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Dietary Factors and Prevention: Risk of End-Stage Kidney Disease by Fruit and Vegetable Consumption

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Abstract

Background: The association between fruit and vegetable (FV) intake and the risk of end-stage kidney disease (ESKD) has not been examined in the general population and fully explored in chronic kidney disease (CKD). We prospectively evaluated this relationship in US representative sample of adults and evaluated consistency by the presence or absence, and severity, of CKD.

Methods: We used data from the Third National Health and Nutrition Examination Survey (1988–1994) linked with the US Renal Data System, including 14,725 adults aged ≥20 years and

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Author Contributions

T.B., J.J.C., and N.R.P. were responsible for concept, analytic design, data analysis, interpretation of results, and manuscript preparation. C.E.M. helped with the interpretation of results and preparation of manuscript. H.M., R.S., N.R.B., and K.S. helped with the interpretation of results, gave thoughtful comments, and critically reviewed the manuscript.

Statement of Ethics

This study is approved by the University of California, San Francisco Institutional Review Board (Committee on Human Research application #10–04162) and by the Research Data Center of the National Center of Health Statistics (#1508).

Conflict of Interest Statement

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with follow-up for ESKD through 2008. Daily FV intake was ascertained using a food frequency questionnaire. We examined the association between selected categories of FV intake and ESKD using a Fine Gray competing risk model adjusting for sociodemographics, lifestyle, clinical and nutritional factors, estimated glomerular filtration rate, and albuminuria. We evaluated whether risk varied in individuals with severe versus any CKD.

Results: 230 participants (1.5%) developed ESKD during follow-up. In the adjusted model, compared to highest intake, those in lowest categories of FV intake had a higher risk of ESKD, for <2 times/day (1.45 [1.24–1.68]), 2 to <3 times/day (1.40 [1.18–1.61]), 3 to <4 times/day (1.25 [1.04–1.46]), and 4 to <6 times/day (1.14 [0.97–1.31]). There was suggestion of heterogeneity (p for interaction = 0.03) with possible stronger inverse association in patients with CKD than those without CKD. After stratification, we obtained similar strong inverse association when we examined ESKD incidence across intake of FVs in participants with CKD stages 1–4 ($n = 5,346$) and specifically in those with CKD stages 3–4 ($n = 1,084$).

Conclusions: Low intake of FVs was associated with higher risk of ESKD in US adults with and without CKD, supporting an emerging body of literature on the potential benefits of plant-rich diets for prevention of ESKD.

Introduction

Chronic kidney disease (CKD) is a prevalent complex disease and is fast becoming a growing public health problem, leading to premature mortality or poor quality of life, imposing a heavy burden on health-care systems [1, 2]. Available evidence reveals that the global prevalence of CKD has a sharply increasing trend from 2000 to 2016, affecting 10–15% of general populations [3]. Aging, hypertension, diabetes, hyperlipidemia, smoking, and poor dietary intake have been identified as risk factors for CKD occurrence [4, 5]. There is relatively little knowledge as to how to prevent CKD and most of the recommendations stem from lifestyle modifications extrapolated from lowering blood pressure and cardiovascular disease (CVD) risk [6, 7], which is lowering the intake of salt.

Diet may influence the occurrence of CKD. Studies examining adherence to a Mediterranean diet or a Dietary Approaches to Stop Hypertension (DASH) diet, or patterns of diet consistent with vegetarian, pro-vegetarian or healthy plant-based foods in the general population have shown consistent associations with a lower CKD prevalence and a lower incidence rate of CKD [8, 9]. Emerging evidence in patients with CKD suggests these diets may be helpful to delay progression to end-stage kidney disease (ESKD) and prevent complications [10]. Both the diets encourage whole foods, such as fruits, vegetables, beans/legumes, whole grains, and nuts with a restriction on the amount of animal protein consumed. However, it is not known whether a single component of these diets, that is, a higher intake of fruits and vegetables (FVs), associates with the lower risk of ESKD. The effectiveness of an increasing FV consumption has only been tested in selected patients with CKD stages 3–4 with hypertension and macroalbuminuria in a small trial, and FV intake was found to be as effective as sodium bicarbonate in delaying CKD decline [12, 13]. Despite such a positive association noted in individuals with advanced CKD, consuming FVs is traditionally discouraged in this group as a hyperkalemia prevention strategy [11]. The existence of an association between higher FV intake and lower risk of ESKD may

inform patient discussions in clinical practice around lifestyle modifications for primary prevention of CKD and secondary disease prevention of CKD such as CVD protection and type 2 diabetes. Delayed progression of CKD has major beneficial effects on both the patient and health-care system. Studies on the general population examining the impact of FV intake on the risk of ESKD have not been conducted, a mini review of the cohort studies available in literature is listed under Table 1.

This study aimed to examine the association between daily number FV intake at baseline and the incidence rate of ESKD in a US representative sample of adults. As a primary hypothesis, we evaluated whether associations differed among individuals with and without baseline CKD and whether they differ for those with severe CKD.

