AJN
American Journal
of Nephrology

Novel Research Findings

Am J Nephrol 2022;53:503–512
DOI: 10.1159/000524382

Received: December 28, 2021
Accepted: March 18, 2022
Published online: May 24, 2022

Nut Consumption and Effects on Chronic Kidney Disease and Mortality in the United States

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Keywords
Nuts intake · Chronic kidney disease · Prevalence · Mortality · National Health and Nutrition Examination Survey

Abstract
Background: Nuts have been found to have beneficial effects on some diseases, including cardiovascular disease and cancer, in several studies. However, there are few studies to show the effects of nuts on chronic kidney disease (CKD). Thus, we conducted this study to examine the association between the consumption frequency of nuts and the prevalence and mortality of CKD among adults in the USA. ***Methods:*** We analyzed data from 6,072 individuals (aged ≥20 years) who participated in the NHANES 2003–2006 following the scheduled procedure. Data on death were provided by the CDC. A logistic regression model was used to evaluate the association between nut consumption frequency and the prevalence of CKD. A Cox proportional hazards regression model was performed to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between nut consumption frequency and all-cause mortality and cardiovascular mortality in the CKD and non-CKD populations. ***Results:*** Consuming nuts 1–6 times per week was associated with a lower prevalence of CKD (model 3: OR: 0.67; 95% CI: 0.49–0.91). In addition, higher nut consumption was significantly associated with lower all-cause and cardiovascular mortality in the non-CKD population. For the CKD population, a consistently significant inverse association could be seen between consuming nuts 1–6 per week and all-cause mortality (model 3: HR: 0.63; 95% CI: 0.47–0.86). No groups showed a significant difference in cardiovascular mortality compared with the reference in the full model. ***Conclusion:*** We recommend the CKD population to have an adequate intake of nuts 1–6 times per week, while the consumption frequency can be more flexible for the non-CKD. Further prospective studies should be conducted to confirm this conclusion.

Introduction

Chronic kidney disease (CKD), manifested by dysfunction in the function and/or structure of the kidney, has become a public health question worldwide [1, 2]. Due to the increasing number of kidney disease risk factors, including the aging population, diabetes, obesity, and hypertension, the global prevalence of CKD has increased by 29.3% from 1990 to 2017 [3]. When CKD pro-

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gresses to end-stage renal disease (ESRD), patients can die or receive costly renal replacement therapy, posing a massive health and economic burden [4, 5]. Thus, preventing CKD and delaying the progression are of expanding concern. Nutritional therapy (NT) is a key part of CKD management aimed at slowing the progression of renal failure, minimizing the harmful effects of uremic toxins, reducing albuminuria, maintaining the balance of nutrient intake, and lowering the occurrence of secondary complications [6]. A summary of NT embodies adequate caloric intake and less intake of proteins, phosphorus, sodium, potassium, and organic acids. However, no consensus on detailed recommended foods or dietaries has been reached [6].

Nuts are nutrient-dense foods containing salutary compounds, including unsaturated fatty acids, vegetable protein, fiber, phytosterols, vitamins, minerals, and phenols [7, 8]. They have been found to have beneficial effects on cardiovascular diseases (CVDs), obesity, cancers, and nonalcoholic fatty liver disease in epidemiologic studies and clinical trials [9–16]. Emerging evidence suggests that they may work by reducing oxidative stress and inflammation and improving vascular reactivity, insulin resistance, and lipid metabolism disorder [17–21]. Meanwhile, few adverse events related to eating nuts have been reported. Thus, regular nut consumption is recommended for both the healthy population and the CVD population and has been incorporated into several healthy dietary patterns.

In view of nuts' unique benefits on CVDs and metabolism, we suppose that nuts may work in CKD as well since CKD is closely related to the diseases given above [22]. In addition, several pathways or risk factors, including hyperglycemia, hypertension, lipid metabolism disorder, and inflammation, which could be improved by nuts, have been proven to be pivotal in the pathogenesis of CKD [23–26]. There is also some clinical evidence showing that nuts can improve the health status of patients with CKD [27–30]. However, the sample size of the existing research is relatively small, such that there is no definitive evidence favoring nut benefits in CKD. In addition, nuts are also rich in protein and phosphorus, which is at variance with the recommended restricted diet for patients with CKD by means of low phosphorus and limited protein intake. As a consequence, whether nuts should be incorporated into NT for CKD and the daily allowance need to be confirmed.

Hence, it is of vital importance to confirm the benefit of nuts for people with CKD and the upper limit of consumption for them. The objective of this study was to examine the association between nut consumption frequency and the prevalence and mortality of CKD in the American adult population.

Materials and Methods

Study Participants

The study used cross-sectional data collected from the 2003–2006 National Health and Nutrition Examination Surveys (NHANES). NHANES has been conducted since 1999, approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board, with informed consent provided by all participants [31]. They were carried out based on a sampling design of stratified multistage probability among noninstitutionalized residents in the USA every 2 years. The collected data included both household questionnaires and laboratory tests about health and nutrition status.

