

Caffeine consumption and mortality in chronic kidney disease: a nationally representative analysis

Miguel Bigotte Vieira^{1,*}, Rita Magriço^{2,*}, Catarina Viegas Dias³, Lia Leitão⁴ and João Sérgio Neves^{5,6}

¹Nephrology and Renal Transplantation Department, Centro Hospitalar Lisboa Norte, Lisbon, Portugal, ²Nephrology Department, Hospital Garcia de Orta, Almada, Portugal, ³NOVA Medical School, Lisbon, Portugal, ⁴Neurology Department, Hospital Prof. Doutor Fernando Fonseca, Amadora, Portugal, ⁵Department of Endocrinology, Diabetes and Metabolism, Centro Hospitalar de São João, Porto, Portugal and ⁶Department of Surgery and Physiology, Cardiovascular Research Center, Faculty of Medicine, University of Porto, Porto, Portugal

Correspondence and offprint requests to: Miguel Bigotte Vieira; E-mail: mbigottevieira@gmail.com

*These authors contributed equally to the present study.

ABSTRACT

Background. An inverse relationship between coffee consumption and mortality has been reported in the general population. However, the association between caffeine consumption and mortality in patients with chronic kidney disease (CKD) remains uncertain.

Methods. We analysed 4863 non-institutionalized USA adults with CKD [defined by an estimated glomerular filtration rate (eGFR) of 15–60 mL/min/1.73 m² and/or a urinary albumin:creatinine ratio >30 mg/g] in a nationwide study using the National Health and Nutrition Examination Survey (NHANES) 1999–2010. Caffeine consumption was evaluated by 24-h dietary recalls at baseline and all-cause, cardiovascular and cancer mortality were evaluated until 31 December 2011. We also performed an analysis of caffeine consumption according to its source (coffee, tea and soft drinks). Quartiles of caffeine consumption were <28.2 mg/day (Q1), 28.2–103.0 (Q2), 103.01–213.5 (Q3) and >213.5 (Q4).

Results. During a median follow-up of 60 months, 1283 participants died. Comparing with Q1 of caffeine consumption, the adjusted hazard ratio for all-cause mortality was 0.74 [95% confidence interval (CI) 0.60–0.91] for Q2, 0.74 (95% CI 0.62–0.89) for Q3 and 0.78 (95% CI 0.62–0.98) for Q4 ($P=0.02$ for trend across quartiles). There were no significant interactions between caffeine consumption quartiles and CKD stages or urinary albumin:creatinine ratio categories regarding all-cause mortality.

Conclusions. We detected an inverse association between caffeine consumption and all-cause mortality among participants with CKD.

Keywords: caffeine, coffee, CKD, cancer, cardiovascular

INTRODUCTION

Caffeine is consumed in several types of beverages, mainly coffee, tea and soft drinks. It is estimated that ~89% of the adult USA population consumes caffeine daily [1]. Thus the

detection of even a small health-promoting effect associated with caffeine consumption could have a substantial impact on public health.

Chronic kidney disease (CKD) is associated with increased health care costs and high morbidity and mortality. Approximately 14% of adults in the USA have CKD and the prevalence of CKD is expected to continue to increase worldwide [2–4].

Previous epidemiological studies have suggested an association between coffee consumption and slower progression of CKD [5–8]. An inverse relationship between coffee consumption and mortality has been reported in the general population [7, 9]. However, the association between caffeine consumption and mortality in patients with CKD remains unclear.

We hypothesized that caffeine consumption might be associated with lower mortality among participants with CKD. We examined the National Health and Nutrition Examination Survey (NHANES) 1999–2010 database to evaluate the effect of caffeine consumption and caffeine source on all-cause, cardiovascular and cancer mortality among participants with CKD.