Materials and Methods

Study Design and Population

We analyzed a cohort using data from the Third National Health and Nutrition Examination Survey (NHANES III) that were linked with the United States Renal Data System (USRDS) and Mortality files by the Centers for Disease Control and Prevention's National Center for Health Statistics (NCHS) ($n = 18,825$ adults). NHANES III is a nationally representative probability survey of US noninstitutionalized civilians conducted between 1988 and 1994 by the NCHS. We excluded 1,225 NHANES III adults younger than 20 years of age, 61 participants with missing dietary information, 105 participants who were pregnant, and 2,709 participants were ineligible for linkage resulting in an analytic sample of 14,725. The linked NHANES III-USRDS-Mortality files contain information on participants diagnosed with ESKD and mortality follow-up data from the start of NHANES III participation to the end of the linkage interval. The ESKD data used were from the Combined ESKD Patient Profile and Death Notification (form 2746) File. This information was based on the results from linking NHANES III participant data, USRDS administrative records, and the National Death Index (NDI) death certificate records (based on probabilistic techniques), the details of which are provided elsewhere [14, 15]. We chose the criteria for linkage defined for the USRDS records as they were more stringent than the criteria defined for NDI records. The linkage eligibility variable (CMS_Medicare_Match) in the NCHS-CMS Medicare feasibility file was used and participants were linked to the USRDS records if the linkage eligibility variable took the value 1 (i.e., for linkage eligibility and linked).

Sociodemographic and Clinical Measurements

Medical history and demographic data were collected through a standardized questionnaire conducted at the participant's home followed by a medical examination and laboratory testing that occurred in a mobile examination center [16]. Sociodemographic factors were also assessed during the interview. Racial/ethnic categories were self-reported by NHANES III participants and assigned as non-Hispanic white (NHW), non-Hispanic black (NHB), Mexican American (MA), or other race/ethnicities. Self-reported information on socioeconomic status (SES), that is, education and income, were also included. Self-reported income was assessed using the ratio of household income to the US household poverty level (poverty income ratio) [16].

Diabetes (other than during pregnancy) was defined by measured hemoglobin A1C (HbA1C) $\geq 6.5\%$ [17]. Hypertension was defined as a measured average of systolic blood pressure (SBP) ≥ 140 mm Hg [18, 19]. Body mass index (BMI) was calculated as weight in kilograms divided by the measured height in meters squared. A physical activity questionnaire was administered at a home interview for all participants. They were asked about the frequency of leisure time activity in the past month. This included the frequency of walking a mile without stopping, running or jogging, riding a bicycle or exercise bike, swimming, aerobics, dancing, calisthenics, garden or yard work, lifting weights, or other activities.

FV Intake

Dietary intake was collected through an in-person food frequency questionnaire (FFQ) conducted by interviewers with a knowledge of food preparation and nutrient composition. Specifically, from the NHANES III FFQ, 2 sections on fruits (questions, namely, HAN3AS, HAN3BS, HAN3CS, HAN3DS, HAN3ES, and HANFS) and vegetables (questions, namely, HAN4AS, HAN4BS, HAN4CS, HAN4DS, HAN4ES, HAN4FS, HAN4GS, HAN4HS, HAN4IS, HAN4JS, HAN4KS, and HAN4LS) asked questions to assess how many times per day, week, or month (over the past 30 days) the participants consumed fruits and vegetables.

Meat and fish intake was determined by the questions asked in the FFQ, such as consumption of (1) bacon/sausage/processed meats; (2) liver and other organ meats; (3) beef; (4) pork and ham; (5) shrimp, clams, etc.; and (6) fish, and was treated as a continuous variable. Daily frequency of intake was calculated by dividing reported intake by 30 for intake reported by month or by 7 for those reporting weekly [20]. Food codes, food weight, and nutrient values were based on data from the US Department of Agriculture, industry, and other sources [21].

Measurement of Albuminuria and Kidney Function and Classification of CKD

Serum creatinine measurements obtained using a kinetic rate Jaffé method in NHANES III were recalibrated to standardized creatinine measurements obtained at the Cleveland Clinic Research Laboratory (Cleveland, OH, USA) as standard creatinine = $0.184 + 0.960 \times$ measured serum creatinine [22]. Random spot urine samples were obtained and frozen. Urine albumin was measured using a solid-phase fluorescence immunoassay, and urine creatinine was measured using the modified Jaffé kinetic method in the same laboratory. Estimated glomerular filtration rate (eGFR) was calculated through determination of SCr using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [23]. Albuminuria, which is calculated as the urinary albumin-to-creatinine ratio (UACR), is expressed as milligrams of albumin per gram of creatinine (mg/g Cr) using American Diabetes Association categories: normal (<30 mg/g Cr), and albuminuria (≥ 30 mg/g Cr) [24]. We defined the stages of CKD at baseline according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative CKD classification [25] based on the level of kidney function (eGFR) and the presence or absence of kidney damage (albuminuria). CKD stages 1 and 2 was defined by single assessment of albuminuria (i.e., no estimation of persistence) and eGFR ≥ 90 and $60\text{--}89$ mL/min/1.73 m², respectively, while stages 3 and 4 were defined as $30\text{--}59$ and $15\text{--}29$ mL/min/1.73 m², respectively.

Outcomes

The development of ESKD, that is, initiation of maintenance dialysis or kidney transplantation, was defined as entry into the (USRDS) Registry from the time of enrollment into NHANES III through December 31, 2008. ESKD data are available for those NHANES III participants who agreed to provide personal identification data to NCHS and whom NCHS was able to match with USRDS administrative records [26]. Mortality was ascertained through the National Death Index [27] starting from the time of enrollment and followed through December 31, 2008. Mortality status for NHANES III survey participants was ascertained primarily through probabilistic record matching with the NDI. All participants with sufficient identifying data were eligible for mortality linkage. Those participants whose records did not meet the minimum data requirements were ineligible for the mortality linkage, and this resulted in a loss of sample size. We censored all the data up to December 31, 2008, to keep the time frames equal.

