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ORIGINAL CONTRIBUTION

Intakes of long-chain omega-3 polyunsaturated fatty acids and non-fried fish in relation to incidence of chronic kidney disease in young adults: a 25-year follow-up

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Abstract

Purpose The prevalence of chronic kidney disease (CKD) is increasing rapidly in many countries and has become a major public health concern. Although intakes of long-chain omega-3 polyunsaturated fatty acids (LCω3PUFA) and its food source—fish—may have renal protective effects, little is known about the longitudinal association between these dietary factors and CKD incidence.

Methods A total of 4133 healthy individuals of black and white race aged 18–30 at baseline (1985–1986) from the Coronary Artery Risk Development in Young Adults study were enrolled and followed up over 25 years. LCω3PUFA and fish intake were assessed by an interview-based dietary history questionnaire at baseline, year 7 (1992–1993) and 20 (2005–2006).

Results Four hundred and eighty-nine incident cases of CKD were identified. After adjustment for potential confounders, LCω3PUFA intake was inversely associated with CKD incidence [HR = 0.73 (95% CI 0.60–0.89), $P = 0.002$, with one standard division (0.19 g/day) increment in LCω3PUFA]. This inverse association was persisted among females [0.64 (95% CI 0.48, 0.84; $P = 0.002$], but not males ($P_{\text{interaction}} = 0.070$). A marginal significant inverse association was also found between non-fried fish consumption and CKD incidence (HR = 0.86, 95% CI 0.73, 1.01; $P = 0.073$).

Conclusions Dietary LCω3PUFA intake was inversely associated with incidence of CKD among American young adults over 25 years of follow-up. The suggestive evidence of the inverse association between non-fried fish consumption with CKD incidence needs further confirmation.

Keywords Chronic kidney disease · Proteinuria · Fish · Long-chain omega-3 polyunsaturated fatty acids

Abbreviations

AA	African American
CARDIA	Coronary Artery Risk Development in Young Adults
CKD	Chronic kidney disease
eGFR	Estimated glomerular filtration rate
EPA	Eicosapentaenoic acid
EU	Exercise units
GFR	Glomerular filtration rate
Hg	Hydrargyrum: mercury
LCω3PUFA	Long-chain omega-3 polyunsaturated fatty acids
PA	Physical activity
Se	Selenium

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Introduction

The global prevalence of chronic kidney disease (CKD) from 1999 to 2014 was around 11%, and CKD is an independent risk factor for cardiovascular morbidity and decreased quality of life [1, 2]. Moreover, the prevalence is increasing rapidly in many countries and has become a major public health concern [2–5]. Because the final common pathway of chronic kidney damage often involves inflammation and fibrosis [2], intake of long-chain omega-3 polyunsaturated fatty acids (LCω3PUFA) via fish oil supplements or non-fried fish is considered beneficial, since they can down-regulate pro-inflammatory cytokine production and oxidative stress, and express endothelial leukocyte adhesion molecules, thereby protecting kidney function [6, 7]. To date, numerous studies have reported inverse associations of LCω3PUFA intake with cardiovascular diseases [8], hypertension [9], and endothelial function [10], all of which can increase risk of CKD [11]. In addition, fish oil is often prescribed in patients with IgA nephropathy [12]. However, some studies have shown no or at most a weak preventive effect on cardiovascular outcomes [13–15].

Fish is enriched in LCω3PUFA species that include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [16]. Despite the benefits which these fatty acids provide, fish consumption may come with the potential for harm from contaminants such as mercury (Hg) [16]. However, fish is also a dietary source of selenium (Se) that can increase Hg elimination and ameliorate its toxic effects [17, 18]. Thus, it is important to consider both the benefits and risks of consuming fish as routes of exposure to LCω3PUFA, Se, and Hg [9].

Few epidemiological studies have examined the putative association between fish oil and a decline in glomerular filtration rate (GFR) [6, 19, 20] and the association between fish oil and albuminuria in the general population [21]. Two studies have shown that fish oil consumption was associated with a reduced likelihood of CKD. A cross-sectional study reported that dietary intake of LCω3PUFA and fish was inversely associated with risk of prevalent CKD [20]. An Italian population-based cohort study of 931 adults aged ≥ 65 years showed that polyunsaturated fatty acid levels at enrollment were inversely associated with risk of developing reduced creatinine clearance during a 3-year follow-up [19]. However, whether the findings can be generalized to younger individuals with a long observational period is uncertain. Conversely, a study that examined the association between fish consumption and nephropathy in American Indians found no association between fish consumption and risk of nephropathy [21]. However, fish items consumed were predominantly deep-fried in the study. Because of the gap in knowledge about the longitudinal association of intakes of LCω3PUFA and fish with incidence of CKD, we undertook the present analysis using data from a large cohort of young adults participating in the Coronary Artery Risk Development in Young Adults (CARDIA) study.