MATERIALS AND METHODS

Study design and population

We performed an analysis of the NHANES database. The NHANES is a periodic survey conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC). The NHANES is a stratified, multistage survey using a nationally representative sample of the non-institutionalized civilian population of the USA. Participants are selected at random through a complex statistical process each year and they complete personal structured interviews at home and then undergo a physical examination at a mobile examination centre, including height, weight and laboratory measurements [10]. The NCHS Research Ethics Review Board reviewed and approved the NHANES and all participants

provided written informed consent. We used data from 1999 to 2010 (62 160 people). We restricted our analysis to non-pregnant individuals ≥ 18 years of age (33 931 subjects) and included only participants with CKD [defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² (using the Chronic Kidney Disease Epidemiology Collaboration equation) and/or a urinary albumin:creatinine ratio > 30 mg/g] (5696 subjects). We excluded participants with CKD Stage 5 and participants that were either on haemodialysis or peritoneal dialysis (107 subjects).

We also excluded from our analysis participants with missing information on mortality (five subjects). In order to assess the quality and completeness of a survey participant's response to the dietary recall section, we used the dietary recall status evaluated by the interviewer and only included the ones that were classified as 'reliable and met the minimum criteria'. Finally, 4863 participants were included in our analysis.

Caffeine consumption and nutritional assessment

In all cycles of the NHANES 1999–2010, a 24-h dietary recall was collected. All food items and quantities consumed in the 24 h preceding the interview were recorded using an automated multiple-pass method. For participants in the 1999–2002 NHANES, only one in-person 24-h dietary recall was performed. The cycles starting from 2003 onwards included two recalls. The first recall in person and the second one via telephone were collected 3–10 days after the first dietary interview but not on the same day of the week. We used the nutritional information from foods and beverages collected in the single 24-h dietary recall to calculate the caffeine, energy and nutrient intakes of participants in the 1999–2002 NHANES. For participants in the 2003–10 NHANES we used the mean of the nutritional information from both recalls [11]. The NHANES included information regarding the nutrient source by the type of food ingested. These data were used to ascertain the quantity of caffeine ingested from coffee, tea or soft drink for each participant. We evaluated the impact of caffeine consumption obtained from each of the three types of drinks on different outcomes.

Participants were grouped according to the quartile of daily intake of caffeine from all sources. Due to a lower number of participants with caffeine intake from coffee, tea and soft drinks, and due to the high variability of caffeine in these beverages, we divided these participants into three categories: no consumption, consumption below median and consumption above median.

STUDY OUTCOMES

The primary outcome was time to death. As secondary outcomes we used time to cardiovascular mortality and time to death by cancer. Mortality status and cause of mortality were determined by NHANES-linked National Death Index public-access files through 31 December 2011.

Statistical analysis

All calculations took into account the complex survey design of the NHANES database and were analysed according to the

CDC analytic recommendations [12]. The sample weight that was used was the 'day 1 dietary weight'. We computed combined weights in accordance with the NHANES Analytic Reporting Guidelines. Survey procedures were used in all analyses to account for the complex, stratified, multistage probability sample design of the NHANES. The method used for variance estimation was the Taylor linearized variance estimation. To assess the crude association between caffeine consumption and time to death, we performed a Kaplan–Meier curve and log-rank test. We performed a Cox proportional hazards model (Model 1) adjusted for the following potential confounders: age, gender, race (Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black and other), annual family income ($< \$25 000$, $\$25 000$ – $\$75 000$ and $> \$75 000$), smoking status (never smoker, current smoker or former smoker), CKD stage, eGFR (> 90 , 60 – 90 , 30 – 59 and 15 – 29 mL/min/1.73 m²) and urinary albumin:creatinine ratio (0 – 30 , 30 – 300 and > 300 mg/g). We also performed a second model (Model 2) including the previously mentioned variables plus the following: education level (< 9 th grade, 9 th– 11 th grade, high school graduate, some college or associate's degree, college graduate and above), alcohol consumption (no alcohol consumption, < 20 g/day, ≥ 20 g/day), daily carbohydrate consumption (grams of carbohydrate/100 kcal), polyunsaturated:saturated fatty acids ratio, dietary protein (g/100 kcal), dietary fibre (g/100 kcal), dietary potassium (mg), body mass index (BMI; < 20.0 , 20.0 – < 25.0 , 25.0 – < 30.0 , 30.0 – < 35.0 , 35.0 – < 40.0 and ≥ 40.0 kg/m²), diabetes mellitus, hypertension, dyslipidaemia, previous myocardial infarction and previous stroke. We assessed the extent to which CKD stage and urinary albumin:creatinine ratio modified the effect of caffeine consumption on mortality with a likelihood ratio test for interaction. We also performed a sensitivity analysis excluding patients that died during the first 12 months of follow-up.

