Title
Nut Consumption and Renal Function Among Women With a History of Gestational Diabetes

Journal
Journal of Renal Nutrition, 30(5)

ISSN
1051-2276

Authors
Ajjarapu, Aparna S
Hinkle, Stefanie N
Wu, Jing
et al.

Publication Date
2020-09-01

DOI
10.1053/j.jrn.2019.10.005

Peer reviewed

HHS Public Access

Author manuscript

J Ren Nutr. Author manuscript; available in PMC 2021 September 01.

Published in final edited form as:

J Ren Nutr. 2020 September ; 30(5): 415–422. doi:10.1053/j.jrn.2019.10.005.

Nut consumption and renal function among women with a history of gestational diabetes

Aparna S Ajjarapu[1], **Stefanie N Hinkle**[1], **Jing Wu**[2], **Mengying Li**[1], **Shristi Rawal**[3], **Ellen C Francis**[4], **Liwei Chen**[5], **Georgia Pitsava**[1], **Anne A Bjerregaard**[6], **Louise G Grunnet**[7], **Allan Vaag**[8], **Yeyi Zhu**[9], **Ronald C W Ma**[10], **Peter Damm**[11], **James L Mills**[1], **Sjurdur F Olsen**[12], **Cuilin Zhang**[13]

[1]Division of Intramural Population Health Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland. [2]TPG/Glotech, Rockville, Maryland. [3]Department of Nutritional Sciences, School of Health Professions, Rutgers University, Newark, New Jersey. [4]Division of Intramural Population Health Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland; National Institutes of Health Graduate Partnerships Program, Bethesda, Maryland; Department of Public Health Sciences, Clemson University, Clemson, South Carolina. [5]Department of Epidemiology, Fielding School of Public Health, University of California, Los Angeles, California. [6]Department of Epidemiology Research, Center for Fetal Programming, Statens Serum Institut, Copenhagen, Denmark. [7]Department of Endocrinology-Diabetes and Bone-metabolic Research Unit, Rigshospitalet, Copenhagen, Denmark. [8]Cardiovascular and Metabolic Disease (CVMD) Translational Medicine Unit, Early Clinical Development, IMED Biotech Unit, AstraZeneca, Gothenburg, Sweden. [9]Division of Research, Kaiser Permanente Northern California, Oakland, California; Department of Epidemiology and Biostatistics, University of California, San Francisco, California. [10]Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong, China. [11]Department of Obstetrics, Center for Pregnant Women with Diabetes, Rigshospitalet, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark. [12]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, Massachusetts. [13]Division of Intramural Population Health Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland.

Abstract

Objective: Nut intake has been associated with reduced cardiometabolic risk, but few studies have examined its association with renal function. We examined associations between nut intake and renal function among women with previous gestational diabetes mellitus (GDM), a population with an increased risk for renal dysfunction.

CORRESPONDING AUTHOR: Dr. Cuilin Zhang, Division of Intramural Population Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, 6710B Rockledge Drive, MSC 7004, Bethesda, MD 20817. Office: (301)-435-6917. Fax: 301-402-2084. zhangcu@mail.nih.gov.

DATA SHARING: The analytic code used for the analysis described in the manuscript is available on request. The data described in the manuscript are not currently available for sharing. Please contact Dr. Cuilin Zhang for more information (zhangcu@mail.nih.gov).

Design and Methods: This study included 607 women with a history of GDM who participated in the Diabetes & Women's Health Study (2012–2014) follow-up clinical exam in Denmark. At the clinic, biospecimens were collected and habitual intake of nuts (9 types) in the past year was assessed using a food frequency questionnaire. A total of 330 women free of major chronic diseases were included in the analysis. Total nut intake was classified as none (≤1 serving/month), monthly (2–3 servings/month), weekly (1–6 servings/week), and daily (≥1 serving/day). One serving was defined as 28g. Renal function markers included estimated glomerular rate (eGFR) and urinary albumin-to-creatinine ratio (UACR), calculated based on plasma creatinine (mg/dL), and urinary albumin (mg/L), and creatinine (mg/dL) measurements, respectively. We estimated percent differences with 95% confidence intervals (CI) for each outcome by nut intake, adjusted for current body mass index, age, physical activity, energy intake, alcohol consumption, and vegetables intake.

Results: We observed a non-linear association between total nut intake and UACR with lowest UACR values among women with weekly intake. Compared to women with weekly intake (n=222), the adjusted UACR values were higher by 86% [95% CI: 15%, 202%], 24% [−1%, 54%], and 117% [22%, 288%] among women with no (n=13), monthly (n=86), and daily (n=9) intake, respectively. Compared to weekly consumers, daily nut consumers also had 9% [0%, 19%] significantly higher eGFR values but eGFR values were similar among women with no and monthly intake.

Conclusion: Moderate nut consumption may be beneficial to kidney health among women with prior GDM.

Keywords

nuts; diet; gestational diabetes; renal function; kidney

INTRODUCTION

Chronic kidney disease (CKD), described as abnormalities in kidney structure and function,[1] has an average global prevalence of 13.4%[2] and is associated with increased risk of cardiovascular disease, premature mortality, and decreased quality of life.[3] Of note, elevated renal function markers that do not meet the established clinical thresholds for renal disease have also been associated with a significantly increased risk for renal impairment and all-cause mortality.[4,5] Therefore, it is important to study subclinical renal disorders and identify strategies to promote renal function to ultimately prevent CKD and reduce the significant healthcare costs and morbidity associated with this disease, especially among populations at increased risk for impaired renal function.[6]

In a recent prospective cohort study, women with prior gestational diabetes mellitus (GDM) compared to women without a history of GDM had an increased risk for subclinical renal dysfunction as indicated by an increased estimated glomerular filtration rate (eGFR) and elevated urinary albumin-to-creatinine ratio (UACR) 9–16 years after the index pregnancy.[7] Findings from this study along with others suggest that women with a history of GDM represent a population at an increased risk for impaired renal function.[8,9] Therefore,

identifying potentially modifiable factors to prevent renal dysfunction, such as dietary factors, is essential, particularly among women with a history of GDM.

