ORIGINAL RESEARCH

A Prospective Study of Dietary Meat Intake and Risk of Incident Chronic Kidney Disease

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Objective: The aim of the present study was to investigate the association of different meat intake and substitution of them with risk of incident chronic kidney disease (CKD).

Methods: At the baseline, habitual dietary intakes of 4881 participants of the Tehran Lipid and Glucose Study who were free of CKD were assessed by a valid and reliable food-frequency questionnaire. Logistic regression, adjusted for age, sex, smoking, total energy intake, triglycerides, body mass index, physical activity, hypertension, and diabetes, was used to assess the relationship between major protein sources of food (total red meat, unprocessed red meat, and processed red meat) and incident CKD. Odds ratios (ORs) and 95% confidence intervals (CIs) for the CKD were estimated for substituting one serving of total red meat with one serving of low-fat dairy, nuts, whole grains, and legumes.

Results: The mean ± standard deviation age of participants was 40.1 ± 12.8 years. After adjustment for confounders, compared with the lowest quartile of total red meat intake, OR of incident CKD in the highest quartile was 1.73 (95% CI: 1.33 to 2.24; *P* for trend <0.001) in the final model. OR for participants in the highest compared with that in the lowest quartile of processed red meat was 1.99 (95% CI: 2.54 to 2.56; *P* for trend <0.001). In the substitution analyses, replacing 1 serving of total red meat and processed meat with 1 serving of low-fat dairy, nuts, whole grains, and legumes was associated with a lower risk of incident CKD.

Conclusions: Higher consumption of total red meat and processed meat was associated with increased risk of incident CKD. Furthermore, substitution of total red and processed meat in the diet with other sources of dietary protein was associated with lower CKD risk.

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Introduction

THE ROLE OF dietary protein intake in the progression of kidney disease has always been a critical debate. Decline of kidney function was noted with higher intake of animal protein but not plant protein, emphasizing the importance of protein sources rather than the quantity of them regarding adverse health consequences.[1] To this point, understanding the role of various dietary protein sources on incidence of chronic kidney disease (CKD) is important.

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Meat is a major source of protein in most diets. Epidemiological evidence showed that meat intake, particularly red meat, affects multiple metabolic functions[2] and increases risks of diabetes,[3] cardiovascular disease (CVD),[4] and certain cancers.[5] On the other hand, we have previously demonstrated that higher intakes of plant sources of protein including whole grains, nuts, and legumes have favorable effects on kidney function.[6] A large cohort study from US adults investigating the association between dietary meat intake and incident CKD found that a higher intake of red meat and processed meat was associated with an increased risk of CKD.[7] They have also revealed that substituting nuts, low-fat dairy products, and legumes for some of the red and processed meat in the diet was associated with lower risk of CKD.[7]

To our knowledge, the study that has examined substitution of plant-based dietary proteins for total red meat, red meat, and processed meat on the risk of incidence of CKD has not been assessed in developing nations. Therefore, the first aim of the present study was to investigate the association of total meat, red meat, and processed meat with risk of incident CKD in a large population-based cohort of middle-aged adults with normal kidney function at baseline. We also examined the association of substituting other individual protein-rich foods for total meat, read meat, and processed meat with incident CKD.

Method

Study Population

For the present study, participants were selected from the Tehran Lipid and Glucose Study (TLGS) that is a prospective population-based cohort study being conducted on a sample of residents under coverage of 3 medical health centers in district no. 13 of Tehran, the capital of Iran, to determine the prevalence and incidence of noncommunicable diseases (NCD) and related risk factors.[8] The first examination cycle was performed in 1999–2001 and the prospective ongoing follow-up assessments at 3-year intervals were conducted, which are surveys II (2002-2005), III (2006-2008), IV (2009-2011), and V (2012-2015).

For the present study, during the fourth examination cycle of the TLGS (2009-2011), of 12,823 participants who had completed data on their medical histories and had undergone physical examinations, 7,956 participants were randomly selected for dietary assessment. From those, 6,686 individuals aged ≥20 years were selected. Pregnant and lactating women and those with missing information on covariates, with a history of myocardial infarction, stroke, and cancer, and those who reported daily energy intakes outside the range of 800-4,200 kcal/day, were excluded. To evaluate the incidence, we also excluded participants who had CKD at baseline. After 3 years of follow-up, 4,881 participants remained for the final analysis. Median (25-75 interquartile range) follow-up time was 3.12 (2.84-3.57) years and response rate was 80%.

Characteristics of participants who were followed up for 3 years were similar to those of the total population with completed food frequency questionnaire (FFQ). Of participants with follow-up data, 45.7% were men compared with 45.0% in the fourth phase of TLGS with completed FFQ. The percentages of the participants aged ≥65 years in the follow-up group versus those with completed FFQ at the fourth phase were 3.4% and 5.8%, respectively. At baseline, 8.4% (n = 668 of 7,956) of participants were smokers and the mean triglyceride concentration was 139.9 mg/dl compared with 38.4 mg/dl in 7.8% (n = 380 of 4,881) of those with follow-up.