Materials and methods

Design and participants

The CARDIA study is an ongoing, multicenter, prospective cohort study of the development and determinants of cardiovascular risk factors in young adults aged 18–30 years at recruitment. Details of study design have been published elsewhere [22]. In brief, 5114 male and female participants of both black and white races were recruited in 1985 and 1986 (Y0) in four cities in the United States (Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA). The cohort was designed to be balanced by age, sex, race, and education. The follow-up examinations were conducted in 1987–1988 (Y2), 1990–1991 (Y5), 1992–1993 (Y7), 1995–1996 (Y10), 2000–2001 (Y15), 2005–2006 (Y20), and 2010–2011 (Y25). Retention rate of the surviving cohort in each follow-up was 90.4, 85.1, 79.9, 77.2, 71.8, 69.3, and 68.4%, respectively.

We excluded participants who reported an implausible total energy intake (< 800 or > 8000 kcal/day for males, and < 600 or > 6000 kcal/day for females) ($n = 30$), with missing data on exposure variables at all diet assessments ($n = 4$) and smoking status ($n = 54$), with CKD at baseline ($n = 6$), and participants without follow-up information for defining incidence of CKD ($n = 664$). To be conservative, we also excluded females who were pregnant at any examination ($n = 223$). The remaining 4133 participants were included in the main analysis. Of these, 3690 participants with toenail Se and Hg available were included in the analyses of the effect modification of Se and Hg on the associations of interest. A written informed consent form was obtained from all participants. Supplemental Fig. 1 in the appendix shows the enrollment flow. The study design, data collection, and analyses were approved by the institutional review boards of the participating centers.

Ascertainment of fish consumption and LCω3PUFA intake

The CARDIA Diet History questionnaire is an interviewer-administered quantitative food-frequency questionnaire designed to assess habitual eating patterns. The validity and reproducibility of CARDIA food-frequency questionnaire have been described in the previous studies [23, 24].

The correlation coefficients for logarithmically transformed nutrient values and energy-adjusted nutrient values from two dietary histories are 0.50–0.80 for whites and 0.30–0.70 for blacks [24]. Briefly, diet assessment was conducted three times at Y0, Y7, and Y20. Participants were asked to recall their usual dietary intakes using the previous 30 days as the time frame. Daily intake of each food or beverage group was calculated as the sum of the number of servings consumed per day. Fish consumption was categorized into fried and non-fried fish, recognizing that the health impact may be influenced by the preparation method [25]. Because of the skewed and narrow distribution of fried fish consumption, we did not use fried fish as an exposure separately, but adjusted for fried fish intake when examining the association between non-fried fish intake and incidence of CKD. Nutrient intake was estimated using an adaptively updated nutrient database version 36 (Nutrition Data System for Research 2005 from the Nutrition Coordinating Center at the University of Minnesota, Minneapolis, MN). In this study, LCω3PUFA intake was defined as the sum of DHA, EPA, and docosapentaenoic acid from all dietary sources. Because of the relatively small amount and the narrow distribution, docosapentaenoic acid was not analyzed as a separate exposure.

Ascertainment of CKD

We defined CKD as an estimated GFR (eGFR) < 60 mL/min per 1.73 m^2 or albuminuria > 30 mg/g (urine albumin/creatinine) [2]. eGFR was estimated at Y0, Y10, Y15, Y20, and Y25 using the CKD-EPI (epidemiology collaboration) Creatinine Equation [26]. Albuminuria was determined from a single, untimed (spot) urine sample collected at Y10, Y15, Y20, and Y25 examinations. Urine albumin concentrations were measured using a nephelometric procedure with a specific anti-albumin monoclonal antibody. Between study years 0 and 20, creatinine was measured using a modified-rate Jaffe method and standardized to NIST standards. In Y25 examination, creatinine was measured using the Roche enzymatic method and standardized to NIST standards. Urine albumin–creatinine ratios were standardized to sex and race and expressed in milligrams per gram of creatinine [27].