Multiple imputation by chained equations was used for dealing with missing data regarding covariates [13]. Twenty imputations per missing observation were performed. A test for trend over increasing caffeine consumption categories was conducted where each category median was modelled as a continuous variable in the regression. Continuous variables are presented as means with standard deviations except for polyunsaturated:saturated fatty acids ratio, fibre, eGFR and urinary albumin:creatinine ratio, which were summarized using median (interquartile range) due to their right-skewed distributions. Categorical variables are presented as percentages with 95% confidence intervals (CIs). A two-sided P-value < 0.05 was considered statistically significant. Analyses were performed using Stata version 14.2 (StataCorp, College Station, TX, USA).

RESULTS

Association of caffeine consumption with dietary, demographic and clinical characteristics

Caffeine consumption at baseline was associated with several other dietary, demographic and clinical characteristics (Table 1). Compared with people who consumed a smaller amount of caffeine-containing beverages, caffeine consumers

Table 1. Baseline characteristics of the study participants

Baseline characteristics	Caffeine consumption quartile			
	Q1 (<28.20 mg/day)	Q2 (28.20–103.00 mg/day)	Q3 (103.01–213.50 mg/day)	Q4 (>213.50 mg/day)
Gender (male), %	39	35	40	56
Age (years), mean (SD)	61 (20)	60 (20)	61 (18)	59 (16)
Non-Hispanic white, %	64	67	76	87
Annual family income <\$25 000, %	48	42	40	34
Education level: <9th grade, %	15	13	11	8
Current smokers, %	11	11	15	28
Former smokers, %	30	33	38	41
Caffeine consumption (mg/day), median (IQR)	3 (0–10)	65 (48–86)	148 (124–178)	316 (256–446)
Alcohol consumption >20 /day, %	10	8	9	14
Carbohydrates per day (g/100 kcal), mean (SD)	12.7 (2.7)	12.6 (2.4)	12.5 (2.5)	11.8 (2.5)
Polyunsaturated:saturated fatty acids ratio, median (IQR)	0.69 (0.45–0.96)	0.64 (0.47–0.88)	0.67 (0.49–0.92)	0.62 (0.43–84)
Fibre per day (g/100 kcal), median (IQR)	0.82 (0.60–1.11)	0.80 (0.58–1.05)	0.80 (0.58–1.10)	0.74 (0.55–0.97)
Potassium per day (mg), mean (SD)	2378 (1111)	2333 (1066)	2466 (959)	2912 (1106)
Protein per day (g/100 kcal), mean (SD)	4.1 (1.2)	4.00 (1.0)	4.0 (1.1)	4.0 (1.1)
BMI (kg/m ²), mean (SD)	28.8 (6.8)	29.3 (7.1)	29.4 (7.3)	29.6 (6.9)
eGFR, median (IQR)	66 (51–97)	61 (50–99)	67 (52–96)	67 (53–94)
Urinary albumin:creatinine ratio, median (IQR)	44 (17–90)	42 (13–98)	37 (13–76)	42 (12–102)
Diabetes, %	23	23	22	25
Hypertension, %	56	55	55	52
Dyslipidaemia, %	53	50	49	53
Previous cardiac infarct, %	18	13	14	16
Previous stroke, %	10	8	9	7

Continuous variables are presented as means with standard deviations except for polyunsaturated:saturated fatty acids ratio, fibres, eGFR and urinary albumin:creatinine ratio, which were summarized using median (interquartile range) due to their right-skewed distributions. Categorical variables are presented as percent with 95% confidence intervals (CIs). IQR, interquartile range; Q, quartile.

were more likely to be male, non-Hispanic white, have a higher education level and higher annual income, be current or former smokers, have higher alcohol consumption and have fewer previous strokes. Regarding dietary factors, they ingested more potassium and less carbohydrates and fibres and had a lower polyunsaturated:saturated fatty acids ratio.