In this study, we included individuals who participated in the NHANES 2003–2006 with complete data from the Food Frequency Questionnaire (FFQ) (n = 12,259). Participants who were <20 years old, had missing data on age, sex, ethnicity, and kidney function information (n = 9,073) and had no or invalidated data on covariates needed for later analysis (including daily intake of energy, protein, carbohydrate, sugar, fat, smoke, alcohol use, obesity, triglycerides (TG) (mg/dL), total cholesterol (TC) (mg/dL), high-density lipoprotein cholesterol (HDL cholesterol) (mg/dL), hypertension and diabetes) were excluded. The final sample size included in this analysis was 6,072.

Mortality

The outcome of the study was death data during the follow-up period. Data on death included mortality status, causes of death, and follow-up time for all participants and were provided by the Centers for Disease Control and Prevention [32]. The 9 specific causes of death consisted of heart disease, malignant neoplasms, chronic lower respiratory disease, accidents, cerebrovascular disease, Alzheimer's disease, diabetes, influenza or pneumonia, nephritis/nephrotic syndrome/nephrosis, and all other causes. A total of 1,033 subjects died during the follow-up (mean follow-up time, 11.0 years).

Ascertainment of CKD

Serum creatinine values used a Jaffé rate reaction and were converted to estimated glomerular filtration rate (eGFR) using the established Chronic Kidney Disease Epidemiology Collaboration equation [1, 2]. The measurement of urinary albumin and creatinine used a solid-phase fluorescent immunoassay and a Jaffé rate reaction. The population diagnosed with CKD was those with an eGFR less than 60 mL/min/1.73 m^2 or urinary albumin-to-creatinine ratio (UACR) greater than or equal to 30 mg/g by KDIGO [1, 2]. The CKD population was divided into G1-G5 according to GFR categories by KDIGO [1, 2].

Dietary Assessment

Dietary intake was assessed using the FFQ in NHANES 2003–2006 about the consumption frequency of 124 food items during the past 12 months [33]. It was administered every 2 years and included two 24-h dietary recall interviews and interview informa-

tion. The consumption frequency of nuts was categorized as "never," "1–6 times per year," "7–11 times per year," "1 time per month," "2–3 times per month," "1 time per week," "2 times per week," "3–4 times per week," "5–6 times per week," "1 time per day," and "2 or more times per day." In this study, we finally defined five groups to describe the consumption frequency of nuts, including "never," "1–11 times per year," "1–3 times per month," "1–6 times per week," and "more than once a day." We obtained dietary intake of several nutrients, including energy (kcal), protein (g), carbohydrate (g), sugar (g), fat (g), saturated fatty acid (g), monounsaturated fatty acids (g), polyunsaturated fatty acids (g), dietary phosphorus (mg), dietary sodium (mg), and dietary potassium (mg), estimated by the FFQ data.

Assessment of Covariates

Demographic information on gender, age, and race/ethnicity was collected in the home by trained interviewers during the interview using a computer-assisted personal interviewing methodology. Body mass index (BMI, kg/m^2) was calculated as weight divided by height squared, both measured when participants were wearing light clothing without shoes. Data on lifestyle habits (smoking, alcohol use) and prevalence of diseases (hypertension, diabetes, congestive heart failure, coronary heart disease, stroke, cancer) were obtained from Household Interview Component Questionnaires, consisting of Screener Questionnaire, Family Interview Questionnaire, and Sample Person Questionnaire.

Randomly collected urine specimens were collected by the clean-catch technique into sterile 250-mL polyethylene containers. Urinary creatinine analysis uses a Jaffé rate reaction, and urinary albumin was measured by solid-phase fluorescent immunoassay. The analysis of TC and TG used enzymatic methods. HDL cholesterol was measured using the direct immunoassay method. CRP was measured by latex-enhanced nephelometry. The NHANES quality assurance and quality control procedures can be found on the NHANES website.