Ascertainment of toenail se and Hg

Details of assessment have been described previously [9]. Briefly, Se and Hg levels were analyzed by instrumental neutron-activation analysis at the University of Missouri Research Reactor. The average coefficient of variation in duplicate toenail sub-samples was 2.5% for Se and 6.8% for Hg. The toenail concentrations of Se or Hg were suggested to be useful biomarkers of exposure in which a single sample was assumed to represent long-term exposure, since toenail clippings reflect 9–12 months of exposure [28–30].

Ascertainment of covariates

Age, race, sex, smoking status, and hyperlipidemia were defined using Y10 data and measured in all available CARDIA participants. Age, race, sex, and smoking status were obtained by self-report. The major lifestyle variables and clinical measurements were reevaluated at the follow-up examinations. Cumulative average alcohol consumption was classified into four groups based on daily intake measured using a validated questionnaire. Physical activity (PA) was assessed using the interviewer-administered and validated CARDIA PA history questionnaire [31]. The PA score was calculated in exercise units, which reflect the frequency and duration of activity over the previous year. A score of 100 exercise units is approximately equivalent to participation in vigorous activity for 2–3 h/week for 6 months of the year. The cumulative average PA was categorized into quartiles. At baseline, respondents were asked if they had a history of "kidney problems" (yes/no). If yes, respondents were asked to clarify if they had a history of kidney stones, nephritis, pyelonephritis, glomerulonephritis, kidney infection, or other kidney disease (yes/no). In this study, "kidney diseases" represents self-reported history of kidney stones, nephritis, pyelonephritis, glomerulonephritis, kidney infection, or other kidney disease at baseline (yes/no).

Statistical analysis

Baseline characteristics of study population were described as means (SDs), medians (IQRs), or proportions based on their properties and distributions. Cox proportional hazards models were used to examine intakes of LCω3PUFA, DHA, EPA, or non-fried fish in relation to incidence of CKD by calculating multivariable-adjusted HRs and 95% confidence intervals. Schoenfeld residual test was performed to check the proportional hazards assumption [32]. Incident CKD was defined at Y10, Y15, Y20, and Y25. Each participant contributed person-time from baseline to the date when incident CKD was determined, censored or the end of the study, whichever came first.

To reduce measurement errors caused by within-person variation and to best represent the long-term dietary intakes, we used cumulative average nutrient intake from the measurements at Y0, Y7, and Y20 in the main analysis. For example, we related the average LCω3PUFA intake reported at Y0 and Y7 to the new cases identified at Y10 and Y15; and the average LCω3PUFA intake reported at Y0, Y7, and Y20 to the new cases identified at Y20 and Y25. To test the robustness of model selection, we replaced "cumulative average model" with "baseline model", and

"most-recent model", respectively [33, 34]. In addition, we used a sequential covariate-adjusted strategy in the Cox model. Model 1 (initial model): adjustment for age, sex, race, and study center. Model 2 (final model): Model 1 with additional adjustment for BMI, education, current smoker, alcohol consumption, PA, and total energy, and reported kidney diseases. In Model 2, fried fish consumption was also adjusted when non-fried fish was examined. To determine whether sex or race was an effect modifier, the interaction of sex or race with the exposures of interest was detected by likelihood-ratio test. We also examined whether baseline fasting glucose, urinary creatinine, and toenail Se and Hg levels would modify the results. In addition, we conducted the following sensitivity analyses based on the final model (Model 2). First, we further adjusted for a few potential dietary confounders, including intakes of magnesium, calcium, sodium, potassium, and phosphorous (Model 3a). Second, we additionally adjusted for baseline creatinine and glucose (Model 3b) on top of Model 2. Third, we re-performed model 2 under a reduced sample size at *n* 3690 including only participants with toenail trace element data available (Model 3c). Fourth, we adjusted for Hg, and cadmium (Model 3d), and further added Se (Model 3e) on top of Model 3c. While baseline glucose is included in Model 3b, we also replaced it with: (1) cumulative glucose levels; or (2) baseline diabetes; or (3) incident diabetes; none of the results were substantially changed. We also performed a sensitivity analysis by adding baseline GFR, blood pressure (either baseline or cumulative), and blood pressure lowering medication at time of CKD ascertainment to the model and the results were materially unchanged.

All analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, North Carolina, USA) with nominal significance level set as 0.05, and 0.10 for detecting main effect and interaction, respectively.

Results

Baseline characteristics of the study participants are shown in Table 1. The average intake of LCω3PUFAs was 0.17 g/day and the mean age of the participants was 25.0 years. Of the 4133 participants, 53.2% were women and 49.8% were blacks. The mean eGFR was 123.5 mL/min per 1.73 m^2 and the average follow-up time was 22.3 years.

During the 25-year follow-up, 489 incident cases of CKD were identified. Among them, there were 426/24 cases with moderately/severely increased albuminuria, and 56 cases with decreased eGFR. There were 17 cases with both abnormal eGFR and albuminuria (12/5: moderately/severely increased albuminuria). Table 2 shows the associations of intake of LCω3PUFA and non-fried fish with incident CKD. Higher LCω3PUFA intake had a significantly lower incidence of CKD [HR = 0.73 (0.60–0.89), $P = 0.002$] in model 2. Similar inverse associations were observed for EPA (0.76 (0.62, 0.94), $P = 0.010$) and DHA (0.72 (0.59, 0.87), $P < 0.001$) intake with incident CKD. A marginally significant inverse association was found between non-fried fish consumption and incidence of CKD [0.86 (0.73, 1.01), $P = 0.073$].

To determine potential effect modifiers for the associations of interest, we conducted stratified analyses according to several pre-specified factors (Table 3). The associations between LCω3PUFA and CKD were modified by sex, but not by race, Se, or Hg levels. The observed inverse associations persisted in females [HR = 0.64 (0.48, 0.84), $P = 0.002$], but not in males [HR = 0.91 (0.71, 1.18), $P = 0.489$] with a P value of 0.070 for interaction, indicating a suggestive heterogeneity by sex.

To test the robustness of our findings, several sensitivity analyses were conducted and results were presented in Table 2 (model 3a–model 3e). The findings were overall not appreciably changed. In addition, we used midpoint

Table 1 Baseline characteristics of the study participants: the CARDIA Study (1985–2010) ($n = 4133$)

Characteristics	Mean ± SD, median (IQR), or proportion (%)
LCω3PUFA (g/day)	0.17 ± 0.19
DHA (g/day)	0.08 ± 0.09
EPA (g/day)	0.06 ± 0.08
Non-fried fish (serving/day)	0.95 ± 0.98
Fried fish (serving/day)	0.06 ± 0.27
Age (year)	25.0 ± 3.6
Education (year)	13.9 ± 2.3
Female (%)	53.2
Black (%)	49.8
Current smoker (%)	28.8
Alcohol intake (mL/day)	4.8 (0–14.7)
Physical activity (EU)	365 (200–577)
BMI (kg/m^2)	24.6 ± 5.1
Dietary intake	
Total energy (kcal/day)	2802.4 ± 1312.2
Magnesium (mg/day)	396.3 ± 229.2
Calcium (mg/day)	1292.6 ± 855.3
Sodium (mg/day)	4279.5 ± 2391.8
Potassium (mg/day)	3745.5 ± 1956.5
Phosphorous (mg/day)	1820.8 ± 998.9
eGFR (mL/min per 1.73 m^2)	123.5 ± 15.5

BMI body mass index, *CARDIA* Coronary Artery Risk Development in Young Adults, *DHA* docosahexaenoic acid, *eGFR* estimated glomerular filtration rate, *EPA* eicosapentaenoic acid, *EU* exercise unit, *IQR* inter-quartile range, *LCω3PUFA* long-chain omega-3 polyunsaturated fatty acids, *SD* standard deviation

Table 2 Associations of incident CKD by intakes of LCω3PUFA/non-fried fish: the CARDIA Study (1985–2010) ($n=4133$)