Statistical Analysis

All continuous variables were tested for normality before statistical analysis. The Kolmogorov-Smirnov test was performed to determine if normality of the distribution of the parameters is consistent with the data. Comparisons between groups were performed using analysis of variance with a normal distribution and χ^2 test or Fisher's exact test for categorical variables. Data that did not show a normal distribution were compared using Kruskal-Wallis test. FVs intake was categorized into selected categories; <2, 2 to <3, 3 to <4, 4 to <6, and ≥ 6 times/day. A *p* value for the crude dose-response association of each sociodemographic or clinical variable (outcome) across selected categories of FV intake was obtained using a linear regression model on the categories' median values for numeric data (e.g., mean age) and ordinal logistic regression on the categories' median values for categorical data (e.g., proportions of current and past smokers).

Lower FV intake has been linked with a higher risk of mortality related to CVD. From data available from several epidemiological studies, it is obvious that patients with CKD are more prone to develop CVD and CVD kills people with CKD more frequently and prematurely [28]. We used the Fine Gray competing risk method with death from CVD as the competing event to explore the relation (relative hazard [RH] and 95% confidence interval [CI]) between FV intake, comparing each FV category with reference category (≥ 6 times/day, the highest intake), and rate of ESKD events. Korn and Graubard [29] CI was calculated for the risk estimates. Confounders considered to be clinically related to the exposure and outcome were included in multivariable models. The model was adjusted for age, sex, race/ethnicity, SES, meat and fish intake, HbA1C, SBP, eGFR, and UACR, all measured at baseline. Prior literature [18, 19] has demonstrated SBP imparting highest risk of decline in kidney function compared to diastolic BP, pulse pressure, and mean arterial pressure; therefore, we adjusted our model for SBP. Tests for trend were performed using median intake values in the selected categories as continuous variables in competing risk analysis. Additional competing risk models were run to test the robustness of the findings in those with manifest CKD of any severity (stages 1–4 of severity), and then separately in those with stages 3–4 of severity.

Cause-Specific Hazards Model

Multivariable cause-specific hazards models were used to assess the association of FV intake with development of ESKD in the general population and subsequently in adults with established CKD (i.e., any CKD and advanced/severe CKD). The models were adjusted for age, sex, race/ethnicity, SES, meat and fish intake, HbA1C, SBP, eGFR, and UACR, all measured at baseline.

Adjusted dietary weights and balanced repeated replication weights accounting for linkage eligibility were produced by fitting a marginal model. These weights were then used in the survey procedures as the final weights following the analytical guidelines for NHANES III data [30, 31]. Results were considered significant if $p < 0.05$. All analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Baseline Characteristics

Baseline characteristics of participants ($n = 14,725$) according to selected categories of FV intake are reported in Table 2. FV intake was categorized into selected categories; <2 , 2 to <3 , 3 to <4 , 4 to <6 , and ≥ 6 times/day. Mean age at baseline was 50.1 ± 0.8 years, and 49.3% were men. Mean eGFR was 100.1 ± 14.2 mL/min/1.73 m². The median FV intake was 3.6 times/day. Participants consuming FVs ≥ 6 times/day (highest FV intake) were older and more likely to be women, had a lesser proportion of participants with lower poverty income ratio and lower levels of education than those in the lowest quintile. Additionally, those eating FVs ≥ 6 times/day had higher HbA1C, higher systolic blood pressure, and lower BMI than those eating <2 times/day.

Association of FV Intake with Risk of ESKD in All Adult NHANES III Participants

Over a median follow-up period of up to 9.2 years, 1.5% of participants ($n = 230$) developed ESKD and 9.3% of participants ($n = 1,370$) died due to CVD. In crude analysis (model 1), the risk of ESKD was higher across the categories of FV intake when compared with ≥ 6 times/day (Table 3a). In the fully adjusted model (model 6), there remained a graded relationship (p for linear trend = 0.01). Compared to the highest FV intake, participants with <2 times/day (RH [95% CI] = (1.45 [1.24–1.68])), those with 2 to <3 times/day (1.40 [1.18–1.61]), and those with 3 to <4 times/day (1.25 [1.04–1.46]) remained at significantly higher ESKD risk (Fig. 1a; Table 3a). A test for interaction in the fully adjusted model showed that the inverse association between FV intake and CKD status was stronger for persons with CKD than for persons without CKD (p for interaction = 0.03).

Risk of ESKD in NHANES III Adult Participants with CKD at Baseline

A total of 5,346 NHANES III participants were classified as having CKD stages 1–4 based on eGFR and albuminuria measures. Their general characteristics are shown in online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000514754. A total of 8.8% of this sample ($n = 180$) progressed to ESKD and 19.4% ($n = 1,037$) died due to CVD. In fully adjusted models, we observed a higher ESKD risk across decreasing categories of FV intake (p for trend = 0.05). Compared to the highest intake, eating FV <2

times/day (1.41 [1.18–1.62]), 2 to <3 times/day (1.46 [1.25–1.69]), and 3 to <4 times/day (1.19 [1.00–1.36]) were all associated with a statistically significant higher ESKD risk (Fig. 1b; Table 3b model 6).