Statistical Analysis

The baseline demographic characteristics, nutrient/healthy status, and laboratory examination for the study population were described by the five groups of nut consumption frequencies. Categorical variables are presented as frequencies (relative frequencies, %). Continuous variables were first tested by graphical representation and Shapiro-Wilk tests to differentiate normally distributed variables and skewed distribution variables. Normally distributed continuous variables are presented as the means (standard deviation), and skewed distribution variables are presented as medians (1st quartile–3rd quartile). Comparisons of categorical variables, including sex, race/ethnicity, smoking status, alcohol use, hypertension, diabetes, BMI, congestive heart failure, and stroke, were tested by Pearson's χ^2 test. Comparisons of continuous variables were tested by Student's *t* test if normally distributed or the Mann-Whitney U test if not. A logistic regression model was used to analyze the association between nut consumption frequency and the prevalence of CKD. Three models were finally fitted. Model 1 was a crude model adjusted for three factors: age (continuous: years), gender (dichotomous: men or women), and race/ethnicity (categorical: non-Hispanic white, non-Hispanic black, other). Model 2 was additionally adjusted for dietary intake of energy (continuous: kcal), protein (continuous: g), carbohydrate (continuous: g), sugar (continuous: g), and fat (continuous: g). Smoking status (categorical: "never," "ever," "current"), alcohol use (categorical: "never," "ever," "current"), obesity defined by BMI (categorical: "BMI < 25," "25–<30," ">30"), TG (continuous: mg/dL), TC (continuous: mg/dL), HDL cholesterol (continuous: mg/dL), hypertension, and diabetes were additionally adjusted in Model 3. Cox proportional hazards regression was used to estimate hazard ratios and 95% confidence intervals (CIs) for the association between nut consumption frequency and all-cause mortality and cardiovascular mortality in the CKD and non-CKD populations. The adjusted variances of model 1 and model 2 for the non-CKD population were the same as those in logistic regression models. The additional adjusted factors for model 3 were coronary heart disease (dichotomous: if or not), congestive heart failure (dichotomous: if or not), stroke (dichotomous: if or not), and cancer (dichotomous: if or not) at baseline. The additional adjusted factors of model 2 and model 3 for the CKD population compared with the non-CKD population were eGFR (continuous: mL/min/1.73 m^2) and UACR (continuous: mg/g). SPSS version 26 was used for all analyses (SPSS Inc., Chicago, IL, USA).

Result

The baseline characteristics of the 6,072 participants stratified according to the nut consumption frequency are presented in Table 1. Compared with those who had a lower nut consumption frequency, those consuming nuts more than once a day were more likely to be older, thinner, and nonsmoker, with higher levels of HDL cholesterol and lower levels of CRP. Meanwhile, individuals consuming nuts more than once a day tended to have a higher intake of total energy, protein, monounsaturated fatty acids, polyunsaturated fatty acids, phosphorus, and potassium compared to other groups. The total number of the CKD population at baseline was 1,203 (distribution of patients by stages of CKD: G1: 284; G2: 273; G3: 594; G4: 46; G5: 6).

Table 2 shows the association between the frequency of nut consumption and the prevalence of CKD. Consuming nuts 1–6 per week was associated with a lower risk of CKD in all three models (model 1: odds ratio [OR]: 0.53; 95% CI: 0.40–0.70; model 2: OR: 0.52; 95% CI: 0.40–0.70; model 3: OR: 0.67; 95% CI: 0.49–0.91, $p < 0.05$). In model 1, after adjusting for potential confounders, including age, gender, and race/ethnicity, compared to those never consuming nuts, the OR and 95% CI of CKD were 0.73 (0.57–0.93) for individuals consuming nuts 1–11 times per year, 0.74 (0.57–0.95) for individuals consuming nuts 1–3 per month, 0.53 (0.40–0.70) for individuals consuming nuts 1–6 per week, and 0.61 (0.36–1.02) for individuals consuming nuts more than once a day. The association existed only substantially in the "1–6 per week" groups after adjusting for nutrient-related fac-

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DOI: 10.1159/000524382

Table 1. Baseline characteristics of participants by frequency of nut consumption, NHANES, 2003–2006