	LCω3PUFA[a]		DHA[a]		EPA[a]		Non-fried fish[a]	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Model 1[b]	0.74 (0.61, 0.90)	0.002	0.71 (0.59, 0.85)	< 0.001	0.78 (0.64, 0.96)	0.017	0.86 (0.74, 1.01)	0.064
Model 2[c]	0.73 (0.60, 0.89)	0.002	0.72 (0.59, 0.87)	< 0.001	0.76 (0.62, 0.94)	0.010	0.86 (0.73, 1.01)	0.073
Model 3a[d]	0.72 (0.59, 0.88)	0.002	0.71 (0.58, 0.86)	< 0.001	0.75 (0.61, 0.92)	0.007	0.85 (0.72, 0.999)	0.045
Model 3b[e]	0.76 (0.62, 0.93)	0.008	0.74 (0.61, 0.90)	< 0.001	0.79 (0.64, 0.97)	0.022	0.88 (0.75, 1.03)	0.112
Model 3c[f]	0.74 (0.60, 0.91)	0.004	0.70 (0.57, 0.86)	< 0.001	0.78 (0.63, 0.97)	0.023	0.86 (0.73, 1.02)	0.092
Model 3d[g]	0.73 (0.59, 0.90)	0.003	0.69 (0.56, 0.85)	< 0.001	0.77 (0.62, 0.96)	0.018	0.86 (0.72, 1.02)	0.078
Model 3e[h]	0.72 (0.58, 0.90)	0.003	0.68 (0.56, 0.84)	< 0.001	0.77 (0.61, 0.95)	0.017	0.86 (0.72, 1.02)	0.077

Data are HR (95% CIs). All models were constructed using the Cox proportional hazard model and the exposures were the cumulative average intake before the event

BMI body mass index, *CARDIA* Coronary Artery Risk Development in Young Adults, *CI* confidence interval, *CKD* chronic kidney disease, *DHA* docosahexaenoic acid, *EPA* eicosapentaenoic acid, *HR* hazard ratio, *LCω3PUFA* long-chain omega-3 polyunsaturated fatty acids

[a]Every 1 SD increment for intakes of LCω3PUFA (SD = 0.19 g/day), DHA (SD = 0.09 g/day), and EPA (SD = 0.08 g/day), and every serving/day increment for non-fried fish consumption

[b]Model 1: adjustment for age (continuous), sex, race (black or white), and study center

[c]Model 2: model 1 with additional adjustment for BMI (continuous), education (continuous), current smoker (yes or no), alcohol consumption (0, 0.1–4.9, 5.0–9.9, 10.0–19.9, or ≥ 20 g/day), physical activity (quartiles), and total energy (quartiles), and personal kidney problems (yes or no). Fried fish intake (yes or no) was adjusted only in models when the exposure was non-fried fish intake

[d]Model 3a: model 2 with additional adjustment for dietary intakes (quartiles) of magnesium, calcium, sodium, potassium, and phosphorous

[e]Model 3b: model 2 with additional adjustment for baseline creatinine (continuous) and glucose (continuous)

[f]Model 3c: model 2 under a reduced sample size at $n=3690$ with trace elements measured

[g]Model 3d: model 3c with additional adjustment for toenail measurements (quartiles) of mercury, and cadmium

[h]Model 3e: model 3d with additional adjustment for toenail selenium (quartiles)

imputation instead of right-point imputation considering the interval-censored nature of the outcome; the results remained. Moreover, we replaced "cumulative average model" with "baseline model" and "most-recent model" for dietary intake; the main findings were consistent excepting some results were somewhat attenuated (data not shown).

Discussion

In this 25-year follow-up prospective study, LCω3PUFA intake and non-fried fish consumption exhibited overall inverse relations with incidence of CKD in young American adults. Findings from this study suggest that non-fried fish consumption may be beneficial with respect to primary prevention of CKD.

To our knowledge, no previous studies have investigated whether there are sex-dependent differences in the relation between fish consumption and incidence of CKD. A cross-sectional study of 2600 adults aged ≥ 50 years reported an association of increased dietary intake of LCω3PUFA and fish with a reduced risk of CKD [20]. A population-based cohort study of 931 adults aged ≥ 65 years showed that higher plasma polyunsaturated fatty acid levels at enrollment were associated with a lower risk of developing renal insufficiency during a 3-year follow-up [19]. Our study strengthens these findings given that our timeline of 25 years is substantially longer; studies investigating kidney disease outcomes require at least a 5-to-10-year follow-up. Our study adds new evidence that fish consumption in young adulthood may be beneficial to primary prevention of CKD later in life.

LCω3PUFA can interfere with several stages of renal fibrosis by acting directly on renal cells and modulating several pathophysiological responses [7], such as apoptosis, inflammation, migration, proliferation, and differentiation [35, 36]. In addition, dietary fish oil may reduce blood pressure [8] and proteinuria in patients with hypertension through a mechanism mediated by the vasorelaxant response to LCω3PUFA [7] and by their modulation of transforming growth factor-beta, renin, fibronectin, and nitric oxide synthesis [37, 38].