Caffeine consumption and mortality

During a median follow-up of 60 months (27 724 total person-years), 1283 (26%) participants died. In the unadjusted analysis (Figure 1), and also after multivariable analysis (Table 2), an inverse association between caffeine and all-cause mortality was observed among participants with CKD. Comparing with the first quartile (Q1) of caffeine consumption, the adjusted hazard ratio (HR) for all-cause mortality was 0.74 (95% CI 0.60–0.91) for Q2, 0.75 (95% CI 0.61–0.92) for Q3 and 0.75 (95% CI 0.59–0.97) for Q4 ($P=0.02$, for trend across quartiles).

Specific causes of mortality were also examined. There were 368 deaths due to cardiovascular events and 226 deaths due to cancer. In the univariate and also multivariable analysis, there was no significant association between caffeine consumption and cardiovascular or cancer mortality (Table 2).

There was no significant interaction between caffeine consumption quartiles and CKD stages regarding all-cause mortality. There was no significant interaction between caffeine consumption quartiles and urinary albumin:creatinine ratio categories regarding all-cause mortality (Figure 2).

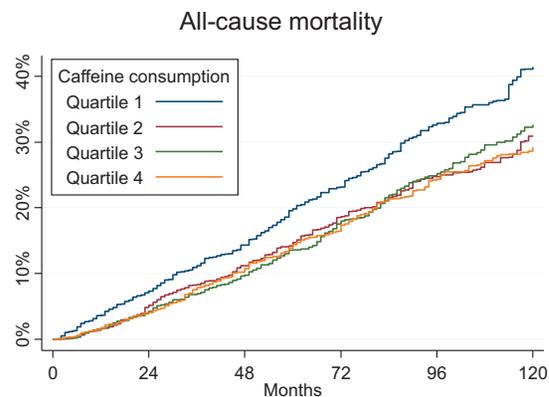


FIGURE 1: Kaplan–Meier curves for all-cause mortality by caffeine consumption quartiles.

The sensitivity analysis, which excluded patients that died during the first 12 months of follow-up, presented results that were consistent with the main analyses (Supplementary data, Table S4).

Source of caffeine consumption and mortality

An analysis of caffeine consumption according to its source (coffee, tea and soft drinks) was also performed (Supplementary data, Tables S1–S3). In the adjusted analysis, no significant association between caffeine consumption from coffee and all-cause mortality was observed in patients with CKD. Comparing with

Table 2. Association of caffeine consumption with all-cause, cardiovascular and cancer mortality

Outcomes	Q1 (<28.20 mg/day)	Q2 (28.20-103.00 mg/day)	Q3 (103.01-213.50 mg/day)	Q4 (>213.50 mg/day)	P-value for trend
All-cause mortality					
Deaths, <i>n</i> (%)	397 (28)	318 (24)	311 (26)	257 (27)	
Unadjusted HR	–	0.74 (0.60–0.91)	0.73 (0.59–0.90)	0.69 (0.55–0.87)	0.001
Model 1 aHR	–	0.74 (0.61–0.90)	0.74 (0.60–0.90)	0.66 (0.61–0.96)	0.02
Model 2 aHR	–	0.74 (0.60–0.91)	0.75 (0.61–0.92)	0.75 (0.59–0.97)	0.02
CV mortality					
Deaths, <i>n</i> (%)	106 (8)	94 (7)	88 (7)	80 (8)	
Unadjusted HR	–	0.84 (0.57–1.25)	0.91 (0.64–1.29)	0.94 (0.61–1.46)	0.9
Model 1 aHR	–	0.85 (0.59–1.24)	0.93 (0.63–1.36)	1.06 (0.63–1.80)	0.8
Model 2 aHR	–	0.82 (0.57–1.19)	0.91 (0.63–1.31)	1.12 (0.68–1.85)	0.7
Cancer mortality					
Deaths, <i>n</i> (%)	70 (5)	46 (4)	57 (5)	53 (6)	
Unadjusted HR	–	0.71 (0.45–1.12)	0.81 (0.56–1.16)	0.89 (0.57–1.38)	0.7
Model 1 aHR	–	0.78 (0.48–1.26)	0.82 (0.56–1.21)	0.85 (0.53–1.237)	0.5
Model 2 aHR	–	0.80 (0.49–1.30)	0.85 (0.58–1.26)	0.90 (0.54–1.52)	0.7

Continuous variables are presented as means with standard deviations. Categorical variables are presented as percent with 95% confidence intervals (CIs).

