population. Details of the survey methods and procedures have been previously described.[20–22] The first survey was conducted during 1992–1994, and examined 3654 of 4433 eligible participants (82.4%) identified in the census. Follow-up examinations were conducted after 5 years during 1997–1999, when 2335 (75.0% of survivors) participated. A repeat door-to-door census was conducted in 1999. This identified 1378 newly eligible residents who had moved into the area or reached the eligible age group, of whom 1174 (85.2%) participated. The second survey thus included a total of 3509 participants.

The population in both cross-sections had fairly similar characteristics to the Australian population of comparable age.[23] Participants were invited to a local clinic for a detailed medical examination and collection of baseline information relating to potential predictors of CKD.

### Blood collection and other generic exposure assessment

At the time of both cross-sectional analyses, doctors and trained nurses collected fasting blood samples in a subsequent morning visit, which were centrifuged on site. Laboratory tests were performed at the Institute of Clinical Pathology & Medical Research at Westmead Hospital (NSW, Australia) within 5 h of collection. Serum creatinine was measured in all patients by the modified kinetic Jaffe reaction using an EPX biochemistry analyser (Abbott reagent; Abbott Laboratories, North Chicago, IL, USA) for the first cross-section and a Hitachi 747 biochemistry analyser (Roche reagent; Roche Products Ltd., NSW, Australia) in the second cross-section, with a coefficient of variation <2.3% for both cross-sections. Data were collected on gender, age, presence of diabetes, hypertension, history of angina, myocardial infarction, gout, self-reported history of hypercholesterolaemia, stroke, diagnosis of cancer, smoking status, physical exercise, alcohol consumption, caffeine consumption, school qualification, marital status, housing status (person living alone or with someone) and other generic variables.

### Specific exposure (nutrient and fluid intakes) assessment

Before attending the medical examination, participants were sent a 145 item food frequency questionnaire (FFQ), which they returned at the time of the clinic visit. The FFQ was a semi-quantitative instrument modified from a Willett FFQ (24) for Australian diet and vernacular and included portion size estimates for food and fluids. It was produced using larger font for easier reading by older, potentially visually impaired people. The FFQ was found to be reliable in this population and to have reasonable concurrent validity compared with weighed food records collected over 1 year.[24,25] Participants were also asked about frequency, strength, brand and type of any nutritional supplements taken. Analyses were conducted for nutrients from diet and some selected nutrients from diet and supplements. Specific exposure assessed from the FFQ included minerals, trace elements, anti-oxidants and fluid (in detail, β-carotene, retinol, thiamine, riboflavin, phosphorus, magnesium, calcium, zinc, folate, protein, carbohydrage, starch, total sugar, fibre, mono- and polyunsaturated fat and total fluid).

### Outcome assessment

The outcome of interest was CKD. We estimated kidney function from serum creatinine using the Cockcroft-Gault formula, a calculated estimate of the GFR.[26] In women, the results were multiplied by 0.85. Values were adjusted for body surface area (body surface area ($m^2$) = (height × weight)$^{0.5}$/60) and expressed in mL/min per 1.73 $m^2$. The Cockcroft-Gault equation was chosen for estimating GFR as this was the standard equation in use at the time of our first cross-sectional analysis. CKD was defined as a Cockcroft-Gault clearance <50 mL/min per 1.73 $m^2$, the median value observed in our studied population. More recently, the Modification of Diet in Renal Disease (MDRD) equation has been introduced to estimate GFR and the Kidney Disease Outcome Quality Initiative proposed five stages for classification of GFR, with a GFR cut point <60 mL/min per 1.73 $m^2$ used to define moderate CKD. We therefore also compared the results of our primary outcome of interest (Cockcroft-Gault GFR <50 mL/min per 1.73 $m^2$) with those obtained using MDRD GFR <60 mL/min per 1.73 $m^2$ as a sensitivity analysis. Urine was not collected in our study so urinary protein excretion was not included in assessment of renal function.

### Data management

All data coding, entry and cleaning were performed by staff who were masked to individuals' identity. For information deriving from FFQs, all questionnaires with between 13 and 25 missing values were checked and corrected for data entry errors, if identified. After data cleaning, if more than 12 FFQ questions (8% of the questionnaire) or an entire page (even if <12 blank questions) remained blank, then these questionnaires were excluded (349 subjects in the first and 107 subjects in the second cross-section). Subjects with

daily energy intakes calculated from the FFQ of less than 2500 kJ or greater than 18 000 kJ were excluded from analyses (18 subjects in the first and 27 subjects in the second cross-section) as these extremes of energy intake were considered implausible. Finally, we identified subjects whose calculated nutrient intakes lay in the upper or lower 2% of the distribution of intakes for each nutrient of interest. The FFQ food items, which contributed to the extreme intake of the relevant nutrient for these identified subjects, were then checked for data entry and coding accuracy and errors were corrected where identified.