ESKD Incidence in Participants with CKD Stage 3–4 at Baseline

A total of 1,084 NHANES III participants were classified as having CKD stages 3–4. Their general characteristics are shown in online suppl. Table 2. During followup, 120 (11.1%) participants developed ESKD and 239 (22.1%) died due to CVD. In this group, we noted a non-linear trend across FV quintiles and ESKD incidence in each of the models (Table 3c). The RHs were substantially attenuated with the adjustment for the clinical factors (i.e., HbA1C, systolic blood pressure, model 5) across the categories of FV intake. In the fully adjusted model (model 6), compared to highest intake, those in lowest categories of FV intake had a greater RH of ESKD – for 4 to <6 times/day: 1.04 [0.93–1.25], for 3 to <4 times/day: 1.21 [1.05–1.42], for 2 to <3 times/day: 1.39 [1.18–1.60], and for <2 times/day: 1.12 [1.00–1.33] (Fig. 1c; Table 3c).

Cause-Specific Hazards Model

The multivariable cause-specific hazards model yielded similar results compared with those estimated using the competing risk model in all the 3 groups (data not shown). In the general population, the RH of ESKD in the fully adjusted model was 1.38 (1.12–1.53) for <2 times/day, 1.31 (1.10–1.49) for 2 to <3 times/day, 1.23 (1.03–1.40) for 3 to <4 times/day, and 1.17 (0.97–1.33) for 4 to <6 times/day. The RH of ESKD in the fully adjusted model in adults with CKD was 1.36 (1.16–1.58) for <2 times/day, 1.40 (1.19–1.61) for 2 to <3 times/day, 1.21 (1.00–1.37) for 3 to <4 times/day, and 1.09 (0.93–1.24) for 4 to <6 times/day. Last, in adults with CKD stage 3–4, the RH of ESKD was 1.19 (1.01–1.40) for <2 times/day, 1.41 (1.16–1.63) for 2 to <3 times/day, 1.25 (1.03–1.48) for 3 to <4 times/day, and 1.07 (0.95–1.34) for 4 to <6 times/day.

Discussion

This study demonstrates a consistent inverse association between daily very low intake (<3 times) of FVs and risk of ESKD among adult NHANES III participants, suggesting daily higher intake of FVs may be effective in preventing progression to ESKD. Our observation of an association between higher FV intake and low ESKD risk in the general US population align with a Korean study [32] reporting higher risk of incident CKD (development of eGFR <60 mL/min/1.73 m² during follow-up) and lower acid load among participants consuming low amounts of FVs. Collectively, they both expand previous studies evaluating the adherence of dietary patterns rich in plant-based foods and CKD risk [9]. For instance, in the Atherosclerosis Risk in Communities cohort, a greater adherence to various plant-based diet indices was consistently associated with the risk of incident CKD [33]. In a prospective observational Northern Manhattan Study (*N* = 900), plant-based diets were associated with a 12% lower risk of decline in eGFR compared with meat-based diets [34]. Mediterranean diet patterns and Dietary Approaches to Stop Hypertension diet patterns, which also emphasize the intake of FVs, have been associated with a lower risk of incident CKD and ESKD [35, 36].

Our observation of a similar association between higher FVs and low ESKD risk in individuals with manifest CKD is interesting; we are not aware of any study that has addressed this before. Four well-designed RCTs by Goraya et al. [12, 13, 37, 38] have demonstrated that FVs provide a comparable benefit to sodium bicarbonate by improving metabolic acidosis and GFR preservation in people with nondialysis CKD. The largest of these studies [13] involved 108 patients with macroalbuminuria and CKD stage 3 randomized for 3 years to usual care or interventions designed to reduce dietary acid by 50%, using either sodium bicarbonate or alkali-rich FVs. Both interventions reduced urine excretion of angiotensinogen and preserved eGFR similarly and to a greater extent than usual care [38]. Owing to hyperkalemia fears, this trial excluded individuals with diabetes with plasma K levels >4.6 mEq/L. Our results thus agree with those of this trial and expand the finding to unselected persons with CKD.

There are various mechanisms by which a diet rich in FVs may reduce ESKD risk. One of them may involve the promotion of body's alkalinity. On one hand, the high consumption of meat and refined cereals in modern society is associated with lower urine pH and higher serum bicarbonate [39] more so in the presence of comorbid CKD [40, 41]. However, the intake of FVs, which are net alkalinizing in nature, may neutralize acidosis and its consequences [42]. The predominant anions in FVs are citrate and malate, and when metabolized, they release bicarbonate and thus contribute alkali to the body. In healthy kidneys, excess dietary acid is neutralized and eliminated in the kidneys. But in CKD, the ability to excrete both acid and ammonia, a by-product of the neutralization of acid, is significantly impaired. As such, metabolic acidosis is frequent in persons with CKD and is a well-established risk factor for a faster disease progression [43].

Other mechanisms may involve the variety of healthy nutrients and phytochemicals – including fiber, vitamin C, carotenoids, antioxidants, potassium, and flavonoids – which are present in FVs and may act separately or synergistically in reducing inflammation and oxidative stress [44]. Intake of dietary fiber and FVs has been shown to reduce cholesterol levels, blood pressure, inflammation, and platelet aggregation, and to improve vascular and immune function [45–48]. Furthermore, fiber intake promotes the growth of saccharolytic bacteria [45], which produce short chain fatty acids (alkali) and other anti-inflammatory compounds, and lower the generation of uremic toxins [44]. Uremic toxins, such as P-cresol or indoxyl sulfate, are involved in the onset and progression of CKD through promotion of fibrogenesis in the kidney [49]. Antioxidants in FVs may neutralize reactive oxygen species and reduce DNA damage [46], glucosinolates in cruciferous vegetables induce detoxifying enzymes [47] and intake of FVs may also modulate steroid hormone concentrations and hormone metabolism [47]. A high FV intake may also reduce risk of progression to ESKD indirectly, by displacement of unhealthy foods high in saturated fat, trans fat, glycemic load, and sodium.