Characteristics	Never (*n* = 748)	1–11 times per year (*n* = 1,916)	1–3 per month (*n* = 1,794)	1–6 per week (*n* = 1,399)	More than once a day (*n* = 215)	*p* value
Age, years	51.0 (30.0–71.0)	47.0 (32.0–65.0)	48.0 (34.0–65.0)	54.0 (40.0–68.0)	61.0 (46.3–71.0)	<0.001
Male, *n* (%)	353 (47.2)	883 (46.1)	831 (46.3)	671 (48.0)	93 (43.3)	0.667
Race/ethnicity, *n* (%)						
Non-Hispanic White	335 (44.8)	1,030 (53.8)	1,002 (55.9)	903 (64.6)	145 (67.1)	
Non-Hispanic Black	205 (27.4)	371 (19.4)	310 (17.3)	211 (15.1)	26 (12.5)	<0.001
Other	208 (27.8)	515 (26.8)	482 (26.9)	285 (20.4)	44 (20.4)	
Alcohol use, *n* (%)						
Never	156 (20.9)	247 (12.9)	252 (14.0)	157 (11.2)	37 (17.2)	
Ever	144 (19.2)	339 (17.7)	302 (16.9)	217 (15.6)	38 (17.7)	<0.001
Current	448 (59.9)	1,330 (69.4)	1,240 (69.1)	1,025 (73.2)	140 (65.1)	
Smoke, *n* (%)						
Never	349 (46.6)	965 (50.3)	932 (52.0)	726 (51.9)	113 (52.6)	
Ever	183 (24.5)	506 (26.5)	492 (27.4)	453 (32.4)	77 (35.8)	<0.001
Current	216 (28.9)	445 (23.2)	370 (20.6)	220 (15.7)	25 (11.6)	
Hypertension, *n* (%)	287 (38.4)	620 (32.4)	522 (29.1)	477 (34.1)	79 (36.7)	<0.001
Diabetes, *n* (%)	126 (16.8)	223 (11.6)	213 (11.9)	162 (11.6)	32 (14.9)	0.002
BMI, *n* (%)						
<25	235 (31.4)	547 (28.5)	540 (30.1)	435 (31.1)	84 (39.1)	
25–<30	238 (31.8)	689 (36.0)	608 (33.9)	520 (37.1)	61 (28.4)	0.005
≥30	275 (36.8)	680 (35.5)	646 (36.0)	444 (31.8)	70 (32.6)	
TG, mg/dL	120.5 (81.0–180.0)	122 (80.0–186.8)	116.0 (79.0–176.0)	113.0 (73.0–174.0)	108.5 (72.3–172.5)	0.012
TC, mg/dL	195.5 (166.0–222.0)	197.0 (172.0–226.0)	200.0 (174.0–229.0)	199.0 (173.0–225.0)	199.0 (177.0–225.8)	0.037
HDL cholesterol, mg/dL	50.0 (41.0–62.0)	51.5 (42.0–64.0)	52.0 (43.0–64.0)	54.0 (45.0–66.0)	55.0 (46.0–70.0)	<0.001
Congestive heart failure, *n* (%)	42 (5.6)	77 (4.0)	55 (3.1)	32 (2.3)	7 (3.3)	0.001
Coronary heart disease, *n* (%)	44 (5.9)	88 (4.6)	82 (4.6)	68 (4.9)	12 (5.6)	0.634
Stroke, *n* (%)	44 (5.9)	70 (3.7)	72 (4.0)	45 (3.2)	0 (0.0)	0.001
Cancer, *n* (%)	64 (8.6)	158 (8.2)	151 (8.4)	182 (13.0)	27 (12.6)	<0.001
Energy, kcal	1,772.5 (1,314.8–2,410.3)	1,923.3 (1,478.4–2,474.3)	1,952.0 (1,525.5–2,529.5)	1,983.5 (1,559.5–2,528.6)	2,015.3 (1,469.8–2,547.1)	<0.001
Protein, g	68.8 (49.0–90.5)	73.8 (55.7–96.3)	75.2 (57.3–99.5)	78.0 (60.2–100.2)	81.3 (55.9–102.8)	<0.001
Carbohydrate, g	220.8 (164.7–306.1)	239.9 (181.5–318.2)	238.1 (184.1–315.5)	234.6 (183.9–306.5)	231.3 (181.2–307.6)	0.002
Sugar, g	103.4 (65.5–152.3)	107.8 (71.7–155.5)	102.6 (71.7–149.0)	104.1 (72.2–144.5)	100.1 (65.5–147.0)	0.180
Fat, g	65.3 (44.2–91.3)	70.0 (49.6–95.1)	72.9 (52.5–98.6)	74.8 (54.5–103.3)	74.3 (50.7–105.3)	<0.001
Saturated fatty acid, g	21.2 (14.1–31.5)	23.1 (15.7–32.2)	23.6 (16.4–33.2)	24.1 (17.1–33.5)	22.7 (13.9–32.8)	<0.001
Monounsaturated fatty acids, g	24.0 (15.7–34.4)	25.5 (18.1–35.5)	26.8 (18.8–36.7)	28.0 (19.8–39.0)	28.4 (17.9–41.1)	<0.001
Polyunsaturated fatty acids, g	12.9 (8.2–18.4)	14.4 (9.7–20.3)	14.9 (10.4–21.0)	16.1 (11.1–22.4)	16.5 (11.1–24.4)	<0.001
Dietary phosphorus, mg	1,065.5 (785.3–1,429.3)	1,180.0 (870.0–1,529.2)	1,216.5 (923.0–1,590.0)	1,279.8 (992.9–1,633.1)	1,349.8 (997.8–1,781.6)	<0.001
Dietary sodium, mg	2,791.0 (1,977.6–3,897.6)	3,064.5 (2,231.9–4,021.0)	3,139.5 (2,343.8–4,082.4)	3,155.5 (2,349.8–4,096.0)	2,921.0 (2,265.9–3,873.3)	<0.001
Dietary potassium, mg	2,147.5 (1,560.3–2,814.4)	2,424.8 (1,824.6–3,143.1)	2,543.0 (1,958.0–3,278.0)	2,747.0 (2,099.0–3,437.4)	2,969.5 (2,263.9–3,743.4)	<0.001
Serum potassium	4.0 (3.8–4.2)	4.0 (3.8–4.2)	4.0 (3.8–4.2)	4.0 (3.8–4.2)	4.0 (3.8–4.3)	0.173
Serum phosphorus	3.8 (3.4–4.1)	3.8 (3.5–4.1)	3.8 (3.4–4.1)	3.8 (3.4–4.1)	3.7 (3.4–4.1)	0.702
CRP	0.27 (0.12–0.63)	0.23 (0.09–0.57)	0.23 (0.09–0.51)	0.20 (0.08–0.46)	0.18 (0.06–0.44)	<0.001
eGFR, mL/min/1.73 m^2	94.5 (73.2–113.6)	94.6 (77.3–111.8)	94.1 (76.2–110.3)	89.3 (73.4–103.8)	85.2 (70.4–98.0)	<0.001
UACR, mg/g	7.9 (4.7–18.5)	6.8 (4.4–13.5)	6.5 (4.2–12.8)	6.5 (4.2–13.0)	7.8 (4.8–15.4)	<0.001
CKD, *n* (%)	185 (24.7)	368 (19.2)	334 (18.6)	270 (19.3)	47 (21.8)	0.007
G1, *n* (%)	46 (6.1)	94 (4.9)	78 (4.3)	56 (4.0)	10 (4.7)	0.221
G2, *n* (%)	42 (5.6)	79 (4.1)	82 (4.6)	59 (4.2)	11 (5.1)	0.514
G3, *n* (%)	86 (11.5)	174 (9.1)	162 (9.0)	147 (10.5)	25 (11.6)	0.173
G4–5, *n* (%)	11 (1.5)	21 (1.1)	12 (0.7)	8 (0.6)	0 (0.0)	0.073