Dietary intakes were estimated using the Australian Tables of Food Composition database[14] (Nuttab 90 in the first cross-section and Nuttab 95 in the second).[27]

### Statistical analysis

All statistical analyses were performed using Statistical Analysis System v.8.2 (SAS Institute, Cary, NC, USA). The selected outcome measure was prevalence of CKD, defined as either a Cockcroft-Gault GFR <50 mL/min per 1.73 $m^2$ or an MDRD GFR <60 mL/min per 1.73 $m^2$, to check for consistency and robustness of the findings. The association of the outcome of interest with several generic and nutrition specific risk factors was ascertained by separate logistic regression models in each survey. Nutrient intakes from diet were calculated as energy adjusted intakes using the method suggested by Willett and Stampfer to account for the different total energy intake of subjects, which may be responsible for a relatively higher intake of selected nutrients.[28] Energy adjusted nutrient scores were divided into quintiles of intake. The lowest quintile of intake was used as the reference group in the logistic regression models. All adjusted analyses were performed taking into account the risk factors that were statistically significant in the univariate (unadjusted) comparisons. The Cochran-Mantel-Haenszel method was used to test for trends in stratified analyses. In logistic regression models, we tested for trends in CKD prevalence with increasing nutrient intake by modelling the median value in each nutrient category as a single continuous variable. Results are presented as age-sex adjusted (OR) and multivariate adjusted (AOR) odds ratios with 95% confidence intervals (CI).

## RESULTS

### Characteristics of the study population

Participants with usuable FFQs and measured GFR provided a response rate of 2744/3654 (72.1% of those examined) for the first survey and 2476/3508 (70.6%) for the second. Prevalence of moderate CKD was 23.5–28.7% (male–female) in the first cross-section and 12.4–14.9% in the second cross-section, with mean ages of 66.4 and 65.4 years, respectively. Other characteristics of the studied population are reported in Table 1. A large proportion (range 20.8–32.5) of individuals received antihypertensive medications including ACE inhibitors, beta blockers, calcium channel blockers or diuretics individually or in combination.

### Association of fluid, nutrients, minerals and trace elements and anti-oxidants with the prevalence of CKD

Age-sex adjusted and multivariable adjusted estimates of risk of CKD by exposure to different quintiles of key electrolytes, selected macronutrients and folate are reported in Tables 2 and 3.

In the age-sex adjusted analysis, there was a significantly increased risk of CKD (Cockcroft-Gault GFR <50 mL/min per 1.73 $m^2$) for increasing quintiles of carbohydrate ($P$ for trend = 0.007), sugar ($P$ for trend < 0.0001) and starch ($P$ for trend = 0.013). Factors associated with a significant reduction in risk were increasing quintiles of retinol ($P$ for trend < 0.0001), magnesium ($P$ for trend = 0.001), calcium ($P$ for trend = 0.009), zinc ($P$ for trend < 0.001), phosphorus ($P$ for trend = 0.012), polyunsaturated fat ($P$ for trend = 0.001) and fluid ($P$ for trend 0.002). No significant difference in the risk of CKD was found by exposure to protein ($P$ for trend = 0.20) and total fat ($P$ for trend = 0.99).

After allowing for age, gender, smoking status, presence of cardiovascular disease, hypertension, gout, cancer, blood cholesterol, fibrinogen and haemoglobin levels, increasing quintiles of carbohydrate were associated with a significant increase in the risk of CKD defined as a GFR <50 mL/min per 1.73 $m^2$ (Table 3). There was a 20–70% increase in the likelihood of CKD across quintiles of intake with a statistically significant trend ($P = 0.004$).

Median fluid intake (mL) was 2448 in the first and 2413 in the second cross-sections ($P = 0.68$).

Fluid intake (3rd and 5th quintile of energy adjusted intake) was associated with a 30–50% reduction in the prevalence of CKD defined as Cockcroft-Gault GFR <50 mL/min per 1.73 $m^2$. There was a statistically significant trend indicating that the higher the intake of fluids, the lower the risk ($P = 0.003$). Similarly for magnesium, higher intake levels (2nd, 3rd, 4th and 5th quintile of intake compared with the lowest quintile) were significantly associated with a 30–50% reduction in the likelihood of having a Cockcroft-Gault GFR <50 mL/min per 1.73 $m^2$, with a significant trend ($P = 0.014$). No significant differences in the risk were demonstrated for all other nutrients in this cross-section.

### Comparison between first and second cross-sectional analysis results

The results of the first and second cross-sectional analyses, evaluating association between intake of fluids, nutrients, minerals and trace elements and anti-oxidants with the risk of CKD and by using a different definition of the outcome (Cockcroft-Gault GFR <50 mL/min per 1.73 $m^2$ *versus* MDRD GFR <60 mL/min per 1.73 $m^2$) are compared in Table 4.

The per cent overlap between two surveys was 48.3%.

A significant reduction in the risk of CKD by increasing amounts of fluid intake was validated in three out of four