We observe that though the risk of ESKD in participants with CKD stages 3–4 in the lowest category of intake was attenuated, the statistical significance almost disappeared (1.12 [1.00–1.33]). We attribute this loss of statistical significance to potentially other unmeasured aspects of health status in these participants with advanced CKD (E-value [50] for the risk estimate = 1.49 when taking into account unmeasured confounders), smaller sample size,

and the possibility of linkage eligibility bias; however, this should have been mitigated with the weight adjustments. We note in this regard that they were older, had higher systolic blood pressure, and did not engage in intense physical activity compared to other adults with higher eGFR in our study. Additionally, it is possible that participants at this stage of CKD severity may have received dietary advice to reduce their FV intake to prevent hyperkalemia.

Strengths of this study include a large sample size, nationally representative study population, and long-term follow up. The evaluation of ESKD, the consequential end point in CKD progression, is another strength. Several limitations of our study should be considered. First, participants used an FFQ to report their dietary intakes, which can be subject to recall bias and social desirability bias. However, trained interviewers administered FFQs using visual aids to minimize error. Second, results are representative of the US population in the early 90s, and extrapolation to other periods or countries should be done with caution as diet is determined by many sociocultural factors. Because diet quality has deteriorated over time toward lower intake of fruits and vegetables and higher intake of meat and processed foods ($\beta = -1.53$; $p_{\text{trend}} < 0.001$ for intake of fruits and vegetables, calculated using the food frequency questionnaire, over the years 1994–2006), we speculate the magnitude of observed risk to be potentially higher in the current times. Our findings of a decline in the intake of fruits and vegetables over the period is consistent with the results shown by USDA Economic Research Service researchers who linked the loss-adjusted food availability data and data from 6 national food intake surveys conducted from 1994–1998 to 2007–2008 [51]. Additionally, the laboratory data were also collected long ago. Future prospective studies with periodic/longitudinal data on potassium content and form of the diet (cooked, canned, frozen or fresh fruit and vegetables), metabolic parameters, disease status, as well as other healthy lifestyles are warranted. Third, results are based on one dietary assessment per participant, and may not accurately represent long-term dietary habits. Additionally, the laboratory data were also collected at a single time point. Our confounders were assessed at baseline, and the development of diabetes or hypertension during follow-up (which are known risk factors for ESKD) may also explain our findings. Fourth, there are very few ESKD events and the possibility of linkage eligibility bias in NHANES III. Last, as it is the case for all observational analyses, causality cannot be inferred.

To conclude, low intake of FVs was associated with higher risk of ESKD in US adults with and without CKD, supporting an emerging body of literature on the potential benefits of plant-rich diets for primary and secondary CKD prevention. In the absence of trial evidence, our findings can have clinical implications and may inform patient-centered discussions in clinical practice. In persons with manifest CKD, our results complement recent trial evidence [33] and challenge the well-meaning guidance to limit FV intake to prevent higher dietary potassium load, which may deprive CKD patients, even those with stage 3 or 4 CKD, of the potential benefits of these foods. Further research, particularly on the risks of diet-induced hyperkalemia in advanced CKD patients, is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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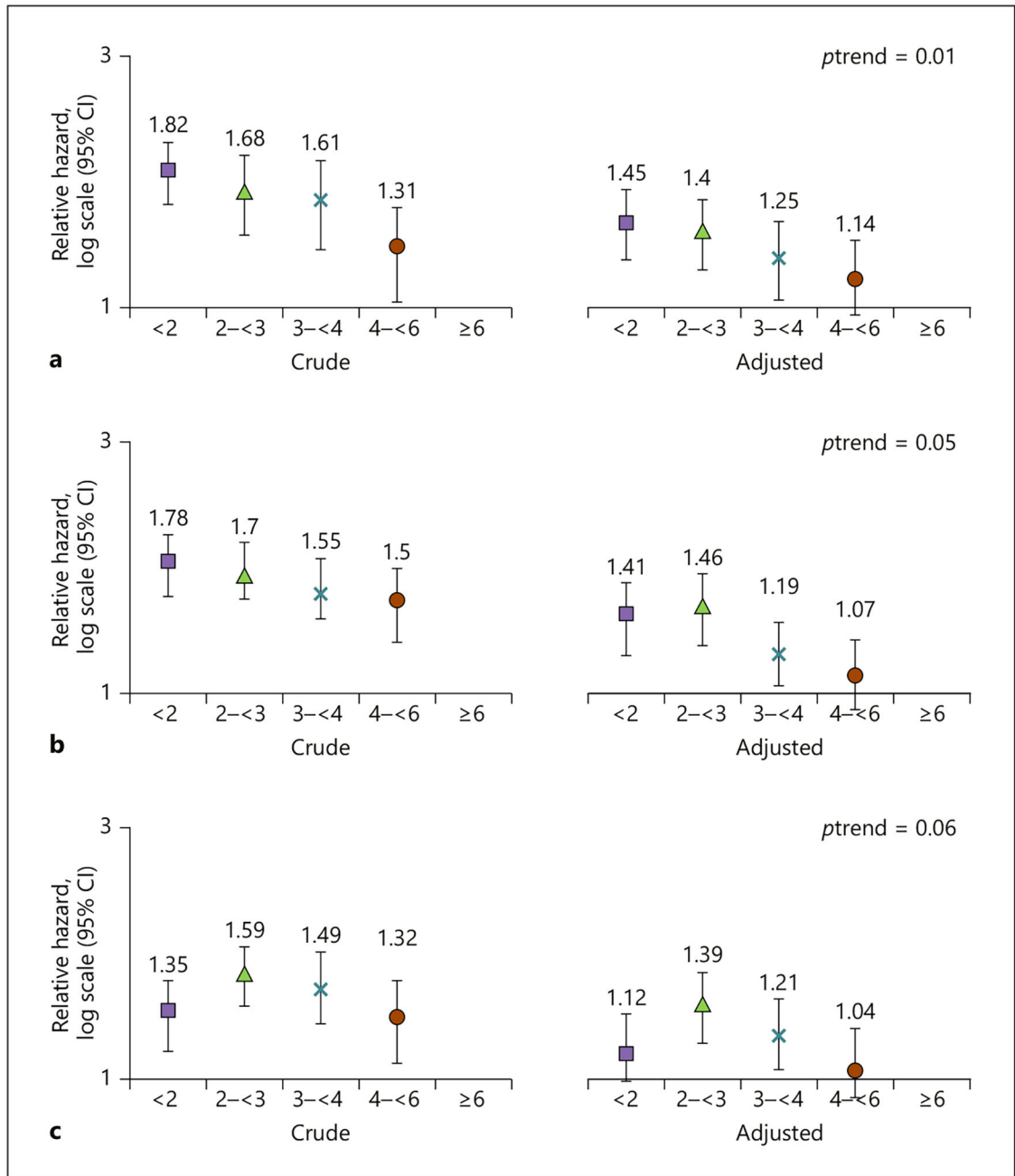