Nuts are nutrient dense foods, rich in bioactive molecules such as polyunsaturated fatty acids (PUFA), L-arginine, fiber, minerals, and antioxidants, which may prevent kidney injury.[10] However, the phosphorus and high protein content in nuts have raised concerns about possible adverse effects of nut intake on renal function,[11,12] thus it is recommended that patients with advanced CKD limit their nut intake.[13] Nut consumption has been associated with a decreased risk for chronic conditions such as type 2 diabetes, metabolic syndrome, and cardiovascular disease,[14,15] however, few studies have investigated associations between nut intake and renal function,[16] especially among individuals before the diagnosis of CKD. As such, the limited research on the role of nuts in maintaining kidney health, particularly in populations at increased risk, presents an important data gap that needs to be addressed.

The aim of the study was to examine the associations between nut consumption and renal function among women with prior GDM.

METHODS

Study Population

The Diabetes & Women's Health (DWH) Study (2012–2014) is a long-term follow-up study of women with prior GDM. The present study is based on data from the DWH Study Danish site, which included women within the Danish National Birth Cohort (DNBC).[17] The DNBC, is a longitudinal cohort of 91,827 pregnant women in Denmark (1996–2002).[18] Women in the DNBC were asked about their GDM status during the index pregnancy through standardized telephone interviews conducted at gestational week 30 and 6 months postpartum. Self-reported GDM status was recorded at an interview during pregnancy or postpartum and GDM diagnosis was determined by reviewing hospital records from the Danish National Patient Registry.[19,20] In the DNBC, 1,274 women were identified as having GDM in the index pregnancy, of whom 790 women participated in the DWH Study follow-up. Women who participated were largely comparable to women who did not participate.[17] Of these women, 607 participated in a clinical exam where they provided biospecimens. To reduce the potential for reverse causation, we excluded women with known chronic conditions at follow-up; type 1 or type 2 diabetes self-reported or diagnosed in the clinic (n=149), self-reported heart disease (n=27), gout (n=5), cancer (n=24), elevated blood pressure in the past year (n=65), or elevated cholesterol in the past year (n=45) (Supplemental Figure 1). Furthermore, women with nut allergies (n=26), missing or implausible energy intake defined as <2,510 or >16,736 kJ/day (n=12)[21] or missing renal function marker data (n=16) were excluded. After applying these exclusion criteria, 330 women remained for analysis. All women gave written informed consent in accordance with the Helsinki II Declaration. The study was approved by the Regional Scientific Ethical Committee of the Capital Region of Denmark (record no. H-4-2013-129).

Exposure Measures

Women completed a semi-quantitative 360-item food frequency questionnaire (FFQ) on their habitual dietary intake during the previous year. The FFQ collected information separately for nine different types of nuts: walnuts, almonds, brazil nuts, pine nuts, hazelnuts, pistachios, cashews, peanuts (not roasted) and other types of nuts or seeds. Frequency choices ranged from “never during the last year” to “two or more servings per day”. Consumption of all nine types was combined and total nut consumption was categorized as: ≤1 serving/month (rarely), 2–3 servings/month (monthly), 1–6 servings/week (weekly), and ≥1 servings/day (daily). We chose these categories to provide public health relevant categories of nut consumption. One serving size of nuts was defined as 28g, which is the standard serving size most frequently used in previous studies investigating associations between nut intake and health outcomes.[22]

Outcome Measures

During the clinic visit, a standardized protocol was used to measure height, weight, and blood pressure. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Morning urine and fasting blood samples were collected and immediately stored at −80°C using a standardized protocol. The biospecimens were assayed for urine albumin (mg/L), urine creatinine (mg/dl), and plasma creatinine (mg/dl) concentrations (Roche Diagnostics, Indianapolis, IN). The interassay coefficients of variation for all assays was ≤6.7%.

Urinary albumin-to-creatinine ratio (UACR) was calculated. Elevated UACR was defined as ≥20 mg/g according to our laboratory reference range values and as used previously.[23–25] Microalbuminuria was defined as UACR >30 mg/g.[26] Estimated glomerular filtration rate (eGFR) was calculated based on plasma creatinine concentration, age, and race using the Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI).[27] Glomerular hyperfiltration was defined as eGFR ≥95th percentile (116.4 mL/min/1.73m^2).[28]

Covariates

Possible risk factors for impaired kidney function were obtained from the DWH Study follow-up questionnaires and clinical exam. Covariates selected *a priori* included current age (years), total energy intake (kJ/day), and current BMI (kg/m^2). Additional covariates were selected based on the statistical significance ($P < 0.05$) of their association with total nut consumption and UACR or eGFR. Habitual intake of vegetables (g/d), legumes (g/d), red meats (g/d), sugar-sweetened beverages (g/d), and alcohol (g/d), moderate to vigorous physical activity (metabolic equivalent hours per week), education (high school or less vs. more than high school education), and nulliparity (yes vs. no) were significantly associated with total nut intake and tested for their significance with either eGFR or UACR. Among these variables, vegetables, alcohol, and moderate to vigorous physical activity were selected as covariates.