**Table 1** Baseline characteristics of participants in the first and second cross-sections

| Variable | Study period 1992–1994 ($n$ = 2744) $n$ (%) | Study period 1997–2000 ($n$ = 2476) $n$ (%) |
|---|---|---|
| Age | | |
| Male | | |
| <60 | 329 (28.6) | 266 (25.0) |
| 60–69 | 445 (38.7) | 401 (37.6) |
| 70–79 | 389 (25.2) | 312 (29.3) |
| >80 | 86 (7.5) | 87 (8.2) |
| Female | | |
| <60 | 435 (29.1) | 383 (27.2) |
| 60–69 | 578 (38.7) | 510 (36.2) |
| 70–79 | 380 (25.4) | 392 (27.8) |
| >80 | 102 (6.8) | 125 (8.9) |
| Comorbidities | | |
| Angina | 298 (11.3) | 244 (9.9) |
| Acute myocardial infarction | 220 (8.4) | 189 (7.7) |
| Stroke | 115 (4.4) | 103 (4.2) |
| Gout | 274 (11.2) | No info |
| Hypertension | 1216 (46.0) | 1261 (51.1) |
| Diabetes | 200 (7.6) | 241 (9.7) |
| Smoking status | | |
| Never smoked | 1267 (48.8) | 1220 (49.5) |
| Current smoker | 359 (13.8) | 223 (9.1) |
| Ex smoker | 971 (37.4) | 1022 (41.5) |
| Body mass index (kg/m$^2$) | | |
| <25 | 1144 (43.3) | 767 (31.0) |
| 25–30 | 1046 (39.6) | 1101 (44.5) |
| >30 | 454 (17.2) | 608 (24.6) |
| GFR (mL/min per 1.73 m$^2$, adjusted for BSA) | | |
| <60 | 10 (1.6) | 2 (0.6) |
| 60–79 | 117 (18.4) | 24 (7.0) |
| 70–79 | 337 (52.8) | 163 (47.7) |
| >80 | 173 (27.2) | 153 (44.7) |
| GFR <50 mL/min per 1.73 m$^2$ (adjusted for BSA) by gender | | |
| Male (total) | 323 (23.5) | 132 (12.4) |
| Female (total) | 520 (28.7) | 210 (14.9) |
| Antihypertensive medication | | |
| ACE-inhibitors† | 216 (7.9) | 380 (15.4) |
| Beta blockers† | 371 (13.5) | 270 (10.9) |
| Calcium channel blocker† | 384 (14.0) | 370 (14.9) |
| Diuretic† | 506 (18.4) | 384 (15.5) |

†Alone or in combination with other drugs. BSA, body-surface area; GFR, glomerular filtration rate.

analyses conducted, specifically in the first survey using a Cockcroft-Gault GFR <50 mL/min per 1.73 m$^2$ as the outcome of interest and in the second survey using both definitions for the outcome of interest (Cockcroft-Gault GFR <50 mL/min per 1.73 m$^2$ and MDRD GFR <60 mL/min per 1.73 m$^2$). The finding of magnesium intake associated with a significant reduction in the prevalence of CKD was validated in all four analyses conducted. The finding of carbohydrate intake associated with an increase in the risk of CKD, found in the first survey using the outcome of a Cockcroft-Gault GFR <50 mL/min per 1.73 m$^2$, was not confirmed in any of the additional validation analyses.

The daily intake of fibre was found to be associated with a significant reduction ($P$ = 0.002) in the prevalence of CKD defined as an MDRD GFR <60 mL/min per 1.73 m$^2$ in the first survey, a finding confirmed in the second survey by using the same definition of CKD. Furthermore, the intake of phosphorus and the intake of calcium were found to be significantly associated with a reduction in the prevalence of CKD in both the first and second surveys.

## DISCUSSION

Fluid consumption appears to be beneficial for kidney function. We found an inverse linear relationship between intake of fluid and prevalence of CKD. The higher the fluid intake, the lower the risk, with an intake of 3.3 L/day associated with a 30–50% reduction in the likelihood compared with an

**Table 2** Association between moderate CKD (GFR < 50 mL/min per 1.73 m$^2$) and energy adjusted intake of fluid and key electrolytes (magnesium, calcium and phosphorus from diet and supplements) in BMES cross-section 1 participants

| Nutrient quintile | Median intake | GFR < 50% (*n*) | Age-sex adjusted OR (95%CI) | Multivariable† adjusted OR (95%CI) |
|---|---|---|---|---|
| Fluid (mL) | | | | |
| Q1 | 1792 | 30.3 (160) | 1.0 (referent) | 1.00 (referent) |
| Q2 | 2190 | 27.7 (146) | 0.71 (0.49–1.02) | 0.68 (0.45–1.02) |
| Q3 | 2453 | 24.4 (129) | 0.69 (0.47–1.00) | 0.64 (0.43–0.97) |
| Q4 | 2713 | 21.6 (114) | 0.65 (0.44–0.94) | 0.67 (0.44–1.01) |
| Q5 | 3181 | 16.6 (88) | 0.54 (0.37–0.80) | 0.50 (0.32–0.77) |
| *P* for trend | | | 0.002 | 0.003 |
| Magnesium (mg) | | | | |
| Q1 | 266 | 30.1 (159) | 1.0 (referent) | 1.00 (referent) |
| Q2 | 309 | 25.7 (136) | 0.79 (0.54–1.14) | 0.71 (0.48–1.07) |
| Q3 | 339 | 21.2 (112) | 0.65 (0.44–0.95) | 0.57 (0.38–0.87) |
| Q4 | 376 | 24.2 (128) | 0.68 (0.47–0.98) | 0.65 (0.43–0.98) |
| Q5 | 433 | 19.3 (102) | 0.53 (0.36–0.77) | 0.57 (0.37–0.87) |
| *P* for trend | | | 0.001 | 0.014 |
| Calcium (mg) | | | | |
| Q1 | 543 | 26.3 (139) | 1.0 (referent) | 1.00 (referent) |
| Q2 | 728 | 28.5 (151) | 1.26 (0.87–1.82) | 1.39 (0.92–2.09) |
| Q3 | 875 | 23.1 (122) | 0.87 (0.60–1.28) | 0.95 (0.63–1.44) |
| Q4 | 1065 | 23.1 (122) | 0.89 (0.61–1.31) | 0.97 (0.64–1.49) |
| Q5 | 1451 | 19.5 (103) | 0.68 (0.47–1.00) | 0.74 (0.49–1.14) |
| *P* for trend | | | 0.009 | 0.035 |
| Phosphorus (mg) | | | | |
| Q1 | 1173 | 26.8 (142) | 1.0 (referent) | 1.0 (referent) |
| Q2 | 1344 | 21.4 (113) | 0.73 (0.50–1.08) | 0.88 (0.57–1.34) |
| Q3 | 1481 | 25.3 (134) | 0.87 (0.59–1.26) | 0.95 (0.63–1.43) |
| Q4 | 1638 | 24.2 (128) | 0.77 (0.52–1.12) | 0.84 (0.55–1.29) |
| Q5 | 1905 | 22.7 (120) | 0.59 (0.40–0.86) | 0.66 (0.43–1.01) |
| *P* for trend | | | 0.012 | 0.052 |