Fig. 1. Association between intake of fruits and vegetables per day and risk of ESKD in all adults ($n = 14,725$, ESKD events = 230, cardiovascular death = 1,370) (a), all stages of CKD ($n = 5,346$, ESKD events = 180, cardiovascular death = 1,037) (b), and stage 3 or 4 CKD ($n = 1,084$, ESKD events = 120, cardiovascular death = 239) (c) using age as a time scale and cardiovascular mortality as a competing risk. The model is adjusted for age, gender, race/ethnicity, socioeconomic status, meat and fish intake, HbA1C, systolic blood pressure, eGFR, and UACR. ESKD, end-stage kidney disease; CKD, chronic kidney disease; eGFR,

estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio; RH, relative hazard; CI, confidence interval.

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Table 1. Review of studies on associations of fruit and vegetable consumption with risk of mortality [32, 52–59]

Study name	Population	Design	Measure of intake	Outcome	Results	Limitations
Fruit and Vegetable Intake and Mortality in Adults undergoing Maintenance Hemodialysis [51]	Hemodialysis population	Cohort study	Global Allergy and Asthma European Network food frequency questionnaire	All-cause mortality	Compared with the lowest tertile of servings per week (0–5, median 2), the adjusted hazard ratios for the middle (5.6–10, median 8) and highest (>10, median 17) tertiles were 0.90 (95% CI, 0.81–1.00) and 0.80 (95% CI, 0.71–0.91) for all-cause mortality, 0.88 (95% CI, 0.76–1.02) and 0.77 (95% CI, 0.66–0.91) for noncardiovascular mortality and 0.95 (95% CI, 0.81–1.11) and 0.84 (95% CI, 0.70–1.00) for cardiovascular mortality, respectively	FV intake was self-reported and comprised one single measurement
Fruit and vegetable consumption and mortality from all causes, cardiovascular disease, and cancer: systematic review and dose-response meta-analysis of prospective cohort studies [52]	General population	Cohort studies	Food frequency questionnaire	All-cause mortality, CVD mortality, and cancer	Higher consumption of fruits and vegetables was significantly associated with a lower risk of all-cause mortality. Pooled hazard ratios of all-cause mortality were 0.95 (95% CI 0.92–0.98) for an increment of one serving a day of fruits and vegetables ($p = 0.001$), 0.94 (0.90–0.98) for fruits ($p = 0.002$), and 0.95 (0.92–0.99) for vegetables ($p = 0.006$)	Food frequency questionnaire may have resulted in errors in measurement
A Diet Rich in Vegetables and Fruit and Incident CKD: A Community-Based Prospective Cohort Study [32]	General population	Community-based prospective cohort study	Semi-quantitative food frequency questionnaire	Incident occurrence of eGFR <60 mL/min/1.73 m ² , incident proteinuria (1+ by dipstick test); mean <i>f/u</i> period = 8.2 years	In a multivariable cause-specific hazards model, the highest tertile of nonfermented vegetable intake was associated with 14% lower risk for incident eGFR <60 mL/min/1.73 m ² than the lowest tertile	Self-reported dietary intake, single ethnicity
The combination of high fruit and vegetable and low saturated fat intakes is more protective against mortality in aging men than is either alone: The Baltimore Longitudinal Study of Aging [53]	Healthy men	Cohort study	Diet records	All-cause mortality	Men consuming the combination of 5 servings of FV/d and 12% energy from SF were 31% less likely to die of any cause ($p < 0.05$), and 76% less likely to die from CHD ($p < 0.001$), relative to those consuming <5 FV and >12% SF	Predominantly white men of relatively high socioeconomic status
Associations of whole-grain, refined-grain, and fruit and vegetable consumption with risks of all-cause mortality and incident coronary artery disease and ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) Study [54]	Middle-aged adults	Cohort study	Semi-quantitative food frequency questionnaire	Total mortality and the incidence of coronary artery disease and ischemic stroke	Over an 11-yr follow-up period, whole-grain intake was inversely associated with total mortality and incident CAD. The risk of ischemic stroke was not significantly related to whole-grain, refined-grain, or fruit and vegetable consumption	Use of the food-frequency questionnaire to characterize whole-grain intake
Fruit and vegetable intake and risk of cardiovascular disease in US adults: the first National Health and Nutrition Examination Survey	General US population	Cohort study	Food frequency questionnaire	Risk of CVD	Consuming fruits and vegetables > or = 3 times/d compared with <1 time/d was associated with a 27% lower stroke incidence (relative risk [RR]: 0.73; 95% CI: 0.57, 0.95; p for trend = 0.01), a 42% lower stroke mortality (0.58; 0.33, 1.02; p for trend = 0.05), a 24% lower ischemic heart disease mortality (0.76; 0.56, 1.03;	FV intake measured at baseline