Model 1 adjusted for age, gender, race, annual family income, smoking status, CKD stage and urinary albumin:creatinine ratio. Model 2 adjusted for variables included in Model 1 plus education level, alcohol consumption, daily carbohydrate consumption, polyunsaturated:saturated fatty acids ratio, dietary protein, dietary fibre, dietary potassium, BMI, diabetes mellitus, hypertension, dyslipidaemia, previous myocardial infarction and previous stroke.

P-values <0.05 are highlighted in bold.

aHR, adjusted hazard ratio; CV, cardiovascular; Q, quartile.

the no consumption group, the adjusted HR was 0.92 (95% CI 0.77–1.11) for the below median group and 0.88 (95% CI 0.71–1.09) for the above median group ($P = 0.2$ for trend across categories). There were also no associations between caffeine consumption from coffee and cardiovascular or cancer mortality.

Regarding caffeine consumption from soft drinks, an inverse association between caffeine and all-cause mortality was found in patients with CKD. Comparing with the no consumption group, the adjusted HR was 0.77 (95% CI 0.60–1.00) for the below median group and 0.69 (95% CI 0.49–0.98) for the above median group ($P = 0.04$ for trend across categories). This association was not observed for cardiovascular or cancer mortality. No significant association between caffeine consumption from tea and all-cause, cardiovascular or cancer mortality was found.

DISCUSSION

Our study showed an inverse association between caffeine and all-cause mortality among participants with CKD. We did not detect a significant association between caffeine consumption and cardiovascular mortality or cancer mortality. There were no significant interactions between caffeine consumption quartiles and CKD stages or urinary albumin:creatinine ratio categories regarding all-cause mortality. Consequently, caffeine consumption appears to be safe through different stages of kidney disease.

Coffee consumption has multiple health-related effects. Coffee consumption has been shown to decrease uric acid levels and increase adiponectin and magnesium levels [14, 15]. An association between coffee consumption and increased eGFR has been detected [16]. However, the higher eGFR among coffee consumers does not appear to result from glomerular hyperfiltration [17]. The addition of a small amount of sugar to coffee does not seem to alter the effect on eGFR [18].

The possible protective effect of coffee might be conferred by the presence of caffeine and antioxidants [19]. Caffeine is a

xanthine that increases intracellular calcium and stimulates the production of nitric oxide through the expression of the endothelial nitric oxide synthase enzyme. Nitric oxide diffuses to the vascular smooth muscle cells and causes vasodilation [20]. Caffeine stimulates the cardiovascular system through the blockade of vascular adenosine receptors [21].

An inverse relationship between coffee consumption and mortality has been observed in the general population and also in different racial/ethnic groups [7]. An analysis of the Multiethnic Cohort from 1993 to 2012, including 185 855 Native Hawaiians, African Americans, Japanese Americans, Latinos and whites 45–75 years of age at recruitment, detected an inverse association between coffee consumption and deaths due to heart disease, cancer, respiratory disease, stroke, diabetes and kidney disease in these ethnic groups, excluding Native Hawaiians [7]. An analysis of three large prospective cohorts detected a significant inverse association between coffee consumption and deaths attributed to cardiovascular disease, neurologic diseases and suicide. However, no significant association between coffee consumption and total cancer mortality was found [5]. Also, in a large prospective US cohort study there was a dose-dependent inverse association between coffee drinking and mortality from all causes, and specifically from heart disease, respiratory disease, stroke, injuries and accidents, diabetes and infections [22].