†Adjusted for age, gender, smoking status, presence of cardiovascular diseases, hypertension, gout, cancer, blood cholesterol, fibrinogen and haemoglobin. BMES, Blue Mountains Eye Study; CKD, chronic kidney disease; GFR, glomerular filtration rate.

intake of 1.7 L/day. We also found an inverse association between magnesium and phosphorus intake and prevalence of moderate CKD, and less consistent evidence of an association between intake of certain nutrients (fibre, calcium) and prevalence of moderate CKD.

The association between fluid, magnesium, phosphorus calcium and fibre and prevalence of CKD show a dose-dependent pattern.

Despite the widespread community-held belief that 'fluid is good for your kidneys', we are not aware of any prior human studies that have analysed this association. Similarly, there have been no previous prospective studies exploring the role of fluid intake in people with CKD. The role of fluid and nutrient intake on CKD has only been assessed in some animal studies. In a rat model of CKD, a progressive increase in urinary protein excretion and systolic blood pressure was found to be significantly slower when intake of water was high compared with no water intake.[29] In rats with subtotal nephrectomy, high fluid intake has also been found to ameliorate tubulointerstitial injury by reducing transforming growth factor-beta mRNA expression in the medullary interstitium. Other animal studies have suggested that urine alkalinization and intake of free water both serve to decrease the rate of progression of CKD.[29] Studies in humans have been limited to kidney stone disease and demonstrate that the risk of developing secondary kidney stones is significantly lower in people who intake high amounts of fluids.[29–31]

The findings of an inverse association between magnesium and phosphorus intake and the prevalence of moderate CKD, and weaker evidence of association between intake of fibre and low prevalence of moderate CKD are consistent with other studies evaluating the association between nutrient intake and chronic vascular diseases. Compared with a standard American diet, the Dietary Approaches to Stop Hypertension diet was found to be associated with a significant reduction in systolic and diastolic blood pressure, with elevated blood pressure, a well-known risk factor for cardiovascular events and death. The Dietary Approaches to Stop Hypertension diet, which emphasizes fruits, vegetables and low-fat dairy products consumption, includes whole grains, poultry, fish and nuts and low consumption of fats, red meat, sweets and sugar-containing beverages, and is therefore rich in potassium, magnesium, calcium and fibre while low in total fat, saturated fat and cholesterol, with a slightly

**Table 3** Association between moderate CKD (GFR < 50 mL/min per 1.73 $m^2$) and energy adjusted intake of selected macronutrients and folate (diet and supplements) in BMES cross-section 1 participants

| Nutrient quintile | Median intake | GFR < 50% (*n*) | Age-sex adjusted OR (95%CI) | Multivariable† adjusted OR (95%CI) |
|---|---|---|---|---|
| Protein (g) | | | | |
| Q1 | 70.4 | 27.2 (144) | 1.0 (referent) | 1.00 (referent) |
| Q2 | 80.0 | 25.0 (132) | 0.84 (0.58–1.22) | 0.88 (0.58–1.33) |
| Q3 | 87.2 | 23.6 (125) | 0.99 (0.68–1.44) | 0.97 (0.64–1.47) |
| Q4 | 94.8 | 22.9 (121) | 0.85 (0.58–1.24) | 0.92 (0.61–1.38) |
| Q5 | 107.1 | 21.7 (115) | 0.76 (0.52–1.12) | 0.72 (0.47–1.10) |
| *P* for trend | | | 0.20 | 0.17 |
| Carbohydrate (g) | | | | |
| Q1 | 184 | 16.9 (89) | 1.0 (referent) | 1.0 (referent) |
| Q2 | 214 | 21.0 (111) | 0.98 (0.66–1.47) | 0.97 (0.63–1.50) |
| Q3 | 233 | 24.4 (129) | 1.27 (0.85–1.88) | 1.25 (0.81–1.93) |
| Q4 | 251 | 25.7 (136) | 1.21 (0.82–1.80) | 1.17 (0.76–1.82) |
| Q5 | 279 | 32.5 (172) | 1.59 (1.09–2.34) | 1.75 (1.16–2.66) |
| *P* for trend | | | 0.007 | 0.004 |
| Total fat (g) | | | | |
| Q1 | 62.3 | 24.5 (130) | 1.0 (referent) | 1.0 (referent) |
| Q2 | 72.6 | 26.5 (140) | 1.40 (0.97–2.03) | 1.34 (0.90–2.01) |
| Q3 | 79.4 | 23.3 (123) | 0.88 (0.60–1.28) | 0.80 (0.52–1.21) |
| Q4 | 86.2 | 24.4 (129) | 1.06 (0.73–1.53) | 1.13 (0.75–1.69) |
| Q5 | 96.4 | 21.7 (115) | 1.13 (0.77–1.65) | 1.17 (0.77–1.78) |
| *P* for trend | | | 0.99 | 0.72 |
| Folate (μg) | | | | |
| Q1 | 243 | 30.1 (159) | 1.0 (referent) | 1.0 (referent) |
| Q2 | 292 | 23.5 (124) | 0.62 (0.43–0.91) | 0.61 (0.40–0.93) |
| Q3 | 329 | 22.3 (118) | 0.63 (0.43–0.91) | 0.66 (0.44–0.99) |
| Q4 | 371 | 21.9 (116) | 0.69 (0.47–0.99) | 0.69 (0.46–1.04) |
| Q5 | 463 | 22.7 (120) | 0.55 (0.37–0.80) | 0.55 (0.36–0.84) |
| *P* for trend | | | 0.011 | 0.023 |