Sex modified the inverse association between LCω3PUFA intake and incidence of CKD in this study. The underlying mechanisms are unclear. The type and number of transcripts and plasma lipid response were significantly different between the sexes after LCω3PUFA supplementation [39, 40]. For example, HDL cholesterol (HDL-C) levels increased significantly for females [40, 41]. In the present study, the HDL-C level was higher in females (55.59 mg/dL) than that in males (50.16 mg/dL). HDL-C might maintain

Table 3 Stratified analysis of associations between intakes of LCω3PUFA/non-fried fish with incident CKD: the CARDIA Study (1985–2010) ($n=4133$)

Stratified variables	LCω3PUFA[a]		Non-fried fish[a]	
	HR (95% CI)[a]	*P* value	HR (95% CI)[a]	*P* value
Sex				
Male	0.91 (0.71, 1.18)	0.489	0.93 (0.76, 1.15)	0.527
Female	0.64 (0.48, 0.84)	0.002	0.75 (0.59, 0.94)	0.012
P for interaction	0.070		0.182	
Race				
Black	0.80 (0.64, 0.999)	0.048	0.83 (0.68, 0.999)	0.047
White	0.80 (0.57, 1.11)	0.185	0.96 (0.74, 1.25)	0.753
P for interaction	0.446		0.955	
Selenium[b]				
< median	0.86 (0.66, 1.11)	0.251	0.86 (0.69, 1.08)	0.191
≥ median	0.70 (0.52, 0.94)	0.016	0.84 (0.66, 1.07)	0.158
P for interaction	0.662		0.702	
Mercury[b]				
< median	0.78 (0.59, 1.04)	0.091	0.79 (0.62, 1.00)	0.052
≥ median	0.78 (0.58, 1.03)	0.082	0.92 (0.73, 1.16)	0.480
P for interaction	0.870		0.325	

Data are HR (95% CIs) except otherwise specified. All models were constructed using the Cox proportional hazards model with adjustment for the covariates listed in model 2 in Table 2

CARDIA Coronary Artery Risk Development in Young Adults, *CI* confidence interval, *CKD* chronic kidney disease, *HR* hazard ratio, *LCω3PUFA* long-chain omega-3 polyunsaturated fatty acids, *SD* standard deviation

[a]Every 0.19 g/day increment (1 SD) for LCω3PUFA intake, and every serving/day increment for non-fried fish consumption

[b]The analyses were conducted with a size-reduced sample ($n=3690$) in which trace elements were measured

and improve renal function through inhibition of intra-renal atherosclerosis [42], inhibiting the accumulation of lipoproteins on the mesangial cells [43], and the antioxidant effect [44]. In addition, the anti-inflammatory effects of LCω3PUFA may be acting via changes in gene expression by sex in various and multiple pathways [39, 45]. Recently, it has been reported that LCω3PUFA interventions might improve insulin resistance in females but not in males [46]. However, further studies are warranted.

Our study found a potential benefit of non-fried fish consumption in relation to incidence of CKD after additional adjustment for dietary intakes of calcium, magnesium, phosphorous, potassium, and sodium in Table 3. A possible explanation is that these mineral levels, which are important to CKD patients, are strong confounders [47, 48]. Fried fish tends to be made from lean fish with little LCω3PUFA compared to fatty fish [49]. More studies are needed to further investigate the health impact of type of fish consumption. In addition, frying may reduce the LCω3PUFA content and generate trans-fatty acids and/or oxidative factors that could substantially attenuate the benefits of fish intake [25, 50]. A cohort study in American Indians who consumed predominantly fried fish found no associations between fish consumption and any measure of nephropathy [21, 29].

Hg and Se concentrations were directly correlated with fish intake [51]. Epidemiological studies indicate a possible benefit of Se intake on Hg's vascular toxicity which can be a risk factor of CKD [9, 16, 52]. However, they were not found to be effect modifiers of the relation between them and CKD events in this study. Additional research is needed to clarify it.