Statistical Methods

Descriptive statistics were conducted to characterize the baseline demographic and clinical characteristics of the study population. The median (interquartile range) was calculated for

continuous variables and frequencies were calculated for categorical variables. Differences in baseline demographic characteristics across frequencies of total nut consumption were tested in continuous and categorical variables by the non-parametric Kruskal-Wallis ANOVA test and chi-square tests, respectively. Differences in the unadjusted UACR and eGFR values and subclinical renal conditions across frequencies of total nut consumption were tested by the non-parametric Kruskal-Wallis ANOVA test and the Fisher's exact test, respectively.

UACR and eGFR were log transformed to achieve normality. Multivariable linear regression was used to estimate the adjusted percent difference in UACR and eGFR values within each frequency category of total nut consumption by exponentiating the estimated coefficient, subtracting 1 and multiplying by 100. Weekly consumption was selected as the reference group as this was the most common category for nut intake. The covariates included in the models were age (years), energy intake (kJ/day), moderate to vigorous physical activity (MET-h/week), alcohol consumption (g/day), and vegetable consumption (g/day). Three models were estimated. Model 1 adjusted for age. Model 2 adjusted for age, energy intake, moderate to vigorous physical activity, alcohol consumption, and vegetable consumption. Model 3 adjusted for model 2 covariates and current BMI. Age was not adjusted for in the eGFR models as it is a component in the CKD-EPI equation used to calculate eGFR.

Logistic regression was used to estimate the association between total nut intake and the binary outcomes of elevated UACR, microalbuminuria, or glomerular hyperfiltration. However, the models did not converge due to the small number of women with these renal conditions (n=29) and thus were not reported.

In the DWH Study follow-up questionnaire, women reported their medication use in the past month. We performed sensitivity analyses excluding women who reported use of medications that could influence the renal function markers concentrations (i.e., angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or diuretics) (n=37). We also performed sensitivity analyses excluding women with glomerular hyperfiltration (n=14) to reduce the potential of confounding from women who might have abnormal filtration pressure of the kidney. To explore which components of the nuts may be driving the observed associations, we individually adjusted the main analysis for the following nutrient variables: phosphorus, sodium, magnesium, PUFA, and total protein.

All analyses were performed using SAS version 9.4 (SAS institute, Cary, NC). P values <0.05 were considered significant.

RESULTS

On average, women consumed 0.2 servings per day (6.8 grams per day) of total nuts. Almonds and hazelnuts were the most frequently consumed (Supplemental Table 1). Table 1 displays participant characteristics by frequency of total nut consumption. Women who consumed nuts daily were more likely to have a lower BMI, had a higher education, and exercised more compared to women who consumed nuts rarely, monthly or weekly. In addition, women who consumed nuts more frequently had higher overall energy intake, and higher intake of vegetables, red meat, sugar-sweetened beverages, and alcohol.

Subclinical renal conditions were rare with only nine women (2.7%) with an elevated UACR, six women (1.8%) with microalbuminuria, and 14 women (4.2%) with glomerular hyperfiltration (Table 2). Prevalence of microalbuminuria and elevated UACR varied significantly by frequency of total nut intake while the prevalence of glomerular hyperfiltration did not. The unadjusted values of UACR and eGFR did not vary significantly by frequency of total nut intake.

Compared to women who consumed nuts weekly (1–6 servings per week), the age-adjusted UACR was significantly higher for women who consumed nuts rarely (≤1 serving per month), monthly (2–3 servings per month) or daily (≥1 serving per day) (Table 3). After adjustment for confounding variables including BMI, women who rarely consumed nuts had 86.2% (15.0%, 201.6%) greater adjusted UACR values and women who consumed nuts daily had 117.4% (22.0%, 287.5%) greater adjusted UACR values as compared to women who consumed nuts weekly. The adjusted UACR values of monthly consumers, were slightly attenuated and no longer significantly greater than weekly consumers (Table 3).

Compared to weekly consumers, daily nut consumers had 9.2% (0.4%,18.7%) greater adjusted eGFR values (Table 3). No differences were observed in the eGFR between women who consumed nuts rarely or monthly and women who consumed nuts weekly.

The association between nut intake and UACR didn’t change materially after additional adjustment for selected nutrients (Table 4). Further exclusion of women with reported use of medications that could influence renal function or exclusion of women with glomerular hyperfiltration did not change the results materially. The results for eGFR were generally similar after adjusting for additional nutrients except among daily consumers. After adjustment for magnesium and sodium the percent difference between weekly and daily consumers was no longer statistically significant.

DISCUSSION

In this cohort of middle-aged Danish women with a history of GDM, we observed a non-linear association between nut consumption and markers of renal function. Increasing nut intake up to weekly consumption was associated with progressively decreasing UACR values. In contrast, both daily consumers and non-consumers had significantly greater UACR values compared to weekly consumers. These results suggest that moderate nut consumption may be beneficial to kidney health among women with a history of GDM who are at increased risk for kidney disease.

Subclinical renal dysfunction among women with prior GDM has been previously indicated by increased eGFR and UACR.[7,8] Women in the present study generally had UACR and eGFR values within the normal range and very few women had subclinical renal conditions. This is to be expected, given that we excluded women with chronic conditions at follow-up, and the relatively young median age of the study participants as older age is an important risk factor for kidney disease.[29] Although clinical renal disease was uncommon in this study sample, UACR values below the threshold for microalbuminuria (i.e., above 10 mg/g) and eGFR values below the threshold for glomerular hyperfiltration (i.e., above 105 ml/min/

1.73m^2) have previously been associated with an increased risk for all-cause mortality in a meta-analysis of general population cohorts and could be precursors of renal impairment.[4] Increasing consumption of nuts, up to weekly, was associated with progressively decreasing UACR values, which may suggest a possible protective role of nuts with respect to kidney health. The significantly greater UACR and eGFR values among daily nut consumers compared to weekly consumers may suggest an increased risk for adverse renal outcomes among this group, although clinical significance of higher eGFR values in this group is unclear as few participants had values indicative of glomerular hyperfiltration. Additionally, the sample size among daily nut consumers was small (n=9), and thus our findings should be interpreted with caution and require replication.