†Adjusted for age, gender, smoking status, presence of cardiovascular diseases, hypertension, gout, cancer, blood cholesterol, fibrinogen and haemoglobin. CKD, chronic kidney disease; GFR, glomerular filtration rate; OR, odds ratio.

increased protein intake.[32] Similarly, the Mediterranean diet, consisting of high intakes of vegetable oils, pasta and rice, sauces, fish and wine, provides an increased intake of oleic acid and reduced intakes of saturated fats and omega-6 fatty acids, has been found to be associated with increased longevity and quality of life in epidemiological studies, as a result of reduced cardiovascular events.[33] Recent studies have also advocated for its cost-effectiveness in patients with previous myocardial infarction. A protective association between higher magnesium intake and type 2 diabetes has also been reported, and experimental studies have demonstrated that magnesium supplementation improves insulin-mediated glucose disposal and insulin secretion.[34–36]

Our study has a number of strengths and limitations. It is based on two cross-sectional surveys, 5 to 6 years apart, of a defined population, with high consent rates. We used a well-validated self-administered FFQ to assess nutritional exposure. Previous validation studies from our group have demonstrated that the FFQ ranks people well, although measurement errors may provide poor absolute total nutrient values. We also identified consistent results using two definitions (different equations) and two different thresholds of the outcome. However, because of the different biochemistry analysers used to measure creatinine in the first and second surveys, which defined a different proportion of the population with CKD, we were unable to compare change in estimated kidney function over time and to assess the association with CKD incidence. Approximately, two-thirds of the study samples overlap between the two surveys; therefore, the validation showed in the two surveys is not entirely independent. The overlapping populations, combined with survival bias (where non surviving individuals from the first cross-section were replaced by new individuals in the second cross-section), may explain the different prevalence of CKD observed in the two. We also cannot rule out residual confounding, which may account for the associations found, including confounding by disease status. People with CKD may drink more to compensate for tubular dysfunction. However, if this had occurred in our study, the true magnitude of relationship between fluid intake and CKD would be even greater than what we had observed. Questions may also be raised relating to whether the observed association is because patients with CKD and comorbid conditions are told to modify their diet as a result of their baseline disease. In

**Table 4** Odds ratio (95% confidence interval) of moderate CKD and selected nutrients, using two different equations for the estimation of glomerular filtration rate, in two consecutive cross-sections