The ethics committee of the Research Institute for Endocrine Sciences of Shahid Beheshti University of Medical Sciences approved the study protocol, and all experiments were performed in accordance with relevant guidelines and regulations. Written informed consent was obtained from all participants.

Dietary Assessment

Trained dietitians during face-to-face interviews assessed dietary intakes of participants by using a FFQ. Participants were asked to designate the frequency of their intake of each food item during the previous year on a daily, weekly, or monthly basis. Food portion size was reported in household measures and then converted to grams. As the Iranian Food Composition Table (FCT) was incomplete, the United States Department of Agriculture (USDA) FCT was used; however, the Iranian FCT was an alternative for traditional Iranian foods that were not listed in the USDA FCT. The FFQ was administered to all participants at the baseline (2009-2011). As major dietary protein sources, the following food groups were identified: unprocessed red meat, processed red meat, red and processed meat intake (combined) as total red meat, poultry, fish, eggs, high-fat dairy products, low-fat dairy products, nuts, whole grains, and legumes.

The reliability and validity of the TLGS FFQ have been previously reported.[9-11] In brief, to study the reliability of the TLGS FFQ, 132 subjects (61 men and 71 women) completed a 168-item FFQ (FFQ1, FFQ2), twice with a 14-month interval. To assess the validity, 12 dietary recalls (DRs) were collected (1 each month) over the 1-year interval. Age- and energy-adjusted and deattenuated Spearman correlation coefficients used to assess validity of the TLGS FFQ for meat intakes were 0.37 and 0.39 in men and women, respectively; age- and energy-adjusted intraclass correlation coefficients, which reflect the reliability of meat intakes in the FFQ, were 0.52 and 0.57 in men and in women, respectively.[11] Overall, these data indicate that the TLGS FFQ provides reasonably valid measures of the average long-term dietary intake.

Measurement of Covariates

Information on physical activity was collected by using a Modifiable Activity Questionnaire to calculate the metabolic equivalents (MET) of the task. High reliability (98%) and moderate validity (47%) were found for the Persian translation of the Modifiable Activity Questionnaire.[12] Low physical activity was considered as MET <600 min/week.[12] Weight was recorded in light clothing to the nearest 0.1 kg on an SECA digital weighing scale (Seca 707; Seca Corporation, Hanover, Maryland; range 0.1-150 kg), and height was measured without shoes to the nearest 0.1 cm. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). Arterial blood pressure was measured manually, using a mercury sphygmomanometer with a suitable cuff size for each participant after a 15-minute rest. Systolic blood pressure (SBP) was determined by the onset of the tapping Korotkoff sound, while diastolic blood pressure (DBP) was determined as the disappearance of the Korotkoff sound. Blood pressure was measured twice, and the average was considered as the participant's blood pressure.

Blood samples were taken from all participants at the TLGS research laboratory after an overnight fasting of 12-14 h. Fasting plasma glucose and 2-hour plasma glucose

(2-hPG; equivalent to 75g anhydrous glucose; Cerestar EP, Spain) were assayed by the enzymatic colorimetric method using glucose oxidase; both inter- and intra-assay coefficients of variation (CVs) were less than 2%. Serum creatinine was measured according to the standard colorimetric Jaffe's kinetic reaction method, and both intra-assay and inter-assay CVs were below 3.1%. All blood analyses were performed at the laboratory for TLGS, the analysis of samples was conducted using the Selectra 2 auto-analyzer (Vital Scientific, Spankeren, Netherlands) commercial kits (Pars Azmoon Inc., Tehran, Iran).

Definitions

Hypertension was defined as SBP/DBP≥140/90 mmHg or current medical therapy for a definite diagnosis of hypertension.

Diabetes was defined as fasting plasma glucose ≥126 mg/dL or 2-hPG ≥200 mg/dL or current therapy for a definite diagnosis of diabetes.[13]

The Modification of Diet in Renal Disease (MDRD) equation formula was used to estimate glomerular filtration rate (eGFR) in ml/min/1.73 m^2 of body surface area.[14] The abbreviated MDRD study equation is as follows:

$$\text{eGFR} = 186\times(\text{Serum creatinine})^{-1.154}\times(\text{Age})^{-0.203}\times(0.742 \text{ if female})\times(1.210 \text{ if African} - \text{American}).$$

Participants were classified based on their eGFR levels by the US National Kidney Foundation guidelines[15]; eGFR≥60 mL/min/1.73m^2 as not having CKD and eGFR<60 mL/min/1.73m^2 as having CKD, which corresponds to stages 3 - 5 of CKD based on the Kidney Disease Outcomes Quality Initiative guidelines.

Statistical Analysis

The study design was prospective; information on diet was collected at baseline (2009-2011) of the present study, and serum creatinine was measured at baseline and after 3 years of follow-up. All dietary exposures were divided into the quartiles. Continuous variables were reported as the age-adjusted mean ± standard error and categorical variables as percentages. We calculated age-adjusted mean values for participants' characteristics using analysis of covariance (ANCOVA). Tests of a trend for continuous and categorical variables across quartiles of the total red meat (as a median value in each quartile) were conducted using linear regression and chi-square test, respectively.