Study name	Population	Design	Measure of intake	Outcome	Results	Limitations
Epidemiologic Follow-up Study [55]	Participants over 45 years of age	Population based cohort study	Self-administered questionnaire	Overall mortality	<i>p</i> for trend = 0.07), a 27% lower cardiovascular disease mortality (0.73; 0.58, 0.92; <i>p</i> for trend = 0.008), and a 15% lower all-cause mortality (0.85; 0.72, 1.00; <i>p</i> for trend = 0.02) after adjustment for established CVD risk factors	Information on FV consumption was self-reported
Fruit and vegetable consumption and all-cause mortality: a dose-response analysis [56]	General population	Prospective cohort study	Country specific dietary questionnaire	All-cause mortality, cardiovascular mortality, cancer	Consumption of FVs was inversely associated with all-cause mortality (for the highest quartile, hazard ratio = 0.90, 95% CI: 0.86, 0.94), with a rate advancement period of 1.12 years (95% CI: 0.70, 1.54), and with a preventable proportion of 2.95%	In comparison with 5 servings FV/d, a lower consumption was progressively associated with shorter survival and higher mortality rates
Increased green and yellow vegetable intake and lowered cancer deaths in an elderly population [58]	Elderly population	Prospective cohort study	Food frequency questionnaire	Cancer	Those in the highest quintile of intake of carotene-containing vegetables had a risk of cancer mortality which was 0.3 (95% confidence limits 0.10–0.96) that of those in the lowest quintile	The groupings of vegetables in the food frequency questionnaire did not allow a more quantitative estimate of carotene intake
Carotenoids, vitamins C and E, and mortality in an elderly population [59]	Community dwelling volunteers aged over 60 years	Cohort study	3-day food record	All-cause, cardiovascular, cancer mortality	Intake of vegetables was inversely associated with overall mortality (<i>p</i> for trend = 0.003) and mortality from heart disease (<i>p</i> for trend = 0.04)	Small sample size, dietary intake measured at one time point

eGFR, estimated glomerular filtration rate; CVD, cardiovascular disease; FVs, fruits and vegetables; CI, confidence interval.

Table 2.

Baseline characteristics according to the selected categories of fruit and vegetable intake in US adults in NHANES III ($n = 14,725$)

Characteristics	<2 times/day ($n = 2,962$)	2 to <3 times/day ($n = 2,897$)	3 to <4 times/day ($n = 3,015$)	4 to <6 times/day ($n = 2,916$)	6 times/day ($n = 2,895$)	<i>p</i> value
Age, mean \pm SE, years	43.3 \pm 4.33	45.7 \pm 6.86	48.9 \pm 5.87	51.6 \pm 5.67	52.8 \pm 6.6	<0.0001
Men, % ^a	52.2	45.7	50.3	47.2	44.4	0.0001
Race/ethnicity, % ^a						
Other	6.3	7.3	6.6	7.0	11.0	<0.0001
Mexican American	3.8	4.3	5.1	5.3	6.7	
Non-Hispanic Black	15.0	10.7	9.2	8.0	8.0	
Non-Hispanic White	74.9	77.7	79.1	79.7	74.3	
SES (PIR 2 or education history < high school, % ^a)	51.9	42.1	40.2	37.1	39.7	<0.0001
Smoker, % ^a						
Never	40.5	42.6	44.9	47.9	52.8	<0.0001
Past	18.4	22.6	26.8	31.3	31.7	
Current	41.1	34.9	28.3	20.8	15.5	
Physical activity, mean \pm SE (in MET)	9.8 \pm 0.12	10.2 \pm 0.21	10.6 \pm 0.20	11.1 \pm 0.18	11.5 \pm 0.19	<0.0001
BMI, mean \pm SE	27.3 \pm 0.31	27.1 \pm 0.29	27.2 \pm 0.27	27.2 \pm 0.24	26.9 \pm 0.21	0.40
HbA1C, mean \pm SE	5.5 \pm 0.01	5.5 \pm 0.02	5.6 \pm 0.04	5.6 \pm 0.04	5.6 \pm 0.05	<0.0001
Systolic blood pressure, mean \pm SE, mm Hg	123.7 \pm 0.6	124.3 \pm 0.6	125.5 \pm 0.8	127.4 \pm 0.8	128 \pm 0.7	<0.0001
eGFR, mean \pm SE, mL/min/1.73 m ²	103.5 \pm 0.08	100.9 \pm 0.09	97.8 \pm 0.10	95.3 \pm 0.09	93.9 \pm 0.09	<0.0001
UACR, median [IQR], mg/g Cr	5.9 [3.4–11.8]	6.0 [3.4–11.7]	6.3 [3.5–13.0]	6.2 [3.7–13.1]	6.5 [3.7–13.5]	0.02
Caloric intake, mean \pm SE, kcal	5,333.9 \pm 240.1	4,956.4 \pm 223.3	4,848.7 \pm 232.7	4,616.6 \pm 212.4	4,980.8 \pm 229.1	0.51
Meat intake, mean \pm SE, times/day	8.4 \pm 0.1	8.0 \pm 0.1	8.1 \pm 0.2	7.8 \pm 0.2	7.3 \pm 0.2	0.05
Fish intake, mean \pm SE, times/day	0.98 \pm 0.05	1.24 \pm 0.04	1.5 \pm 0.1	1.78 \pm 0.06	1.82 \pm 0.05	<0.0001