| Nutrient quintile | Study period 1992–1994 | | | Study period 1997–2000 | | |
|---|---|---|---|---|---|---|
| | Median intake | CG 50† (Adjusted OR, 95%CI)‡ | MDRD60§ (Adjusted OR, 95%CI)‡ | Median intake | CG 50† (Adjusted OR, 95%CI)‡ | MDRD60§ (Adjusted OR, 95%CI)‡ |
| Fluid (mL) | | | | | | |
| Q1 | 1792 | 1.00 (referent) | 1.0 (referent) | 1801 | 1.0 (referent) | 1.0 (Referent) |
| Q2 | 2190 | 0.68 (0.45–1.02) | 0.92 (0.69–1.22) | 2175 | 0.60 (0.38–0.95) | 1.13 (0.80–1.59) |
| Q3 | 2453 | 0.64 (0.43–0.97) | 0.90 (0.68–1.20) | 2434 | 0.89 (0.56–1.40) | 1.00 (0.70–1.43) |
| Q4 | 2713 | 0.67 (0.44–1.01) | 0.87 (0.65–1.16) | 2709 | 0.58 (0.36–0.93) | 0.77 (0.53–1.10) |
| Q5 | 3181 | 0.50 (0.32–0.77) | 0.80 (0.60–1.07) | 3192 | 0.61 (0.38–0.99) | 0.73 (0.5–1.05) |
| *P* for trend | | 0.003 | 0.13 | | 0.05 | 0.02 |
| Magnesium (mg) | | | | | | |
| Q1 | 266 | 1.00 (referent) | 1.0 (referent) | 272 | 1.0 (referent) | 1.0 (referent) |
| Q2 | 309 | 0.71 (0.48–1.07) | 0.94 (0.71–1.26) | 312 | 0.88 (0.56–1.39) | 0.93 (0.66–1.32) |
| Q3 | 339 | 0.57 (0.38–0.87) | 0.71 (0.53–0.95) | 346 | 0.76 (0.47–1.21) | 0.86 (0.61–1.23) |
| Q4 | 376 | 0.65 (0.43–0.98) | 0.81 (0.61–1.1) | 382 | 0.47 (0.28–0.77) | 0.60 (0.41–0.86) |
| Q5 | 433 | 0.57 (0.37–0.87) | 0.65 (0.48–0.87) | 447 | 0.65 (0.41–1.04) | 0.56 (0.39–0.82) |
| *P* for trend | | 0.014 | 0.003 | | 0.015 | 0.0002 |
| Calcium (mg) | | | | | | |
| Q1 | 543 | 1.00 (referent) | 1.0 (referent) | 574 | 1.0 (referent) | 1.0 (referent) |
| Q2 | 728 | 1.39 (0.92–2.09) | 0.96 (0.72–1.28) | 759 | 0.55 (0.35–0.88) | 0.74 (0.52–1.06) |
| Q3 | 875 | 0.95 (0.63–1.44) | 0.99 (0.74–1.3) | 900 | 0.78 (0.49–1.23) | 0.72 (0.51–1.03) |
| Q4 | 1065 | 0.97 (0.64–1.49) | 0.92 (0.69–1.24) | 1086 | 0.40 (0.24–0.65) | 0.53 (0.37–0.76) |
| Q5 | 1451 | 0.74 (0.49–1.14) | 0.83 (0.62–1.11) | 1469 | 0.47 (0.29–0.76) | 0.57 (0.40–0.82) |
| *P* for trend | | 0.035 | 0.16 | | 0.002 | 0.0015 |
| Phosphorus (mg) | | | | | | |
| Q1 | 1173 | 1.0 (referent) | 1.0 (referent) | 1213 | 1.0 (referent) | 1.0 (referent) |
| Q2 | 1344 | 0.88 (0.57–1.34) | 0.92 (0.68–1.23) | 1401 | 1.18 (0.73–1.89) | 1.35 (0.95–1.93) |
| Q3 | 1481 | 0.95 (0.63–1.43) | 1.00 (0.75–1.34) | 1535 | 0.94 (0.58–1.52) | 1.02 (0.71–1.47) |
| Q4 | 1638 | 0.84 (0.55–1.29) | 0.95 (0.71–1.27) | 1680 | 0.83 (0.51–1.34) | 0.91 (0.63–1.32) |
| Q5 | 1905 | 0.66 (0.43–1.01) | 0.72 (0.53–0.96) | 1939 | 0.56 (0.34–0.93) | 0.59 (0.40–0.87) |
| *P* for trend | | 0.05 | 0.033 | | 0.007 | 0.0004 |
| Carbohydrate (g) | | | | | | |
| Q1 | 184 | 1.0 (referent) | 1.0 (referent) | 193 | 1.0 (referent) | 1.0 (referent) |
| Q2 | 214 | 0.97 (0.63–1.50) | 1.19 (0.99–1.22) | 221 | 0.83 (0.49–1.40) | 1.07 (0.73–1.55) |
| Q3 | 233 | 1.25 (0.81–1.93) | 1.24 (0.93–1.66) | 239 | 1.04 (0.63–1.71) | 0.95 (0.65–1.39) |
| Q4 | 251 | 1.17 (0.76–1.82) | 1.33 (0.99–1.78) | 257 | 0.86 (0.52–1.41) | 0.81 (0.56–1.18) |
| Q5 | 279 | 1.75 (1.16–2.66) | 1.22 (0.91–1.64) | 290 | 0.94 (0.57–1.55) | 0.89 (0.61–1.29) |
| *P* for trend | | 0.004 | 0.13 | | 0.89 | 0.26 |
| Fibre (g) | | | | | | |
| Q1 | 16 | 1.0 (referent) | 1.0 (referent) | 18 | 1.0 (referent) | 1.0 (referent) |
| Q2 | 23 | 0.51 (0.33–0.77) | 0.88 (0.66 to 1.18) | 24 | 1.14 (0.70 to 1.85) | 1.13 (0.78 to 1.64) |
| Q3 | 27 | 0.57 (0.37–0.88) | 0.95 (0.71 to 1.28) | 27 | 1.19 (0.72 to 1.95) | 1.26 (0.87 to 1.82) |
| Q4 | 31 | 0.75 (0.49–1.14) | 0.78 (0.58 to 1.05) | 31 | 0.85 (0.2 to 1.40) | 0.99 (0.69 to 1.45) |
| Q5 | 42 | 0.57 (0.37–0.87) | 0.66 (0.48 to 0.89) | 18 | 0.71 (0.44 to 1.17) | 1.0 (referent) |
| *P* for trend | | 0.0714 | 0.0329 | | 0.0113 | 0.0006 |

†For Cockcroft-Gault clearance <50 mL/min per 1.73 $m^2$. ‡Adjusted for age, gender, smoking status, presence of cardiovascular diseases, hypertension, gout (first cross-section only), cancer, blood cholesterol, fibrinogen and haemoglobin. §For modified Modification of Diet in Renal Disease (MDRD) equation <60 mL/min per 1.73 $m^2$. CG, Cockcroft-Gault; CI, confidence interval; CKD, chronic kidney disease; OR, odds ratio.

general, this would be more frequent in patients with more advanced CKD, compared with our outcome of interest, a Cockcroft-Gault clearance <50 mL/min per 1.73 $m^2$, but we may not completely rule out such residual confounding as information on whether patients were on conservative treatment (which includes specific diets) for CKD were not collected.