Before running multivariable logistic regression models, the interaction terms between age, BMI, and quartiles of total red meat intake on the incidence of CKD were examined. The results demonstrated that no significant interaction was present between age categories and quartiles of total red meat intake ($P = .127$) with the incidence of CKD. The same result was observed for the BMI categories and quartiles of total red meat intake ($P = .517$) on the incidence of CKD.

Odds ratio (OR) and 95% confidence intervals (CIs) were calculated for multivariable logistic regression models to examine the association of each quartile of total red meat, red and processed meat when the first quartile was considered as the reference category with incident CKD. In the first model, we adjusted for age, sex, smoking, total energy intake, triglycerides, body mass index, and physical activity, and in the second model, we additionally adjusted for hypertension and diabetes. The trend of OR across increasing quartiles of dietary intakes was calculated when the quartile categories were considered as continuous variables.

We conducted several sensitivity analyses to test the robustness of the results: (1) we further adjusted for percent of energy from carbohydrate or several nutrients (fiber, sodium, magnesium, and polyunsaturated) to clarify the impact of dietary intake; (2) used the energy density of total red meat (serving per day/1000 kcal) as the exposure instead of the crude intake; (3) repeated the analysis after excluding participants who had concurrent diabetes and hypertension, diabetes per se, BMI ≥ 35 kg/m^2, and age ≥ 60 years to minimize the effects of impaired glucose hemostasis, high blood pressure, excess weight, and age on kidney function.

ORs and 95% CIs for CKD were estimated for substituting one serving of total red meat with 1 serving of low-fat dairy, nuts, whole grains, and legumes. In brief, total red meat, low-fat dairy, nuts, whole grains, and legumes were included as continuous variables in the same model. The difference between regression coefficients was used to derive the OR for the substitution. The substitution analysis, based on statistical modeling of observational data, estimated the potential effect of substituting one macronutrient or food for another while holding total energy intake constant. All data were analyzed using the Statistical Package for the Social Sciences program (SPSS) (version 15.0; SPSS Inc, Chicago IL), and P-values <.05 were considered statistically significant.

Results

The mean ± SD age of the 4,881 participants was 40.1 ± 12.8 years, and 47% of them were women. The average intake of total red meat was 1.17 serving per day. After 3 years of follow-up, we observed a CKD incidence

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Table 1. Characteristics and Dietary Intakes of Participants According to Quartiles of the Total Red Meat Intake*

Characteristics	Q1 (n = 1,221)	Q2 (n = 1,220)	Q3 (n = 1,220)	Q4 (n = 1,220)	*P* for Trend†
Age (year)	36.5 ± 0.3	38.3 ± 0.3	40.6 ± 0.4	45.3 ± 0.4	<.001
Males (%)	46.8	55.1	58.0	57.2	<.001
Low physical activity (%)	16.0	15.7	15.7	15.1	<.001
Current smoker (%)	11.3	7.5	7.0	5.4	.202
Body mass index (kg/m^2)	26.8 ± 0.1	27.2 ± 0.1	27.3 ± 0.1	27.6 ± 0.1	.001
Systolic blood pressure (mmHg)	113.9 ± 0.4	112.2 ± 0.4	112.1 ± 0.4	111.5 ± 0.4	<.001
Diastolic blood pressure (mmHg)	76.7 ± 0.3	75.4 ± 0.3	75.6 ± 0.3	74.9 ± 0.3	<.001
Hypertension (%)	13.4	13.4	15.8	18.2	<.001
Fasting plasma glucose (mg/dL)	97.7 ± 0.6	97.1 ± 0.6	96.2 ± 0.6	97.4 ± 0.6	.477
Baseline Cr (mg/dL)	1.02 ± 0.13	1.00 ± 0.14	1.00 ± 0.14	1.00 ± 0.14	<.001
Follow-up Cr (mg/dL)	1.07 ± 0.74	1.05 ± 0.17	1.05 ± 0.17	1.05 ± 0.17	<.001
eGFR (ml/min/1.73 m^2)	76.3 ± 0.2	76.3 ± 0.2	75.8 ± 0.2	76.1 ± 0.3	.422
With CKD (%)	9.3	12.0	12.8	16.2	<.001
Diabetes mellitus (%)	5.3	7.0	6.7	11.7	<.001
Angiotensin-converting enzyme inhibitor (%)	1.2	1.6	2.1	3.5	.426
Daily intakes					
Total energy (Kcal)	2138 ± 19	2409 ± 21	2501 ± 21	2708 ± 69	<.001
Protein (% energy)	14.7 ± 0.1	14.9 ± 0.3	14.8 ± 0.1	15.3 ± 0.1	.068
Carbohydrate (% energy)	59.9 ± 0.2	59.6 ± 0.3	58.5 ± 0.2	57.3 ± 0.2	<.001
Total fat (% energy)	29.3 ± 0.2	30.4 ± 0.7	30.2 ± 0.2	30.6 ± 0.2	.099
Fruits (serving/day)	3.47 ± 0.10	2.87 ± 0.09	2.86 ± 0.09	2.75 ± 0.09	<.001
Vegetables (serving/day)	3.41 ± 0.05	3.20 ± 0.5	3.19 ± 0.05	3.02 ± 0.06	.015
Legumes (serving/day)	0.58 ± 0.01	0.51 ± 0.01	0.50 ± 0.01	0.51 ± 0.02	<.001
Nuts (serving/day)	0.50 ± 0.02	0.46 ± 0.03	0.39 ± 0.02	0.33 ± 0.02	<.001
Dairy (serving/day)	2.09 ± 0.03	1.98 ± 0.03	1.89 ± 0.02	1.91 ± 0.03	<.001
Whole grains (serving/day)	3.29 ± 0.09	3.41 ± 0.11	3.25 ± 0.09	3.52 ± 0.10	.251
Fish (serving/day)	0.21 ± 0.007	0.19 ± 0.009	0.15 ± 0.007	0.13 ± 0.007	<.001
Poultry (serving/day)	0.58 ± 0.02	0.51 ± 0.01	0.50 ± 0.01	0.51 ± 0.02	<.001