We are unaware of previous studies on nut consumption and renal function markers among high risk individuals, such as women with prior GDM. Only one prior study, that we know of, has investigated associations between nut intake and renal function in healthy U.S. adults in the Atherosclerosis Risk in Communities (ARIC) Study.[16] Our findings are generally consistent with those from the ARIC Study, which observed that increasing nut intake was associated with a decreased risk for incident CKD.[16] Although the longer follow up duration of 23 years and the older age range (44–64 years) of ARIC study participants allowed for the examination of clinically relevant outcomes of CKD, our study provides a different perspective in that we investigated continuous outcomes and subclinical markers of renal function in a high-risk population, which has never been investigated before. In addition, our findings of decreased UACR values with increasing nut intake up to weekly intake, are generally consistent with data from experimental studies on animals which demonstrate that rats with induced kidney injury show improvements in renal function after being administered nut extracts.[30,31]

Although the precise underlying molecular mechanisms are unclear, our findings that moderate nut consumption could be beneficial to kidney health are biologically plausible. Nuts are rich in PUFA and minerals such as magnesium, which reduce oxidative stress, inflammation, and endothelial dysfunction[10] and may have contributed to the lower UACR values observed among women who consumed nuts weekly. For instance, increased intake of n-3 PUFAs has been associated with a reduced likelihood of CKD and decline in renal function in both observational studies and clinical trials.[32–34] In addition, PUFAs have been associated with reducing factors known to play a role in the progression of kidney disease such as blood pressure, vascular calcification, oxidative stress, and endothelial dysfunction.[35,36] In our sensitivity analyses, adjusting for PUFA, we observed a slight attenuation in the UACR associations with low nut intake, suggesting that a small proportion of the observed association may potentially be due to PUFAs in nuts.

Of note, nuts are also rich in protein and phosphorus, higher consumption of which are demonstrated to be potentially harmful to kidney health. For instance, in a review of randomized controlled trials on protein intake and urinary measures of kidney function, most studies observed significantly higher eGFR values in response to increased protein intake (from 0.7–1.5 g/kg to 1.8–2.5 g/kg daily) in healthy American adults[37] Similarly, phosphorus rich diets could lead to dysregulation of phosphorus homeostasis and increased renal calcification and endothelial dysfunction.[38] We did, however, adjust for total protein

intake and phosphorus in our sensitivity analyses, and UACR and eGFR values in daily nut consumers remained significantly greater compared to weekly nut consumers, although the confidence intervals were still relatively large.

The strengths of our study include adjustment for an extensive set of potential confounders including major dietary factors and physical activity. We also excluded women with previous chronic diseases which reduced the potential of reverse causation. In addition, the young age of our study sample allowed us to examine continuous markers of renal function in relatively healthy individuals. This provided a unique opportunity to identify modifiable factors that could assist high-risk women in maintaining kidney health.

This study also has some potential limitations. First, as in other observational studies, measurement error of nut intake was inevitable. However, a validation study of a similar food-frequency questionnaire in the Nurses' Health Study, used in previous studies investigating nut intake and health outcomes ,[39] demonstrated to have reasonable validity in the assessment of nut intake with a correlation coefficient of 0.75 between the FFQ and four 1-week diet records of nut intake.[40] Further, we did not have data on the preparation methods of the nuts which could have altered their nutritive content.[10] There are no established clinical guidelines for subclinical renal conditions within the average ranges of UACR and eGFR of our study sample. Nonetheless, the findings from our study are important to report from a prevention perspective of renal disease. Also, the small sample size in our highest (≥1 serving/day) and lowest (≤1 serving/month) nut intake categories, necessitates that our findings be replicated. Our study defined one serving of nuts as 28g, which, for example, equates to about 24 shelled almonds.[41] There is substantial variability in the definition of a serving of nuts, however, we used 28g per serving as it is the most commonly used serving size in previous studies investigating associations between nut intake and health outcomes.[22] Finally, although the nut consumption patterns of our study sample, who consumed mostly almonds and hazelnuts was similar to other reports from Northern Europe, the generalizability of our findings could be reduced for other populations with different underlying nut consumption patterns, like the U.S., which mostly consumes almonds, walnuts, and pecans.[42,43]

In conclusion, our findings suggest that moderate nut consumption (i.e., weekly) may promote kidney health in women with prior GDM who are at high-risk for renal dysfunction. Further studies of large sample size are warranted to confirm the findings, which may assist in the prevention of renal impairment, particularly in high-risk individuals and potentially in the general population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS:

This study was conceived and designed by C.Z. The data were analyzed by S.N.H, J.W., A.S.A, M.L., and C.Z. Funding was obtained by C.Z. The first draft of the manuscript was prepared by A.S.A and S.N.H and was edited with the input from all authors who read and approved of the final manuscript. Conflict of Interest (COI) Statement: Authors Aparna S. Ajjarapu, Stefanie N. Hinkle, Jing Wu, Mengying Li, Shristi Rawal, Ellen Francis, Liwei Chen,

Georgia Pitsava, Anne A. Bjerregaard, Louise G. Grunnet, Yeyi Zhu, Ronald C.W. Ma, Peter Damm, James L. Mills, Sjurdur F. Olsen, and Cuilin Zhang have no potential conflicts of interest relevant to this article. Allan A. Vaag is employed by AstraZeneca. Sources of support: This work was supported by the Intramural Research Program of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development at the National Institutes of Health [contract numbers HHSN275201000020C, HHSN275201500003C, HHSN275201300026I, HSN275201100002I], March of Dimes Birth Defects Foundation [6-FY-96-0240, 6-FY97-0553, 6-FY97-0521, 6-FY00-407], Innovation Fund Denmark [grant number 09-067124 and 11-115923, 'Centre for Fetal Programming'], the Health Foundation [11/263-96], the Heart Foundation [96-2-4-83-22450], the EU (FP7-289346-EarlyNutrition), the Danish Diabetes Academy supported by the Novo Nordisk Foundation, and career development awards from the National Institutes of Health Building Interdisciplinary Research Careers in Women's Health Program (grant # 5K12HD05216) and National Institute of Diabetes and Digestive Kidney Diseases (grant # K01DK120807).