The possible protective effect of caffeine consumption in all-cause mortality was also detected when the analysis was performed according to caffeine consumption from soft drinks. This association was not expected in patients with CKD who consumed soft drinks. Sicker patients may avoid soft drinks with caffeine or the consumption of soft drinks may be associated with protective behaviours not evaluated in the current study (e.g. physical activity). The possible protective effect of caffeine consumption in all-cause mortality was not observed when the analysis was performed according to caffeine

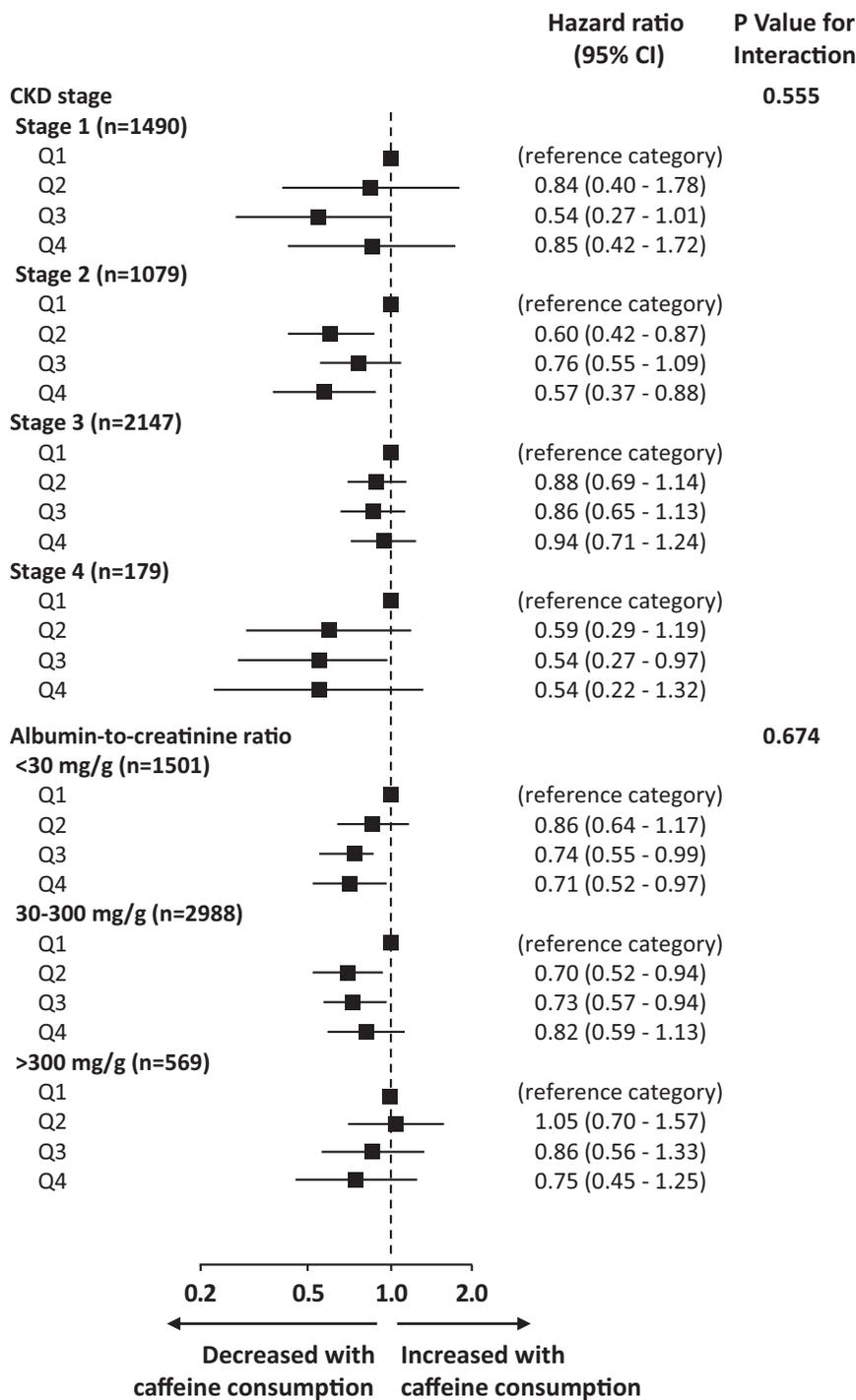


FIGURE 2: HRs for all-cause mortality by CKD stage and urinary albumin:creatinine ratio. Adjusted for age, gender, race, annual family income, smoking status, CKD stage and urinary albumin:creatinine ratio, education level, alcohol consumption, daily carbohydrate consumption, polyunsaturated:saturated fatty acids ratio, dietary protein, dietary fibre, dietary potassium, BMI, diabetes mellitus, hypertension, dyslipidemia, previous myocardial infarction and previous stroke. For CKD stage, model was also adjusted for urinary albumin:creatinine ratio. Q, quartile.

consumption from coffee or tea. We hypothesize that this may be due to a lack of statistical power.

Considering the mean caffeine content per unit of caffeinated beverage (95 mg in 8 oz. of coffee, 48 mg in 8 oz. of tea and 30 mg in 12 oz. of cola), even small quantities of commonly consumed beverages may confer a protective effect regarding

all-cause mortality in patients with CKD [23]. However, the mechanism that confers the protective effect of caffeine consumption is uncertain. It is possible that the same mechanism that justifies the inverse relationship between coffee consumption and mortality reported in the general population also exists with caffeine in patients with CKD [7].

Regarding the strengths of our study, note that the NHANES includes a large number of patients who are non-institutionalized, and NHANES data were systematically collected and included hard outcome measures such as all-cause mortality. The presence of detailed information about the participants allowed for adjustment for the main biologically plausible confounders. As the database includes comprehensive information regarding CKD, NHANES survey data have previously been used to study this disease [24–33]. To our knowledge this is the first study to evaluate the effect of caffeine consumption on mortality in patients with CKD using a large database representative of the USA population.