HDL, high-density lipoprotein; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio; CKD, chronic kidney disease.

Table 2. The associations of nuts consuming frequency with the prevalence of CKD

	Never	1–11 times per year	*p* value	1–3 per month	*p* value	1–6 per week	*p* value	More than once a day	*p* value
Model 1	1.00 (reference)	0.73 (0.57–0.93)	0.012	0.74 (0.57–0.95)	0.017	0.53 (0.40–0.70)	<0.001	0.61 (0.36–1.02)	0.058
Model 2	1.00 (reference)	0.82 (0.64–1.08)	0.115	0.84 (0.65–1.08)	0.169	0.52 (0.40–0.70)	<0.001	0.61 (0.36–1.03)	0.062
Model 3	1.00 (reference)	0.95 (0.73–1.23)	0.673	0.97 (0.74–1.27)	0.822	0.67 (0.49–0.91)	0.010	0.86 (0.49–1.50)	0.589

Model 1 adjusted for age, gender, and race/ethnicity. Model 2 adjusted for age, gender, race/ethnicity, energy, protein, carbohydrate, sugar, and fat. Model 3 adjusted for age, gender, race/ethnicity, energy, protein, carbohydrate, sugar, fat, smoke, alcohol use, obesity, TG (mg/dL), TC (mg/dL), HDL cholesterol (mg/dL), hypertension, and diabetes.

Table 3. The associations of nuts consuming frequency with the mortality in non-CKD population

	Never	1–11 times per year	*p* value	1–3 per month	*p* value	1–6 per week	*p* value	More than once a day	*p* value
a *All-cause mortality*									
Model 1	1.00 (reference)	0.65 (0.50–0.85)	0.001	0.64 (0.49–0.83)	0.001	0.51 (0.38–0.67)	<0.001	0.35 (0.20–0.61)	<0.001
Model 2	1.00 (reference)	0.68 (0.52–0.88)	0.004	0.67 (0.51–0.87)	0.003	0.53 (0.40–0.71)	<0.001	0.38 (0.22–0.67)	0.001
Model 3	1.00 (reference)	0.70 (0.53–0.92)	0.010	0.74 (0.56–0.98)	0.037	0.60 (0.44–0.80)	0.001	0.45 (0.25–0.79)	0.005
b *Cardiovascular mortality*									
Model 1	1.00 (reference)	0.51 (0.30–0.86)	0.012	0.37 (0.21–0.66)	0.001	0.34 (0.19–0.61)	<0.001	0.15 (0.03–0.62)	0.009
Model 2	1.00 (reference)	0.52 (0.30–0.89)	0.016	0.39 (0.22–0.71)	0.002	0.37 (0.20–0.67)	0.001	0.16 (0.04–0.68)	0.013
Model 3	1.00 (reference)	0.48 (0.27–0.85)	0.011	0.44 (0.24–0.83)	0.010	0.43 (0.23–0.82)	0.011	0.18 (0.04–0.80)	0.024

Model 1 adjusted for age, gender, and race/ethnicity. Model 2 adjusted for age, gender, race/ethnicity, energy, protein, carbohydrate, sugar, and fat. Model 3 adjusted for age, gender, race/ethnicity, energy, protein, carbohydrate, sugar, fat, smoke, alcohol use, obesity, TG (mg/dL), TC (mg/dL), HDL cholesterol (mg/dL), hypertension, diabetes, coronary heart disease, congestive heart failure, stroke, cancer, saturated fatty acid (g), monounsaturated fatty acids (g), polyunsaturated fatty acids (g), dietary phosphorus (mg), dietary sodium (mg), dietary potassium (mg), serum potassium, and serum phosphorus.

tors, including protein, carbohydrate, sugar, and fat (model 2). Further adjustment for smoking, alcohol use, obesity, TG (mg/dL), TC (mg/dL), HDL cholesterol (mg/dL), hypertension, and diabetes did not change the result compared to model 2 (model 3).