CKD, chronic kidney disease; Cr, serum creatinine; eGFR, estimated glomerular filtration rate.

*Data represented as age-adjusted (except age and daily intakes) mean ± standard error for continuous variables or percent for categorically distributed variables.

†Linear regression was used for test of trend continuous variables according to the category, and chi-square test for categorical variables.

rate of 12.6% (n = 613). eGFR ranged from 35 to 59 mL/min/1.73m^2 and the mean ± SD eGFR at the end of follow-up was 71.7 ± 11.1 mL/min/1.73m^2. Age-adjusted characteristics for study participants by quartiles of total red meat intake are displayed in Table 1. Compared with the lowest quartile of total red meat intake, participants with the highest quartile were slightly older. In addition, participants in the highest compared with the lowest quartile of total red meat intake were more likely to be men, less likely to be physically active and to have a higher age-adjusted SBP and DBP. Those in the top quartile of total meat intakes had lower prevalence of diabetes than their counterparts in the lowest quartile. We also noted that participants who had the highest quartile of total red meat intake had significantly higher intake of total energy and total fat but lower intakes of fruits, vegetables, legumes, nuts, dairy, fish, and poultry compared with those in the lowest quartile of total red meat intake.

Total red meat intake was positively associated with incidence of CKD in the first model with an OR of 1.88 (95% CI 1.18 -2.43, *P* for trend <.001) when comparing the highest to the lowest quartile. This finding remained significant even after further adjusting for diabetes and hypertension (ORs = 1.73; 95% CI: 1.33-2.24). After controlling for potential confounders, OR for participants in the highest compared with the lowest quartile of processed red meat was 1.99 (95% CI: 1.54-2.56; *P* for trend <.001). When treating dietary exposure as a continuous variable, the elevated risk of incident CKD for one serving/day was 15% (ORs = 1.15; 95% CI: 1.06-1.24) for total red meat and 28% (ORs = 1.28; 95% CI: 1.14-1.43) for processed red meat (Table 2).

In the substitution analyses, replacing one serving of total red meat with one serving of low-fat dairy, nuts, whole grains, and legumes was associated with a lower risk of incident CKD: 17% (OR: 0.83; 95% CI: 0.75-0.93) for low-fat dairy, 16% (OR: 0.84; 95% CI: 0.74-0.95) for nuts, 21% (OR: 0.79; 95% CI, 0.73-0.86) for whole grains, and 19% (OR: 0.81; 95% CI: 0.68-0.97) for legumes. Besides, substituting one daily serving of unprocessed red meat with whole grains and nuts resulted in 15% (95% CI: 0.76-0.95) and 13.9% (95% CI: 0.78-0.99) reduction in CKD risk, respectively. Furthermore, the odds of incident CKD when replacing one serving of processed red meat with one serving of poultry, fish, low-fat dairy, nuts, whole grains, and legumes was 28%, 39%, 26%, 28%, 30%, and 31% (Figure 1).

Table 2. Odds Ratio (95% Confidence Intervals) of Incident Chronic Kidney Disease According to the Dietary Total Red Meat, Unprocessed Red Meat, and Processed Red Meat Intake and per 1-Serving Increase in Intake Among Participants of the Tehran Lipid and Glucose Study

Models	Frequency of Consumption Quartiles				*P* for Trend*	1-serving Per-day Increase
	Q1	Q2	Q3	Q4		
Total red meat, servings per day	0.34	0.68	1.12	2.52		
Case/Total	113/1,221	146/1,220	156/1,220	298/1,220		
Model 1	1.00	1.31 (1.01-1.70)	1.38 (1.06-1.79)	1.88 (1.18-2.43)	<.001	1.18 (1.10-1.27)
Model 2	1.00	1.29 (0.99-1.69)	1.34 (1.03-1.75)	1.73 (1.33-2.24)	<.001	1.15 (1.06-1.24)
Unprocessed red meat, servings per day	0.02	0.18	0.38	1.16		
Case/Total	109/1,249	143/1,320	153/1,105	208/1,207		
Model 1	1.00	1.09 (0.84-1.40)	1.24 (0.96-1.60)	1.32 (1.03-1.71)	.078	1.11 (0.99-1.24)
Model 2	1.00	1.07 (0.82-1.38)	1.22 (0.95-1.58)	1.22 (0.94-1.59)	.279	1.08 (0.95-1.19)
Processed red meat, servings per day	0.21	0.43	0.70	1.61		
Case/Total	132/1,221	144/1,220	164/1,220	173/1,220		
Model 1	1.00	1.22 (0.93-1.59)	1.59 (1.22-2.07)	2.11 (1.64-2.71)	<.001	1.33 (1.18-1.48)
Model 2	1.00	1.21 (0.92-1.57)	1.55 (1.19-2.02)	1.99 (1.54-2.56)	<.001	1.28 (1.14-1.43)