REFERENCES

1. Chapter 1: Definition and classification of CKD. Kidney Int Suppl (2011). 2013;3(1):19–62. [PubMed: 25018975]
2. Hill NR, Fatoba ST, Oke JL, et al. Global Prevalence of Chronic Kidney Disease - A Systematic Review and Meta-Analysis. PLoS One. 2016;11(7):e0158765. [PubMed: 27383068]
3. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351(13):1296–1305. [PubMed: 15385656]
4. Chronic Kidney Disease Prognosis C, Matsushita K, van der Velde M, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010;375(9731):2073–2081. [PubMed: 20483451]
5. Palatini P Glomerular hyperfiltration: a marker of early renal damage in pre-diabetes and pre-hypertension. Nephrol Dial Transplant. 2012;27(5):1708–1714. [PubMed: 22431709]
6. Low S, Su Chi L, Zhang X, et al. Medical Costs Associated with Chronic Kidney Disease Progression in an Asian Population with Type 2 Diabetes Mellitus. Nephrology (Carlton). 2018.
7. Rawal S, Olsen SF, Grunnet LG, et al. Gestational Diabetes Mellitus and Renal Function: A Prospective Study With 9- to 16-Year Follow-up After Pregnancy. Diabetes Care. 2018;41(7):1378–1384. [PubMed: 29728364]
8. Dehmer EW, Phadnis MA, Gunderson EP, et al. Association Between Gestational Diabetes and Incident Maternal CKD: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. Am J Kidney Dis. 2018;71(1):112–122. [PubMed: 29128412]
9. Beharier O, Shoham-Vardi I, Pariente G, et al. Gestational diabetes mellitus is a significant risk factor for long-term maternal renal disease. J Clin Endocrinol Metab. 2015;100(4):1412–1416. [PubMed: 25668200]
10. Ros E Health benefits of nut consumption. Nutrients. 2010;2(7):652–682. [PubMed: 22254047]
11. Knight EL, Stampfer MJ, Hankinson SE, Spiegelman D, Curhan GC. The impact of protein intake on renal function decline in women with normal renal function or mild renal insufficiency. Ann Intern Med. 2003;138(6):460–467. [PubMed: 12639078]
12. White J Crunch on This…A Fresh Look at Nuts for Renal Nutrition. Journal of Renal Nutrition. 2017;27(2):e7–e9.
13. National Institute of Diabetes and Digestive and Kidney Diseases. Nutrition for Advanced Chronic Kidney Disease in Adults 2014; https://www.niddk.nih.gov/health-information/kidney-disease/chronic-kidney-disease-ckd/eating-nutrition/nutrition-advanced-chronic-kidney-disease-adults. Accessed 10 Dec, 2018.
14. Mayhew AJ, de Souza RJ, Meyre D, Anand SS, Mente A. A systematic review and meta-analysis of nut consumption and incident risk of CVD and all-cause mortality. Br J Nutr. 2016;115(2):212–225. [PubMed: 26548503]
15. Luo C, Zhang Y, Ding Y, et al. Nut consumption and risk of type 2 diabetes, cardiovascular disease, and all-cause mortality: a systematic review and meta-analysis. Am J Clin Nutr. 2014;100(1):256–269. [PubMed: 24847854]
16. Haring B, Selvin E, Liang M, et al. Dietary Protein Sources and Risk for Incident Chronic Kidney Disease: Results From the Atherosclerosis Risk in Communities (ARIC) Study. Journal of renal

nutrition : the official journal of the Council on Renal Nutrition of the National Kidney Foundation. 2017;27(4):233–242.