After multivariate adjustments of potential confounders, higher nut consumption was inversely associated with all-cause and cardiovascular mortality in the non-CKD population (Table 3). The full adjusted hazard ratios and 95% CIs for all-cause mortality, compared with participants who never consumed nuts, were 0.70 (0.53–0.92) for participants consuming 1–11 times per year, 0.74 (0.56–0.98) for those consuming 1–3 per month, 0.60 (0.44–0.80) for those consuming 1–6 per week, and 0.45 (0.25–0.79) for those consuming more than once a day (Table 3a, model 3). Table 3b shows the association between nut consumption frequency and CVD mortality in the non-CKD population. After adjustment for confounders above, non-CKD participants consuming nuts at a higher frequency were less likely to die from CVDs.

Table 4 shows the association between nut consumption frequency and all-cause and CVD mortality in the CKD population. In all models, a significant inverse association consistently existed between consuming nuts 1–6 per week and all-cause mortality. In a crude model adjusted for eGFR and UACR, compared to participants never consuming nuts, only those consuming nuts more than once a day showed a nonsignificant result. After fellow multivariate adjustments in model 2 and model 3, all other groups showed no difference from the reference group in all-cause mortality except the "1–6 per week" group. Table 4b shows the association between nut consumption frequency and CVD mortality in the CKD population. Only the "1–11 times per year" and "1–6 per week" groups had a lower risk than the "never" group in model 1 and model 2. No groups showed a significant difference compared with the "never" group in the full model.

Table 4. The associations of nuts consuming frequency with the mortality in CKD population

	Never	1–11 times per year	*p* value	1–3 per month	*p* value	1–6 per week	*p* value	More than once a day	*p* value
a *All-cause mortality*									
Model 1	1.00 (reference)	0.73 (0.57–0.93)	0.012	0.74 (0.57–0.95)	0.017	0.53 (0.40–0.70)	<0.001	0.61 (0.36–1.02)	0.058
Model 2	1.00 (reference)	0.82 (0.64–1.08)	0.115	0.84 (0.65–1.08)	0.169	0.52 (0.40–0.70)	<0.001	0.61 (0.36–1.03)	0.062
Model 3	1.00 (reference)	0.91 (0.70–1.18)	0.460	0.94 (0.72–1.22)	0.619	0.63 (0.47–0.86)	0.003	0.79 (0.46–1.37)	0.396
b *Cardiovascular mortality*									
Model 1	1.00 (reference)	0.58 (0.36–0.93)	0.025	0.79 (0.50–1.24)	0.306	0.47 (0.28–0.78)	0.004	0.58 (0.24–1.39)	0.223
Model 2	1.00 (reference)	0.59 (0.36–0.96)	0.035	0.80 (0.50–1.27)	0.340	0.45 (0.27–0.77)	0.003	0.52 (0.21–1.29)	0.159
Model 3	1.00 (reference)	0.61 (0.37–1.03)	0.065	0.96 (0.59–1.56)	0.872	0.61 (0.36–1.05)	0.075	0.91 (0.35–2.34)	0.842

Model 1 adjusted for the eGFR and UACR. Model 2 adjusted for age, gender, race/ethnicity, eGFR, UACR, energy, protein, carbohydrate, sugar, and fat. Model 3 adjusted for age, gender, race/ethnicity, eGFR, UACR, energy, protein, carbohydrate, sugar, fat, smoke, alcohol use, obesity, TG (mg/dL), TC (mg/dL), HDL cholesterol (mg/dL), hypertension, diabetes, coronary heart disease, congestive heart failure, stroke, cancer, saturated fatty acid (g), monounsaturated fatty acids (g), polyunsaturated fatty acids (g), dietary phosphorus (mg), dietary sodium (mg), dietary potassium (mg), serum potassium, and serum phosphorus.

Discussion

In this cohort study, we found that consuming nuts 1–6 times per week was significantly associated with a lower prevalence of CKD after adjusting for all known risk factors. We confirmed that a higher frequency of consuming nuts was also significantly associated with lower all-cause mortality in the non-CKD population. However, when we attempted to analyze the effect in the CKD population, only participants consuming nuts 1–6 times per week showed lower all-cause mortality in all models. For cardiovascular mortality, a frequency greater than or equal to 1–3 per month was associated with lower cardiovascular mortality in the non-CKD population. Nevertheless, the cardioprotective effects of a higher consumption frequency were not obvious in the CKD population, and no other intake frequency was better than that of the "never" group in the fully adjusted model.