We measured the total fluid content of foods and drinks assessed in the FFQ, rather than from water consumption; the main drinks included in the FFQ were tea, coffee, milk, juices, sweetened drinks and alcohol. The FFQ did not include a specific question about water consumption, so it is likely that the total fluid content reported is an underestimate. The average range of fluid intake in our study was 1.7 to 3.3 L/day, with a mean fluid intake of 2.5 L. This compares favourably with another large population-based study in Australia (National Nutrition Survey 95), in which the mean intake of fluid (including water) of those 65 years and older was 2.9 L/day.[37] Our study was not designed to determine whether water was more beneficial than other forms of fluid. Similarly, we were unable to determine whether naturally occurring sources of fibre, magnesium and phosphorus were more or less beneficial than supplements. We could not include supplement data for some of the nutrients because information from the supplement database was found to be unreliable during our analysis. Their exclusion, however, has been identified as resulting at most in non-differential error as previously reported.[38]

Finally, our outcome measure (which was identified a priori) was based on the Cockcroft-Gault measure of GFR. This was the standard at the time when our first cross-sectional analysis was performed. Other measures of GFR have been more broadly adopted recently, including the MDRD and modified MDRD equations, despite having been only validated in selected populations.[39] We validated our primary analyses by using a more recent definition of moderate CKD, that is using an MDRD GFR <60 mL/min per 1.73 $m^2$ as the outcome. Our conclusions were robust, however, to all definitions of CKD used.

In summary, our data suggest that higher daily fluid intakes (at least 3 L) and certain nutrients may reduce the likelihood of having CKD. Given the strength of these associations, confirmation is required with longitudinal data and a randomized trial, although adherence to a dietary intervention would be challenging. These low-cost interventions have the potential to reduce CKD by about 50%. Until better-quality evidence is available, a high fluid intake should be encouraged strongly.[40,41]

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## REFERENCES

1. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am. J. Kidney Dis.* 2003; **41**: 1–12.
2. Atkins RC. The changing patterns of chronic kidney disease: The need to develop strategies for prevention relevant to different regions and countries. *Kidney Int.* 2005; **68**: S83–5.
3. Best PJ, Reddan DN, Berger PB, Szczech LA, McCullough PA, Califf RM. Cardiovascular disease and chronic kidney disease: Insights and an update. *Am. Heart J.* 2004; **148**: 230–42.
4. Jones CA, McQuillan GM, Kusek JW *et al*. Serum creatinine levels in the US population: Third National Health and Nutrition Examination Survey. *Am. J. Kidney Dis.* 1998; **32**: 992–9.
5. Xue JL, Ma JZ, Louis TA, Collins AJ. Forecast of the number of patients with end-stage renal disease in the United States to the year 2010. *J. Am. Soc. Nephrol.* 2001; **12**: 2753–8.
6. Sarnak MJ, Levey AS, Schoolwerth AC *et al*. Kidney disease as a risk factor for development of cardiovascular disease: A statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology and Epidemiology and Prevention. *Circulation* 2003; **108**: 2154–69.
7. Shlipak MG, Simon JA, Grady D, Lin F, Wenger NK, Eurberg CD. Renal insufficiency and cardiovascular events in postmenopausal women with coronary heart disease. *J. Am. Coll. Cardiol.* 2001; **38**: 705–11.
8. Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: The HOPE randomized trial. *Ann. Intern. Med.* 2001; **134**: 629–36.
9. Nass CM, Reck K. Clinical challenges: The intersection of diabetes, chronic kidney disease, and cardiovascular disease. *Curr. Diab. Rep.* 2004; **4**: 1–2.
10. Chua DY, Bakris GL. Diabetes and chronic kidney disease: Tragedy and challenge. *Blood Purif.* 2004; **22**: 130–35.
11. Cases A. New cardiovascular risk factors and chronic kidney disease. Hypertrophy of the left ventricle. Atrial fibrillation. Smoking. Obesity. Emerging cardiovascular risk factors: Homocysteine, reactive C protein. Fibrinogen. *Nefrologia* 2004; **24**: 62–72.
12. Szromba C. Smoking in chronic kidney disease. *Nephrol. Nurs. J.* 2003; **30**: 578–89.
13. Wheeler DC. Does lipid-lowering therapy slow progression of chronic kidney disease? *Am. J. Kidney Dis.* 2004; **44**: 917–20.
14. Shoham DA, Vupputuri S, Kshirsagar AV. Chronic kidney disease and life course socioeconomic status: A review. *Adv. Chronic Kidney Dis.* 2005; **12**: 56–63.
15. Fathi R, Isbel N, Short L, Haluska B, Johnson D, Marwick TH. The effect of long-term aggressive lipid lowering on ischemic and atherosclerotic burden in patients with chronic kidney disease. *Am. J. Kidney Dis.* 2004; **43**: 45–52.
16. Krane V, Wanner C. The metabolic burden of diabetes and dyslipidaemia in chronic kidney disease. *Nephrol. Dial. Transplant.* 2002; **17**: 23–7.
17. Heintz R. *Kidney in the Hospital and in Out-Patient*. Stutt-gart: Georg Thieme Verlag, 1964.