17. Zhang C, Olsen SF, Hinkle SN, et al. Diabetes & Women's Health (DWH) Study: an observational study of long-term health consequences of gestational diabetes, their determinants and underlying mechanisms in the USA and Denmark. BMJ Open. 2019;9(4):e025517.
18. Olsen J, Melbye M, Olsen SF, et al. The Danish National Birth Cohort--its background, structure and aim. Scand J Public Health. 2001;29(4):300–307. [PubMed: 11775787]
19. Olsen SF, Houshmand-Oeregaard A, Granstrom C, et al. Diagnosing gestational diabetes mellitus in the Danish National Birth Cohort. Acta Obstet Gynecol Scand. 2017;96(5):563–569. [PubMed: 28027410]
20. Zhang C, Hu FB, Olsen SF, et al. Rationale, design, and method of the Diabetes & Women's Health study--a study of long-term health implications of glucose intolerance in pregnancy and their determinants. Acta Obstet Gynecol Scand. 2014;93(11):1123–1130. [PubMed: 24828694]
21. Schulze MB, Manson JE, Ludwig DS, et al. Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. JAMA. 2004;292(8):927–934. [PubMed: 15328324]
22. Aune D, Keum N, Giovannucci E, et al. Nut consumption and risk of cardiovascular disease, total cancer, all-cause and cause-specific mortality: a systematic review and dose-response meta-analysis of prospective studies. BMC Med. 2016;14(1):207. [PubMed: 27916000]
23. Pirro M, Mannarino MR, Francisci D, et al. Urinary albumin-to-creatinine ratio is associated with endothelial dysfunction in HIV-infected patients receiving antiretroviral therapy. Sci Rep. 2016;6:28741. [PubMed: 27353425]
24. Franceschini N, Savitz DA, Kaufman JS, Thorp JM. Maternal urine albumin excretion and pregnancy outcome. Am J Kidney Dis. 2005;45(6):1010–1018. [PubMed: 15957129]
25. Tebbe U, Bramlage P, Luders S, et al. Follow-up of cardiovascular risk markers in hypertensive patients treated with irbesartan: results of the i-SEARCH Plus Registry. J Clin Hypertens (Greenwich). 2010;12(12):909–916. [PubMed: 21122056]
26. Molitch ME, DeFronzo RA, Franz MJ, et al. Nephropathy in diabetes. Diabetes Care. 2004;27 Suppl 1:S79–83. [PubMed: 14693934]
27. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604–612. [PubMed: 19414839]
28. Sasson AN, Cherney DZ. Renal hyperfiltration related to diabetes mellitus and obesity in human disease. World J Diabetes. 2012;3(1):1–6. [PubMed: 22253940]
29. Hallan SI, Matsushita K, Sang Y, et al. Age and association of kidney measures with mortality and end-stage renal disease. JAMA. 2012;308(22):2349–2360. [PubMed: 23111824]
30. Anselmo NA, Paskakulis LC, Garcias RC, et al. Prior intake of Brazil nuts attenuates renal injury induced by ischemia and reperfusion. J Bras Nefrol. 2018;40(1):10–17. [PubMed: 29796584]
31. Olabiyi AA, Carvalho FB, Bottari NB, et al. Tiger nut and walnut extracts modulate extracellular metabolism of ATP and adenosine through the NOS/cGMP/PKG signalling pathway in kidney slices. Phytomedicine. 2018;43:140–149. [PubMed: 29747747]
32. Gopinath B, Harris DC, Flood VM, Burlutsky G, Mitchell P. Consumption of long-chain n-3 PUFA, alpha-linolenic acid and fish is associated with the prevalence of chronic kidney disease. Br J Nutr. 2011;105(9):1361–1368. [PubMed: 21255476]
33. Lauretani F, Semba RD, Bandinelli S, et al. Plasma polyunsaturated fatty acids and the decline of renal function. Clin Chem. 2008;54(3):475–481. [PubMed: 18202159]
34. Miller ER, 3rd, Juraschek SP, Appel LJ, et al. The effect of n-3 long-chain polyunsaturated fatty acid supplementation on urine protein excretion and kidney function: meta-analysis of clinical trials. Am J Clin Nutr. 2009;89(6):1937–1945. [PubMed: 19403630]
35. Egert S, Stehle P. Impact of n-3 fatty acids on endothelial function: results from human interventions studies. Curr Opin Clin Nutr Metab Care. 2011;14(2):121–131. [PubMed: 21252652]
36. Zhao G, Etherton TD, Martin KR, West SG, Gillies PJ, Kris-Etherton PM. Dietary alpha-linolenic acid reduces inflammatory and lipid cardiovascular risk factors in hypercholesterolemic men and women. J Nutr. 2004;134(11):2991–2997. [PubMed: 15514264]

37. Van Elswyk ME, Weatherford CA, McNeill SH. A Systematic Review of Renal Health in Healthy Individuals Associated with Protein Intake above the US Recommended Daily Allowance in Randomized Controlled Trials and Observational Studies. Adv Nutr. 2018;9(4):404–418. [PubMed: 30032227]

38. Chang AR, Anderson C. Dietary Phosphorus Intake and the Kidney. Annual review of nutrition. 2017;37:321–346.

39. Liu G, Guasch-Ferré M, Hu Y, et al. Nut consumption in relation to cardiovascular disease incidence and mortality among patients with diabetes mellitus. Circulation research. 2019;124(6):920–929. [PubMed: 30776978]

40. Salvini S, Hunter DJ, Sampson L, et al. Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. International journal of epidemiology. 1989;18(4):858–867. [PubMed: 2621022]

41. Ku E, Lee BJ, Wei J, Weir MR. Hypertension in CKD: Core Curriculum 2019. Am J Kidney Dis. 2019.

42. Jenab M, Sabate J, Slimani N, et al. Consumption and portion sizes of tree nuts, peanuts and seeds in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohorts from 10 European countries. Br J Nutr. 2006;96 Suppl 2:S12–23.

43. Food Availability (Per Capita) Data System. United States Department of Agriculture 2018 Accessed 04.09.2019.

Practical Application

- Women with a prior history of gestational diabetes, who are at high risk for kidney disease, may benefit from moderate consumption of nuts.

Table 1.

Characteristics of study participants according to frequency of total nut consumption (n=330)