Previous studies have provided substantial evidence of nuts' healthy effects on CVD and some other diseases. However, very little about nuts' benefits in CKD prevention and whether they are helpful for reducing all-cause and cause-specific mortality among people with CKD is known. A meta-analysis showed the association between nut consumption and cause-specific mortality in the adult population, and it showed a nonsignificant association between nut consumption and kidney disease mortality [15]. However, they did not study the effect on disease-specific populations. In contrast, we mainly examined people with CKD and found different effects compared to the non-CKD population. Several clinical trials have previously mentioned the protective effects of Brazil nuts and walnuts in hemodialysis patients [27–29]. But they were all small sample trials with short follow-up times and no death data. In addition, several cohorts have mentioned the relationship between dietary patterns and a lower risk of subsequent kidney disease with the intake of beans and nuts as a recommendation of the dietary pattern [34–36]. However, they always grouped nuts with grains together in those studies; thus, this was a mixed effect given by both nuts and grains. Furthermore, whether it still worked with a higher nut intake could not be proven. Compared to the studies above, our study had a relatively large sample size and tried to determine the single effect of nuts on both the prevalence and mortality of the CKD population. Meanwhile, we had an accurate group to describe more precise information about nut consumption frequency.

The protective effect of nuts on reducing the risk of CKD and partly reducing all-cause mortality may work as its benefits on reducing inflammation and improving lipid metabolism disorders, hypertension, and bowel health. Possible underlying mechanisms and more specific evidence are as follows.

The progression of CKD involves the interaction of many inflammatory mediators, cytokines, injured tubules, immune cells, endothelial cells, and fibroblasts [37, 38]. We suspect that the anti-inflammatory effects that nuts show in other diseases may help to alleviate glomerular injury and slow the progression of CKD [39]. Some studies can support this hypothesis. Ehsani et al. [40] found that a hydroalcoholic extract of *Pistacia* could at-

tenuate renal dysfunction and structural damage through the reduction of inflammation in gentamicin-induced nephrotoxicity in rats. A pilot study showed that Brazil nuts might activate nuclear factor E2-related factor 2 to reduce inflammation in hemodialysis patients [29]. In our study population, the level of serum CRP was lower in groups with a higher frequency, as shown in Table 1. This prompted a higher frequency of nut intake to have an anti-inflammatory effect, which could be a protective factor against CKD.

Lipid metabolism disorder is also a vital part of the pathogenesis of CKD. Hyperlipidemia could cause the formation of renal atherosclerotic plaques and narrow renal arteries and lead to renal ischemia, atrophy, and interstitial fibrosis [41]. It also causes damage by oxidative stress and endoplasmic reticulum stress [42]. Nuts are rich in unsaturated fatty acids and other lipids, which could improve lipid metabolism disorders and might work to protect people from CKD [7]. They lower serum cholesterol by lowering the absorption, inhibiting β-hydroxy β-methylglutaryl-CoA reductase and promoting 7-α hydroxylase activity resulting in elevated bile acid production [43, 44]. A meta-analysis of 61 controlled intervention trials showed that tree nut intake lowered TC, LDL cholesterol, Apo B, and TG [45]. We have a similar result in our study. Groups with a higher frequency had a lower intake of saturated fatty acids, a higher intake of monounsaturated fatty acids and polyunsaturated fatty acids, and a higher level of HDL cholesterol (Table 1). This finding suggested that an improved effect of lipid metabolism could be another protective factor against CKD.

Hypertension is another cause of glomerular disease, along with water-sodium retention and the activation of the renin-angiotensin-aldosterone axis [46, 47]. Although major clinical trials found that nut consumption was not associated with blood pressure (BP) changes [45], it also has potential since nut components were found to improve hypertension. High levels of asymmetric dimethylarginine in the CKD population result in higher BP and cardiovascular risk [48]. Nuts are rich in arginine, a precursor of NO and a potent vasodilator that could antagonize the effect of asymmetric dimethylarginine and regulate vascular tone and BP [43, 48]. In addition, some evidence suggests that nuts rich in unsaturated fatty acids, magnesium, and potassium can improve hypertension [7, 49–52]. Therefore, nuts have potential antihypertensive effects. Regrettably, this expectant antihypertension effect was not significantly seen in the crude description of the baseline (Table 1), consistent with previously reported studies. We wish to observe this effect in a subsequent study.

Another possible mechanism is that nuts work by maintaining the gut microbiota balance and bowel health [53–55]. Lambert et al. [53] found that raw almonds could significantly improve symptoms of constipation in hemodialysis patients. A review of the prebiotic properties of nuts noted that nuts selectively stimulated specific species in the gut microbiota that conferred health benefits to the host [54, 55]. It is worthy of further study. In conclusion, nuts seem to be an appropriate choice to prevent CKD and delay its progression.