Model 1: Adjusted for age, sex, smoking, total energy intake, triglycerides, body mass index, and physical activity.
Model 2: additional adjusting for hypertension and diabetes.
*To calculate the trend of OR across increasing quartiles of meat intake, we considered the quartiles categories as continuous variables.

In the sensitivity analysis, the association of dietary intake of total red meat with incidence of CKD did not substantially change when we further adjusted for intake of carbohydrate (OR = 1.74, 95% CI: 1.33-2.26), fiber (OR = 1.72, 95% CI: 1.33-2.24), sodium (OR = 1.69, 95% CI: 1.30-2.21), magnesium (OR = 1.77, 95% CI: 1.36-2.30), and polyunsaturated fatty acids (OR = 1.65, 95% CI: 1.26-2.16). Furthermore, adjusted ORs for participants in the highest compared with the lowest quartile of energy density of total red meat were 1.64 (95% CI: 1.27-2.14) with no substantial changes in the results. After excluding subjects with concurrent hypertension and diabetes, OR for participants in the highest compared with the lowest quartile of total red meat was 1.87 (95% CI: 1.37-2.56). Participants without diabetes who were in the highest quartile of total red meat intake had lower odds of CKD (OR = 1.82; 95% CI: 1.38-2.42) compared with those in the lowest quartile. Among participants with BMI <30 kg/m^2 and those aged <60 years, higher intakes of total red meat compared with a significant increased risk of incident CKD (OR: 1.90, 95% CK: 1.38-2.61; and OR: 1.64, 95% CK: 1.23-2.17, respectively; data not shown).

Discussion

In this large, population-based cohort study of adults with normal kidney function at baseline, we observed that a higher consumption of total red meat and processed meat were associated with an increased risk of CKD. The positive association was independent of known dietary and nondietary risk factors for CKD as well as hypertension and diabetes. Replacing total red and processed meat in the diet with other sources of dietary protein including nuts, low-fat dairy products, whole grains, and legumes were associated with lower CKD risk.

Supporting evidence revealed that red meat intake has undesirable associations with risks of type 2 diabetes mellitus, cardiovascular disease, variety of cancer, and mortality.[16,17] To date, only a few longitudinal studies have examined the association of long-term dietary protein sources with risk of CKD in individuals with normal kidney function. Haring et al. followed 11,952 from Atherosclerosis Risk in Communities study participants and observed that more than 1.98 serving/d of red and processed meat consumption was associated with a 23% greater risk of CKD[7] and red meat consumption ≥ 1.15 serving/d was associated with a 19% higher risk of CKD, but they reported no significant association between processed meat intake and risk of CKD.[7] Lew et al. conducted a prospective population-based cohort study among 63,257 participants from the Singapore Chinese Health Study and reported that participants who were in the highest quartile of red meat intake (≥48.8 g/d) had a significant 40% increased odds of end-stage renal disease (ESRD).[18] However, different from the current study, the study by Lew et al did not distinguish unprocessed and processed red meats when investigated its relation to incidence of ESRD, and they considered ESRD as an outcome which identified serum creatinine>10 mg/dL, eGFR <15 mL/min/1.73 m^2, undergoing hemodialysis or peritoneal dialysis, or has undergone kidney transplant.

In the present study, we also found that the substitution of one serving of total red meat (sum of processed and unprocessed red meat) per day with a serving of low-fat dairy, nuts, legumes, and whole grains may decrease the