	Frequency of Total Nut Consumption				
Characteristics[1]	**≤1 serving per month (n=13)**	**2–3 servings per month (n=86)**	**1–6 servings per week (n=222)**	**≥1 servings per day (n=9)**	**P-value**[2]
Nuts (g/day)	0.5 (0.2, 0.7)	1.8 (1.4, 2.3)	6.7 (4.2, 11.3)	26.0 (24.9, 29.5)	
Age (years)	44.0 (43.0, 46.0)	43.0 (40.0, 46.0)	44.0 (40.6, 46.0)	42.0 (40.0, 44.0)	0.65
Body Mass Index (kg/m^2)	28.4 (25.4, 36.6)	29.1 (26.1, 33.0)	26.9 (23.8, 31.4)	25.0 (23.7, 27.3)	0.01
<25.0	3 (23.1)	18 (20.9)	77 (34.7)	4 (44.4)	0.15
25–29.9	4 (30.8)	31 (36.1)	76 (34.2)	4 (44.4)	
≥30.0	6 (46.2)	37 (43.0)	69 (31.1)	1 (11.1)	
Parity					0.03
1	1 (7.7)	10 (11.6)	20 (9.0)	2 (22.2)	
2	3 (23.1)	46 (53.5)	93 (41.9)	3 (33.3)	
≥3	7 (53.9)	30 (34.9)	103 (46.4)	4 (44.4)	
Education					0.004
≤ High school	5 (38.5)	14 (16.3)	22 (9.9)	0 (0.0)	
Married	9 (69.2)	74 (86.1)	193 (86.9)	9 (100.0)	0.26
Moderate/Vigorous physical activity (MET-h/week[3])	13.0 (5.1, 46.6)	16.8 (6.3, 30.7)	30.9 (13.2, 53.4)	30.0 (13.0, 112.7)	<0.001
Smoking Status					0.11
Former smokers	4 (30.8)	22 (25.6)	68 (30.6)	4 (44.4)	
Current smokers	5 (38.5)	18 (20.9)	30 (13.5)	0 (0.0)	
Never smokers	4 (30.8)	46 (53.5)	124 (55.9)	5 (55.6)	
Renal Medication use in past month or less	0 (0.0)	1 (1.2)	8 (3.6)	0 (0.0)	0.56
Pregnancy Hypertension Complications	1 (7.7)	3 (3.5)	4 (1.8)	1 (11.1)	0.21
Energy intake (kJ/day)	6129.7 (4500.5, 8869.0)	7213.5 (5822.7, 8832.5)	8321.4(6952.6, 10019.1)	9363.3 (8173.6, 10277.8)	<0.001
Vegetables (g/d)	82.1 (56.7, 139.1)	116.4 (89.2, 167.0)	156.8 (104.3, 248.9)	312.9 (175.8, 345.7)	<0.001
Fruit (g/d)	34.2 (11.7, 68.1)	82.3 (21.8, 116.7)	79.6 (23.3, 171.4)	195.7 (111.8, 261.7)	0.11
Whole grains (g/d)	62.8 (53.4, 131.3)	95.0 (53.3, 120.6)	100.1 (60.2, 147.4)	100.0 (70.1, 124.8)	0.23
Red Meat (g/d)	71.9 (50.3, 88.6)	85.0 (64.8, 101.5)	94.1 (73.7, 110.2)	81.2 (44.5, 100.7)	0.004
Processed Meat (g/d)	4.8 (0.8, 6.5)	4.8 (3.1, 7.6)	5.6 (3.5, 8.3)	5.4 (3.8, 7.4)	0.21
Fish (g/d)	12.1 (7.9, 35.5)	22.4 (12.0, 37.3)	23.8 (11.3, 34.1)	39.5 (32.3, 48.5)	0.20
Dairy (g/d)	558.3 (205.3, 896.2)	433.6 (258.5, 743.3)	505.8 (318.8, 786.2)	681.9 (642.3, 970.8)	0.31
Coffee (g/d)	12.6 (0.0, 117.9)	160.4 (0.1, 675.0)	169.3 (14.5, 517.8)	17.6 (0.1, 387.2)	0.15
Tea (g/d)	5.2 (0.0, 182.4)	23.0 (2.6, 269.8)	54.4 (13.1, 230.0)	157.1 (16.7, 1028.6)	0.09
Sugar-sweetened beverages (g/d)	26.8 (5.4, 120.5)	58.7 (21.7, 102.9)	79.9 (34.7, 173.3)	62.4 (43.0, 90.2)	0.01
Alcohol intake (g/d)	0.0 (0.0, 0.6)	1.5 (0.6, 3.2)	2.7 (1.2, 6.4)	1.2 (0.6, 2.9)	<0.001

[1] Data are presented as median (25th percentile, 75th percentile) for continuous variables and as n (%) for categorical variables.

[2] P-value of the continuous and categorical variables with total nut exposure across frequency of total nut consumption was estimated using the non-parametric Kruskal-Wallis ANOVA test or chi-square tests, respectively.

[3] MET-h/week=Metabolic equivalent hours per week

Table 2.

Renal function markers and subclinical renal conditions according to total nut consumption (n=330)

	Frequency of Total Nut Consumption				
	≤1 serving per month (n=13)	**2–3 servings per month (n=86)**	**1–6 servings per week (n=222)**	**≥1 servings per day (n=9)**	**P-value[3]**
Continuous Outcomes[1]					
Plasma creatinine (mg/dL)	0.7 (0.6, 0.7)	0.7 (0.6, 0.8)	0.7 (0.7, 0.8)	0.7 (0.7, 0.7)	0.70
Urine creatinine (mg/dL)	121.0 (106.0, 191.0)	119.0 (87.0, 157.0)	136.0 (92.0, 177.0)	131.0 (90.0, 140.0)	0.43
UACR[4] levels (mg/g)	3.1 (1.7, 10.9) *	2.1 (1.2, 3.8) *	2.1 (1.3, 2.8)	2.1 (1.9, 4.7) *	0.09
eGFR[5] levels (mL/min/1.73^2)	103.9 (92.8, 110.4)	101.8 (92.4, 108.8)	102.7 (91.8, 108.4)	106.3 (103.6, 110.3) *	0.50
Subclinical Renal Conditions[2]					
Elevated UACR (≥20mg/g)	1 (7.7)	4 (4.7)	3 (1.4)	1 (11.1)	0.04
Microalbuminuria (UACR >30mg/g)	1 (7.7)	2 (2.3)	2 (0.9)	1 (11.1)	0.04
Glomerular hyperfiltration (eGFR ≥95th percentile)	0 (0.0)	5 (5.8)	9 (4.1)	0 (0.0)	0.83

[1] Data presented as median (25th percentile, 75th percentile).