Considering the limitations of our study, caffeine consumption was evaluated by 24-h dietary recalls. It cannot be excluded that data generated using this method may not represent the long-term dietary habits of the participants. We consider that the inclusion of data from non-consecutive recalls to estimate usual dietary intake distributions minimizes this risk. Although we have included additional information regarding diet in the studied population (such as consumption of carbohydrates, saturated fats or fibres) in the analyses, no adjustment was performed for additives present in caffeine-containing beverages. Nonetheless, other studies showed a significant association between coffee consumption and decreased risk of all-cause mortality even after adjustment for coffee additives, such as cream, milk, sugar or honey [8, 34]. Non-food sources of caffeine were not considered in our study. However, these sources correspond only to a small proportion of caffeine ingestion [35]. The absence of association between caffeine consumption and specific causes of mortality may be due to inaccurate classification of the cause of death. However, regardless of the subjacent mechanism, the reduction in all-cause mortality is clinically relevant. As in all observational studies, our analysis has an exploratory nature. Therefore it is possible that residual confounding exists due to unmeasured variables. It is also possible that the differences found are due to chance, or that caffeine consumers also perform other protective behaviours, contributing to a healthy user effect. Physical activity, which may correlate with caffeine consumption, was not included in our analysis [36].

Future research should focus on the benefits of other compounds present in caffeine-containing beverages and on the association between caffeine consumption and mortality in other world regions. It is uncertain if caffeine consumption above a certain threshold may have deleterious health effects. In conclusion, this large observational study showed a significant inverse association between caffeine consumption and all-cause mortality among patients with CKD in the USA. If these results are to be confirmed by prospective studies, advising these patients to drink more caffeine may reduce their mortality. This would be a simple, clinically beneficial and inexpensive option in patients with CKD.

SUPPLEMENTARY DATA

Supplementary data are available at [ndt](#) online.

ACKNOWLEDGEMENTS

We thank the participants and staff of the NHANES.

AUTHORS' CONTRIBUTIONS

M.B.V., R.M., C.V.D., L.L. and J.S.N. contributed to the research idea, literature search, study design, statistical analysis and data analysis/interpretation. Each author contributed important intellectual content during manuscript drafting or revision.

CONFLICT OF INTEREST STATEMENT

None declared.

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Received: 26.2.2018; Editorial decision: 18.6.2018