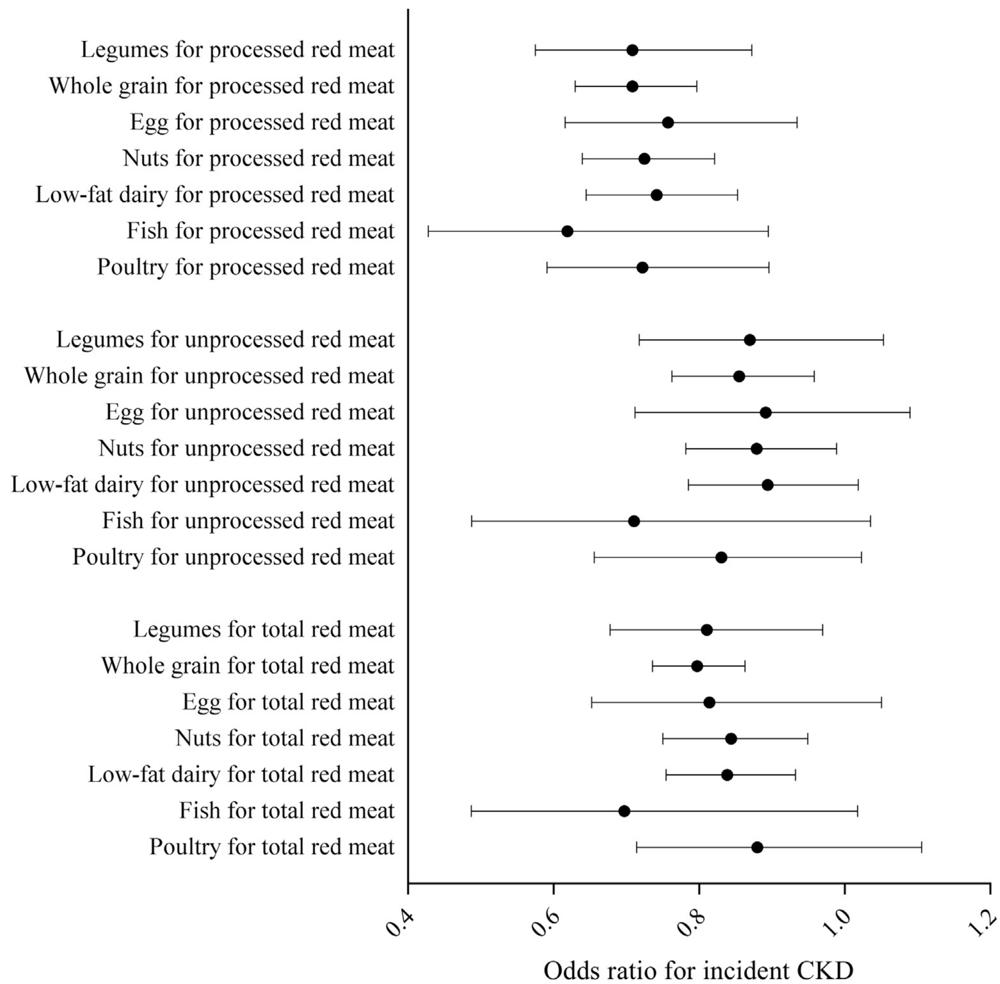

Figure 1. Substituting individual protein-rich foods for total meat, read meat, and processed meat with incident CKD. CKD, chronic kidney disease. *P* values ≤ .05 are considered significantly difference.

risk of CKD. Furthermore, substitution of poultry, fish, low-fat dairy, nuts, egg, whole grains, and legumes for processed red meat was associated with a significantly lower risk of CKD. Haring et al. revealed that replacing one serving of red and processed meat (total red meat) with one serving of legumes and nuts was associated with 31% and 18% increased risk of incident CKD, respectively.[7]

Our finding of a strong undeniable relationship of red meat intake and incident CKD is consistent with the results of our previous study where we examined the association of specific types of protein on kidney function.[1] We previously reported that a higher ratio of animal to plant protein in the daily intake was associated with increased risk of CKD.[1] Another study among women with mild kidney dysfunction (defined as eGFR >55 and < 80 mL/min/1.73 m^2) also revealed that higher intakes of nondairy animal protein might accelerate decline of kidney function.[19] However, analyses of food groups instead of dietary protein intake may be a more appropriate method. An interventional study indicated that an increase in the glomerular filtration rate was induced by animal protein, particularly protein from meat,[20] whereas consumption of protein content of soy beans revealed little or no undesirable effect on kidney function.[21,22] Corresponding to the present study, our observational results over 6.1 years provided the evidence that among vegetable protein sources, whole grains and nuts and legumes were associated with a lower risk for CKD.[6] Taken together, intake of red meat is associated with increased risk for CKD in a dose-dependent manner; moreover, intake of poultry, fish, eggs, or dairy products may even protect against the onset or progression of CKD.

There are several potential mechanisms that could explain the associations of dietary red meat with kidney function. Higher dietary intake of meat generally yields greater dietary acid load that is associated with higher risk of CKD.[23] In contrast, higher intake of plant-based proteins including legumes and nuts can reduce the dietary acid load which decrease the risk of kidney disease progression.[24] Another component of red meat that might be associated with its undesirable effect on kidney function is high content of advanced glycation end products in cooked red meat. Higher intake of advanced glycation end products contributes to induce oxidative stress and inflammation in the body which have harmful impact on kidney function.[25] With the greater caution, our finding revealed that although dietary intake of processed red meat was associated with increased risk of CKD, there was no significant relationship between unprocessed meat and incidence of CKD. Processed and unprocessed red meats contain almost similar amounts of saturated fat, whereas, other components in processed meat, in particular the amount of sodium and added nitrites are relatively higher than those in processed meat, which may explain further undesirable properties of processed meats. Increased dietary sodium might elevate the presence of CVD risk factors, especially hypertension[26] and subsequent glomerular dysfunction.[13] Nitrites and nitrates are commonly added to meats during processing to improve their shelf-life and appearance. Higher intake of dietary nitrites and nitrates might lead to increase in blood nitrite concentrations which was associated with endothelial and kidney dysfunction.[27]