Although our study prompted that nut consumption was related to a lower risk of CKD, the CKD population did not benefit so much in reducing mortality by consuming nuts at a higher frequency compared to the non-CKD population. One most likely reason is that nuts are rich in potassium, protein, and phosphorus, which is a potential risk for the CKD population [7]. People with CKD have an insufficient capacity of their kidneys to excrete potassium, phosphorus, and the metabolic products of proteins especially for patients with ESRD. Table 1 showed that the higher frequency groups had a higher intake of total energy, protein, phosphorus, and potassium. The data indicated that high nut intake had a risk of leading to hyperkalemia, hyperphosphatemia, and rapid loss of renal function. Potassium is critical for the normal activity of the muscles, nerves, and heart by maintaining the cellular membrane potential and neuromuscular function [56]. Severe hyperkalemia could lead to arrhythmia, quadriplegia, and asphyxia and is fatal without emergency treatment [57]. Hyperphosphatemia could lead to vitamin D resistance and hypocalcemia by reducing the expression of the renal 1α-hydroxylase enzyme, resulting in heterotopic calcification and cardiovascular system damage [58]. However, in our study, serum phosphorus and potassium were not significantly different between groups; thus, the risk from hyperkalemia and hyperphosphatemia could not be directly observed. The most likely reason is that the population studied has a relatively small composition of individuals with CKD 4–5. Our study determined that there was no significant benefit shown when consuming nuts at a lower frequency, but a higher frequency would be hazardous for the population with CKD. In general, "1–6 times per week" rather than a higher frequency might be an appropriate choice, in which nuts could continue their good work without causing any complications. More rigorously designed studies are needed to confirm this conclusion.

The strengths of our study included a relatively large nationally representative sample size comprised of men and women, ranging from 20 to 80 years old, repeated and professional assessments of dietary information using household interviews, and comprehensive information for demographic characteristics and healthy examinations; thus, we could carefully adjust most potential confounders for a multitude of potential risk factors. Furthermore, all the participants were followed up to obtain the mortality status and causes of death; thus, the long-term effect of nut intake could be observed.

Nonetheless, there were several limitations as well. First, partial results were from a cross-sectional observational study; hence, the causality between nut consumption and chronic disease could not be proven. Also, it was hard to avoid confounding brought by unknown factors. Similarly, due to the lack of follow-up data on nut consumption, we could only use the baseline data to predict its effect on mortality. Second, selection bias might exist since patients with CKD would have a lower intake of nuts if they had hyperkalemia or hyperphosphatemia. Third, the FFQ relied on the recall for the consumption frequency of the participants. Recall bias could lead to over- or underestimation of nut consumption. Meanwhile, serving size was not mentioned in the interview; thus, consumption frequency could not be equivalent to daily intake. There might be considerable variation in nut intake within the same group. Fourth, due to the lack of data for the ESRD population, the results could not represent the entire CKD population. Fifth, the data size on cause-specific death was relatively small; thus, the results about cardiovascular mortality need further validation. Finally, we could not determine the different effects brought by different nut types due to missing data. Several types of nuts have unique nutritional ingredients and are more suitable for patients with kidney disease than other types. In follow-up studies, we wish to compare the effects of different nut types and try to give a detailed recommendation of nut type and intake for the CKD population.

Conclusions

Our study suggests that an appropriate consumption frequency of nuts, such as "1–6 times per week," is associated with a lower prevalence of CKD in the US adult population. Higher frequent consumption of nuts is a protective factor of a lower death rate for the non-CKD population rather than the CKD population. For patients with kidney disease, having an adequate intake of nuts 1–6 times per week might be a relatively good choice. We add to the connection between nut consumption and CKD independent of a dietary pattern and provide a dietary recommendation for the frequency of nut consumption.

Acknowledgments

We thank all members of the National Center for Health Statistics (NCHS) of the Centers for Disease Control (CDC) and Prevention and the participants who contributed to the National Health and Nutrition Examination Survey.

Statement of Ethics

The current study was a secondary analysis of NHANES data, the original survey was approved by the NCHS's Institutional Review Board, and all participants provided written informed consent. More details are available on the NHANES website.

Conflict of Interest Statement

The authors declare no conflicts of interest.

Funding Sources

This research received no external funding.

Author Contributions

Conceptualization: Koushu Wang and Duo Qian; data curation: Koushu Wang and Duo Qian; methodology: Koushu Wang and Duo Qian; project administration: Yichun Cheng, Shuwang Ge, and Ying Yao; software: Yichun Cheng; supervision: Shuwang Ge and Ying Yao; validation: Yuncan Hu and Yichun Cheng; writing – original draft: Koushu Wang; writing – review and editing: Shuwang Ge and Ying Yao.

Data Availability Statement

All raw data are available on the NHANES and CDC website.

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