This information was based on the results from linking NHANES III, participant data to USRDS, administrative records and to the National Death Index (NDI) death certificate records. SES, socioeconomic status; PIR, poverty income ratio; UACR, urine albumin-creatinine ratio; eGFR, estimated glomerular filtration rate; BMI, body mass index; SE, standard error; IQR, interquartile range; NHANES III, Third National Health and Nutrition Examination Survey; USRDS, United States Renal Data System.

^aWeighted.

Table 3.

Association of FV intake with ESKD using age as a time scale and cardiovascular mortality as a competing risk in (a) the general population ($n = 14,725$, ESKD events = 230, CVD death = 1,370), (b) those with CKD stages 1–4 ($n = 5,346$, ESKD events = 180, CVD death = 1,037), and (c) those with CKD stages 3–4 ($n = 1,084$, ESKD events = 120, CVD death = 239)

RH (95% CI)		<2 times/day	2 to <3 times/day	3 to <4 times/day	4 to <6 times/day	6 times/day
a General population						
Model 1	1.82 (1.57–2.06)	1.68 (1.38–1.94)	1.61 (1.29–1.90)	1.31 (1.03–1.55)	1.0 (ref.)	
Model 2	1.78 (1.52–1.99)	1.60 (1.41–1.87)	1.60 (1.24–1.87)	1.33 (1.10–1.59)	1.0 (ref.)	
Model 3	1.72 (1.54–1.92)	1.69 (1.46–1.96)	1.55 (1.20–1.84)	1.42 (1.20–1.65)	1.0 (ref.)	
Model 4	1.63 (1.39–1.88)	1.52 (1.29–1.74)	1.45 (1.21–1.68)	1.32 (1.14–1.57)	1.0 (ref.)	
Model 5	1.59 (1.33–1.81)	1.47 (1.24–1.69)	1.35 (1.14–1.59)	1.26 (1.05–1.48)	1.0 (ref.)	
Model 6	1.45 (1.24–1.68)	1.40 (1.18–1.61)	1.25 (1.04–1.46)	1.14 (0.97–1.35)	1.0 (ref.)	
b CKD stages 1–4						
Model 1	1.78 (1.53–2.00)	1.70 (1.51–1.93)	1.55 (1.38–1.80)	1.50 (1.25–1.72)	1.0 (ref.)	
Model 2	1.72 (1.56–1.96)	1.72 (1.55–1.91)	1.52 (1.30–1.71)	1.46 (1.22–1.70)	1.0 (ref.)	
Model 3	1.69 (1.50–1.88)	1.68 (1.43–1.85)	1.44 (1.25–1.70)	1.43 (1.21–1.67)	1.0 (ref.)	
Model 4	1.65 (1.41–1.90)	1.63 (1.39–1.88)	1.38 (1.16–1.60)	1.33 (1.14–1.55)	1.0 (ref.)	
Model 5	1.60 (1.36–1.85)	1.58 (1.31–1.80)	1.32 (1.10–1.53)	1.24 (1.05–1.47)	1.0 (ref.)	
Model 6	1.41 (1.18–1.62)	1.46 (1.23–1.69)	1.19 (1.00–1.36)	1.07 (0.93–1.26)	1.0 (ref.)	
c CKD stages 3–4						
Model 1	1.35 (1.13–1.54)	1.59 (1.38–1.79)	1.49 (1.28–1.75)	1.32 (1.08–1.54)	1.0 (ref.)	
Model 2	1.33 (1.10–1.52)	1.55 (1.37–1.74)	1.46 (1.24–1.71)	1.30 (1.11–1.51)	1.0 (ref.)	
Model 3	1.22 (1.02–1.43)	1.53 (1.25–1.70)	1.40 (1.20–1.64)	1.31 (1.10–1.51)	1.0 (ref.)	
Model 4	1.17 (1.04–1.38)	1.49 (1.29–1.71)	1.36 (1.16–1.58)	1.27 (1.07–1.46)	1.0 (ref.)	
Model 5	1.15 (1.01–1.35)	1.44 (1.25–1.68)	1.29 (1.10–1.48)	1.16 (1.00–1.35)	1.0 (ref.)	
Model 6	1.12 (1.00–1.33)	1.39 (1.18–1.60)	1.21 (1.05–1.42)	1.04 (0.93–1.25)	1.0 (ref.)	

Model 1, crude; model 2, model 1 + adjusted for age, gender, race/ethnicity; model 3, model 2 + adjusted for socio-economic status; model 4, model 3 + adjusted for meat and fish intake; model 5, model 4 + adjusted for HbA1c, systolic blood pressure; model 6, model 5 + adjusted for eGFR, UACR. RH, relative hazard; ESKD, end-stage kidney disease; CVD, cardiovascular disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio; FV intake, fruit and vegetable intake.