Higher dietary intake of plant-based foods including whole grains, legumes, and nuts were associated with decreased risk of CKD by affecting several known cardiometabolic risk factors, such as amelioration of blood lipid profiles, blood pressure, insulin hemostasis, oxidative stress, inflammatory markers, and endothelial function.[6,28-30] In addition, plant-based sources of proteins are rich in potassium, magnesium, calcium, and vitamin C which were associated with the lower dietary acid load and subsequent improvement in kidney function.[23] Moreover, dietary intake of poultry, fish, eggs, or dairy products protects against onset or progression of CKD, and it might be due to the removal of red meat on the amelioration of fatty acid profile and reduced urinary albumin excretion.[31] Besides, intervention by chicken-based diet for 1 year indicated a reduction in urinary albumin excretion equal to treatment with angiotensin-converting enzyme inhibitor.[32] Low-fat dairy was inversely associated with albumin-to-creatinine ratio (ACR),[33] might be because of high content of branched-chain amino acids in dairy foods which have lower impact on kidney.[34,35] Furthermore, milk proteins, vitamin D, magnesium, and calcium may contribute to these associations.[36,37]

Limitations of this investigation need to be mentioned. First, as in most epidemiologic studies, our definition of CKD is based on a limited number of isolated creatinine measurements that were not repeated within 3 months to confirm a chronic reduction in glomerular filtration rate. Second, despite controlling for various confounders in our analysis, residual confounding due to unknown or unmeasured confounders cannot be excluded. Third, data on the proteinuria, cystatin C, uric acid, albumin, hospitalization, and nephrotoxic medications of the participants were not available. Fourth, it should be emphasized to readers that the method used to measure creatinine was not calibrated by the isotope dilution-mass spectrometry (IDMS) method and this is an important limitation of the report and its generalizability in kidney disease. Future studies should take care to include the conversion from the Jaffe kinetic-rate method and the IDMS method for reporting serum creatinine concentration.

Of the study's noteworthy strengths, unlike previous studies, the present one provided data based on habitual dietary intakes in a population-based sample of participants, therefore, increasing the generalizability of its results. In conclusion, higher consumption of total red meat and processed meat were associated with a 71% and 99% increased risk of incident CKD, respectively, which was independent of hypertension and diabetes. Furthermore, substitution of total red and processed meat in the diet with other sources of dietary protein including nuts, low-fat dairy products, whole grains, and legumes were associated with lower CKD risk. Our findings highlight the difference between dietary protein sources in kidney function rather than total protein intake.

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References

1. Yuzbashian E, Asghari G, Mirmiran P, Hosseini FS, Azizi F. Associations of dietary macronutrients with glomerular filtration rate and kidney dysfunction: Tehran lipid and glucose study. *J Nephrol*. 2015;28:173-180.

2. Babio N, Sorlí M, Bulló M, et al. Association between red meat consumption and metabolic syndrome in a Mediterranean population at high cardiovascular risk: cross-sectional and 1-year follow-up assessment. *Nutr Metab Cardiovasc Dis*. 2012;22:200-207.

3. Pan A, Sun Q, Bernstein AM, et al. Red meat consumption and risk of type 2 diabetes: 3 cohorts of US adults and an updated meta-analysis. *Am J Clin Nutr*. 2011;94:1088-1096.

4. Micha R, Wallace SK, Mozaffarian D. Red and processed meat consumption and risk of incident coronary heart disease, stroke, and diabetes mellitus. *Circulation*. 2010;121:2271-2283.

5. Cross AJ, Leitzmann MF, Gail MH, Hollenbeck AR, Schatzkin A, Sinha R. A prospective study of red and processed meat intake in relation to cancer risk. *PLoS Med*. 2007;4:e325.

6. Asghari G, Yuzbashian E, Mirmiran P, Azizi F. The association between dietary approaches to stop hypertension and incidence of chronic kidney disease in adults: the Tehran lipid and glucose study. *Nephrol Dial Transplant*. 2017;32(suppl_2):ii224-ii230.

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7. 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. *J Ren Nutr.* 2017;27:233-242.

8. Azizi F, Ghanbarian A, Momenan AA, et al. Prevention of non-communicable disease in a population in nutrition transition: Tehran lipid and glucose study phase II. *Trials.* 2009;10:5.

9. Mirmiran P, Esfahani FH, Mehrabi Y, Hedayati M, Azizi F. Reliability and relative validity of an FFQ for nutrients in the Tehran Lipid and Glucose Study. *Public Health Nutr.* 2010;13:654-662.

10. Asghari G, Rezazadeh A, Hosseini-Esfahani F, Mehrabi Y, Mirmiran P, Azizi F. Reliability, comparative validity and stability of dietary patterns derived from an FFQ in the Tehran Lipid and Glucose Study. *Br J Nutr.* 2012;108:1109-1117.

11. Esfahani FH, Asghari G, Mirmiran P, Azizi F. Reproducibility and relative validity of food group intake in a food frequency questionnaire developed for the Tehran Lipid and Glucose Study. *J Epidemiol.* 2010;20:150-158.

12. Momenan AA, Delshad M, Sarbazi N, Rezaei Ghaleh N, Ghanbarian A, Azizi F. Reliability and validity of the Modifiable Activity Questionnaire (MAQ) in an Iranian urban adult population. *Arch Iranian Med.* 2012;15:279-282.