[2] Data presented as n (%).

[3] P-value of the continuous and categorical variables with total nut exposure across frequency of total nut consumption was estimated using the non-parametric Kruskal-Wallis ANOVA test or the Fisher's exact test, respectively.

[4] UACR=urinary albumin-to-creatinine ratio

[5] eGFR=estimated glomerular filtration rate

* significantly different from reference group (1–6 servings per week).

Table 3.

Adjusted percent differences of renal function markers according to total nut consumption (n=330)

	Adjusted % difference (95% CI), by Frequency of Total Nut Consumption			
	≤ 1 serving per month (n=13)	**2–3 servings per month (n=86)**	**1–6 servings er week (n=222)**	**≥ 1 servings per day (n=9)**
UACR[4]				
Model 1[1]	97.1 (22.6, 217.0)	27.4 (3.1, 57.4)	0.0 (Reference)	94.6 (10.5, 242.9)
Model 2[2]	88.7 (16.5, 206.5)	25.3 (0.5, 56.8)	0.0 (Reference)	116.4 (21.4, 285.7)
Model 3[3]	86.2 (15.0, 201.6)	23.6 (−1.0, 54.2)	0.0 (Reference)	117.4 (22.0, 287.5)
eGFR[5]				
Model 2[2]	−0.1 (−6.8, 7.1)	−0.9 (−4.0, 2.3)	0.0 (Reference)	9.1 (0.3, 18.6)
Model 3[3]	−0.3 (−7.0, 6.9)	−1.1 (−4.2, 2.1)	0.0 (Reference)	9.2 (0.4, 18.7)

[1]Model 1 was adjusted for age.

[2]Model 2 was additionally adjusted for energy intake, moderate to vigorous physical activity, alcohol consumption, and vegetables.

[3]Model 3 was additionally adjusted for current BMI.

[4]UACR=urinary albumin-to-creatinine ratio

[5]eGFR=estimated glomerular filtration rate. eGFR models were not adjusted for age as it is a component in the CKD-EPI equation used to calculate eGFR.

Table 4.

Sensitivity analyses adjusting for additional nutrients (n=330), and excluding women with renal medication use or glomerular hyperfiltration

	Adjusted % difference (95%CI), by Frequency of Total Nut Consumption			
	≤1 serving per month (n=13)	2–3 servings per month (n=86)	1–6 servings per week (n=222)	≥1 servings per day (n=9)
UACR[5]				
Fully adjusted[1]	86.2 (15.0, 201.6)	23.6 (−1.0, 54.2)	0.0 (Reference)	117.4 (22.0, 287.5)
Phosphorus[2]	84.3 (13.8, 198.6)	22.1 (−2.3, 52.5)	0.0 (Reference)	115.2 (20.7, 283.7)
Sodium[2]	86.2 (14.8, 201.9)	23.6 (−1.1, 54.3)	0.0 (Reference)	117.0 (20.8, 289.8)
Magnesium[2]	92.6 (18.4, 213.4)	23.5 (−1.1, 54.1)	0.0 (Reference)	111.6 (18.4, 278.2)
PUFA[2]	80.1 (10.7, 193.0)	22.3 (−2.1, 52.8)	0.0 (Reference)	122.8 (24.7, 298.0)
Total Protein[2]	87.4 (15.8, 203.4)	22.3 (−2.1, 52.6)	0.0 (Reference)	123.6 (25.4, 298.7)
Excluded women with past renal medication use[3]	87.5 (15.2, 205.2)	25.9 (0.4, 57.9)	0.0 (Reference)	116.6 (20.8, 288.2)
Excluded women with glomerular hyperfiltration[3]	90.9 (22.9, 197.0)	13.0 (−8.2, 39.1)	0.0 (Reference)	120.6 (30.1, 273.9)
eGFR[4]				
Fully adjusted[1]	−0.3 (−7.0, 6.9)	−1.1 (−4.2, 2.1)	0.0 (Reference)	9.2 (0.4, 18.7)
Phosphorus[2]	−0.5 (−7.2, 6.7)	−1.3 (−4.5, 1.9)	0.0 (Reference)	8.9 (0.2, 18.4)
Sodium[2]	−0.5 (−7.2, 6.6)	−1.1 (−4.2, 2.2)	0.0 (Reference)	7.8 (−0.9, 17.3)
Magnesium[2]	−0.3 (−6.5, 7.6)	−1.1 (−4.2, 2.1)	0.0 (Reference)	8.7 (−0.1, 18.2)
PUFA[2]	−1.0 (−7.7, 6.3)	−1.3 (−4.4, 1.9)	0.0 (Reference)	9.7 (0.9, 19.3)
Total Protein[2]	−0.3 (−7.0, 6.9)	−1.1 (−4.2, 2.2)	0.0 (Reference)	9.1 (0.3, 18.7)
Excluded women with past renal medication use[3]	−0.5 (−7.2, 6.6)	−1.5 (−4.6, 1.8)	0.0 (Reference)	8.8 (0.1, 18.3)
Excluded women with glomerular hyperfiltration[3]	0.7 (−5.9, 7.8)	−1.3 (−4.5, 1.9)	0.0 (Reference)	9.7 (1.1, 19.0)

[1] Fully adjusted model as reported in Table 3 was adjusted for age, energy intake, moderate to vigorous physical activity, alcohol consumption, vegetables, and current BMI.

[2] Fully adjusted model and additionally adjusted for the specified nutrient.

[3] Fully adjusted model with specified exclusion criteria.

[4] eGFR=estimated glomerular filtration rate. eGFR models were not adjusted for age as it is a component in the CKD-EPI equation used to calculate eGFR.

[5] UACR=urinary albumin-to-creatinine ratio