18. Stefanski A, Ritz E, Amann K. Factors affecting progression of renal failure-Experimental data. In: Kopple JD, Massry SG (eds). *Nutritional Management of Renal Disease*. Baltimore: Williams & Wilkins, 1997; 277–316.
19. Wenzel UO, Hebert LA, Stahl RAK, Krenz I. My doctor said I should drink a lot! Recommendations for fluid intake in patients with chronic kidney disease. *Clin. J. Am. Soc. Nephrol.* 2006; **1**: 344–6.
20. Mitchell P, Smith W, Attebo K, Wang JJ. Prevalence of age-related maculopathy in Australia. The Blue Mountains Eye Study. *Ophthalmology* 1995; **102**: 1450–60.
21. Cumming RG, Mitchell P, Leeder SR. Use of inhaled corticosteroids and the risk of cataracts. *N. Engl. J. Med.* 1997; **337**: 8–14.
22. Cugati S, Kifley A, Mitchell P, Wang JJ. Temporal trends in the age-specific prevalence of diabetes and diabetic retinopathy in older persons: Population-based survey findings. *Diabetes Res. Clin. Pract.* 2006; **74**: 301–8.
23. Foran S, Wang JJ, Mitchell P. Causes of visual impairment in two older population cross-sections: The Blue Mountains Eye Study. *Ophthalmic Epidemiol.* 2003; **10**: 215–25.
24. Willett WC, Sampson L, Browne ML *et al*. The use of a self-administered questionnaire to assess diet four years in the past. *Am. J. Epidemiol.* 1988; **127**: 188–99.
25. Flood VM, Smith WT, Webb KL, Mitchell P. Issues in assessing the validity of nutrient data obtained from a food-frequency questionnaire: Folate and vitamin B12 examples. *Public Health Nutr.* 2004; **7**: 751–6.
26. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; **16**: 31–41.
27. Department of Commonwealth Services and Health. *NUTTAB90 and NUTTAB95 Nutrient Data Tables for Use in Australia*. Canberra: Australian Government Publishing Services, 1990; 1995.
28. Willett WC, Stampfer MJ. Total energy intake: Implications for epidemiologic analyses. *Am. J. Epidiol.* 1986; **124**: 17–27.
29. Bouby N, Bachman S, Bichet D, Bankir L. Effect of water intake on the progression of chronic renal failure in 5/6 nephrectomized rat. *Am. J. Physiol.* 1990; **258**: 973–99.
30. Hirvonen T, Pietinen P, Virtanen M, Albanes D, Virtamo J. Nutrient intake and use of beverages and the risk of kidney stones among male smokers. *Am. J. Epidemiol.* 1999; **150**: 187–94.
31. Taylor EN, Stampfer MJ, Curhan GC. Dietary factors and the risk of incident kidney stones in men: New insights after 14 years of follow-up. *J. Am. Soc. Nephrol.* 2004; **15**: 3225–32.
32. Appel LJ, Moore TJ, Obarzanek E *et al*. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N. Engl. J. Med.* 1997; **336**: 1117–24.
33. Waijers PM, Ocke MC, van Rossum CT *et al*. Dietary patterns and survival in older Dutch women. *Am. J. Clin. Nutr.* 2006; **83**: 1170–76.
34. Song Y, Manson JE, Buring JE, Liu S. Dietary magnesium intake in relation to plasma insulin levels and risk of type 2 diabetes in women. *Diabetes Care* 2004; **27**: 59–65.
35. Balon TW, Gu JL, Tokuyama Y, Jasman AP, Nadler JL. Magnesium supplementation reduces development of diabetes in a rat model of spontaneous NIDDM. *Am. J. Physiol.* 1995; **269**: E745–52.
36. Saris NE, Mervaala E, Karppanen H, Khawaja JA, Lewenstam A. Magnesium. An update on physiological, clinical and analytical aspects. *Clin. Chim. Acta* 2000; **294**: 1–26.
37. ABS. National Nutrition Survey, Foods Eaten, Australia. Australian Bureau of Statistics: Camberra, Cat No 4804.0. 1999 (McLennan W and Podger A).
38. Kuzniarz M, Mitchell P, Cumming RG, Flood VM. Use of vitamin supplements and cataract: The Blue Mountains Eye Study. *Am. J. Ophthalmol.* 2000; **132**: 19–26.
39. Kuan Y, Hossain M, Surman J, El Nahas AM, Haylor J. GFR prediction using the MDRD and Cockcroft and Gault equations in patients with end-stage renal disease. *Nephrol. Dial. Transplant.* 2005; **20**: 2394–401.
40. NHMRC. Editor: Colin Binns. Dietary Guidelines for Older Australians. Commonwealth of Australia, 1999.
41. NHMRC and Dept Health and Ageing. Nutrient Reference Values for Australia and New Zealand. Commonwealth of Australia. 2006.