13. Tohidi M, Hasheminia M, Mohebi R, et al. Incidence of chronic kidney disease and its risk factors, results of over 10 year follow up in an Iranian cohort. *PLoS One.* 2012;7:e45304.

14. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med.* 1999;130:461-470.

15. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J kidney Dis.* 2002;39(2 Suppl 1):S1-S266.

16. Larsson SC, Orsini N. Red meat and processed meat consumption and all-cause mortality: a meta-analysis. *Am J Epidemiol.* 2014;179:282-289.

17. Kim Y, Keogh J, Clifton P. A review of potential metabolic etiologies of the observed association between red meat consumption and development of type 2 diabetes mellitus. *Metabolism.* 2015;64:768-779.

18. Lew QJ, Jafar TH, Koh HW, et al. Red meat intake and risk of ESRD. *J Am Soc Nephrol.* 2017;28:304-312.

19. 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;138:460-467.

20. Wetzels JF, Wiltink PG, van Duijnhoven EM, Hoitsma AJ, Koene RA. Short-term protein restriction in healthy volunteers: effects on renal hemodynamics and renal response to a meat meal. *Clin Nephrol.* 1989;31:311-315.

21. Kontessis P, Jones S, Dodds R, et al. Renal, metabolic and hormonal responses to ingestion of animal and vegetable proteins. *Kidney Int.* 1990;38:136-144.

22. Nakamura H, Ito S, Ebe N, Shibata A. Renal effects of different types of protein in healthy volunteer subjects and diabetic patients. *Diabetes Care.* 1993;16:1071-1075.

23. Mirmiran P, Yuzbashian E, Bahadoran Z, Asghari G, Azizi F. Dietary acid-base load and risk of chronic kidney disease in adults: Tehran Lipid and Glucose Study. *Iran J Kidney Dis.* 2016;10:119-125.

24. Engberink MF, Bakker SJ, Brink EJ, et al. Dietary acid load and risk of hypertension: the Rotterdam Study. *Am J Clin Nutr.* 2012;95:1438-1444.

25. Kellow NJ, Coughlan MT. Effect of diet-derived advanced glycation end products on inflammation. *Nutr Rev.* 2015;73:737-759.

26. Yang Q, Liu T, Kuklina EV, et al. Sodium and potassium intake and mortality among US adults: prospective data from the Third National Health and Nutrition Examination Survey. *Arch Intern Med.* 2011;171:1183-1191.

27. Mirmiran P, Bahadoran Z, Golzarand M, Asghari G, Azizi F. Consumption of nitrate containing vegetables and the risk of chronic kidney disease: Tehran Lipid and Glucose Study. *Ren Fail.* 2016;38:937-944.

28. Mathew AV, Seymour EM, Byun J, Pennathur S, Hummel SL. Altered metabolic profile with sodium-restricted dietary approaches to stop hypertension diet in hypertensive heart failure with preserved ejection fraction. *J Card Fail.* 2015;21:963-967.

29. Mokhtari Z, Hosseini S, Miri R, et al. Relationship between dietary approaches to stop hypertension score and alternative healthy eating index score with plasma asymmetrical dimethylarginine levels in patients referring for coronary angiography. *J Hum Nutr Diet.* 2015;28:350-356.

30. Wang HH, Wong MC, Mok RY, et al. Factors associated with grade 1 hypertension: implications for hypertension care based on the Dietary Approaches to Stop Hypertension (DASH) in primary care settings. *BMC Fam Pract.* 2015;16:26.

31. de Mello VD, Zelmanovitz T, Perassolo MS, Azevedo MJ, Gross JL. Withdrawal of red meat from the usual diet reduces albuminuria and improves serum fatty acid profile in type 2 diabetes patients with macroalbuminuria. *Am J Clin Nutr.* 2006;83:1032-1038.

32. de Mello VD, Zelmanovitz T, Azevedo MJ, de Paula TP, Gross JL. Long-term effect of a chicken-based diet versus enalapril on albuminuria in type 2 diabetic patients with microalbuminuria. *J Ren Nutr.* 2008;18:440-447.

33. Nettleton JA, Steffen LM, Palmas W, Burke GL, Jacobs DR Jr. Associations between microalbuminuria and animal foods, plant foods, and dietary patterns in the Multiethnic Study of Atherosclerosis. *Am J Clin Nutr.* 2008;87:1825-1836.

34. Lee KE, Summerill RA. Glomerular filtration rate following administration of individual amino acids in conscious dogs. *Q J Exp Physiol.* 1982;67:459-465.

35. Claris-Appiani A, Assael BM, Tirelli AS, Marra G, Cavanna G. Lack of glomerular hemodynamic stimulation after infusion of branched-chain amino acids. *Kidney Int.* 1988;33:91-94.

36. Pereira MA, Jacobs DR Jr, Van Horn L, Slattery ML, Kartashov AI, Ludwig DS. Dairy consumption, obesity, and the insulin resistance syndrome in young adults: the CARDIA Study. *JAMA.* 2002;287:2081-2089.

37. Liu S, Choi HK, Ford E, et al. A prospective study of dairy intake and the risk of type 2 diabetes in women. *Diabetes care.* 2006;29:1579-1584.