The strengths of our study include a unique 25-year follow-up prospective study involving young adults, in which both EPA and DHA exerted beneficial effects on kidney function, as reported previously [20], and we did stratified analysis according to several pre-specified factors including sex. In addition, multiple in-depth dietary measurements were performed. Moreover, we used the cumulative average dietary intakes obtained from multiple measurements during the follow-up, which should reduce the random measurement error and provide a more precise estimate of habitual intake than would a single measurement. Furthermore, we distinguished non-fried from fried fish, and we conducted a number of sensitivity analyses to test the robustness of our findings. To our knowledge, this is the first long-term follow-up study of the association between intake of LCω3PUFA and fish with incidence of CKD.

This study had several limitations. First, although we controlled for many potential confounders, the possibility of residual confounding or bias from unknown or unmeasured factors could not be completely excluded due to the observational property of this study. However, research or monitoring all food and chemicals commercially available is not possible nor is it desirable, as many do not pose a risk to ecosystems or humans [53]. Second, we do not have albuminuria information at baseline. However, we measured albuminuria at Y10. Therefore, if CKD occurred in some cases before Y10, they would not be missed. Third, this study adjusted for toenail Hg and Se. Although the advantage of toenails as a long-term exposure biomarker of trace elements such as Hg and Se status has been recognized [54], one toenail measurement at baseline may not reflect the changes in their status during the entire follow-up period. Since the changes are likely to be non-differential, the possible association may be attenuated. Fourth, the recent discovery of the apolipoprotein L1 (APOL1) gene variant has helped to explain racial disparities in the progression of CKD between black and white patients [55]. While we were unable to adjust for the APOL1 variant, we did adjust for race and did not find any effect modification by race. Finally, the generalizability of our findings may be limited. All participants were young American adults mainly from four metropolitan areas, and their characteristics may be different from the general population.

In conclusion, our findings indicate that dietary LCω3PUFA intake is inversely associated with CKD incidence. The results add evidence in support of fish consumption, particularly non-fried fish, among apparently healthy American young adults. Further studies are warranted to confirm our findings in other populations.

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Author contribution The manuscript has been read and approved by all coauthors. All individuals listed as authors have substantially contributed to the manuscript preparation, and no one other than the authors listed has contributed significantly to this study. Specifically, IP, PX, and KH contributed to the conception and design of the study. IP, PX, CLT, PK, KL, and KH contributed to the analysis and interpretation of data. All of the listed authors contributed to drafting of the manuscript and revising it critically for important intellectual content.

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Compliance with ethical standards

Conflict of interest None of the authors has any conflict of interest to declare.

References

1. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, Hobbs FD (2016) Global prevalence of chronic kidney disease—a systematic review and meta-analysis. PLoS One 11:e0158765
2. Levey AS, Coresh J (2012) Chronic kidney disease. Lancet (London, England) 379:165–180
3. Saran R, Robinson B, Abbott KC, Agodoa LY, Ayanian J, Bragg-Gresham J, Balkrishnan R, Chen JL, Cope E, Eggers PW, Gillen D, Gipson D, Hailpern SM, Hall YN, Han Y, He K, Herman W, Heung M, Hutton D, Jacobsen SJ, Kalantar-Zadeh K, Kovesdy CP, Li Y, Lu Y, Molnar MZ, Morgenstern H, Nallamothu B, Nguyen DV, O'Hare AM, Obi Y, Plattner B, Pisoni R, Port FK, Rao P, Ravel V, Rhee CM, Sakhuja A, Schaubel DE, Selewski DT, Sim JJ, Song P, Streja E, Kurella Tamura M, Tentori F, White S, Woodside K, Hirth RA, Shahinian V (2017) US Renal Data System 2016 annual data report: epidemiology of kidney disease in the United States. Am J Kidney Dis 69:A7–A8
4. Bruck K, Stel VS, Gambaro G, Hallan S, Volzke H, Arnlov J, Kastarinen M, Guessous I, Vinhas J, Stengel B, Brenner H, Chudek J, Romundstad S, Tomson C, Gonzalez AO, Bello AK, Ferrieres J, Palmieri L, Browne G, Capuano V, Van Biesen W, Zoccali C, Gansevoort R, Navis G, Rothenbacher D, Ferraro PM, Nitsch D, Wanner C, Jager KJ (2016) CKD prevalence varies across the European general population. J Am Soc Nephrol JASN 27:2135–2147
5. Jin DC, Yun SR, Lee SW, Han SW, Kim W, Park J (2016) Current characteristics of dialysis therapy in Korea: 2015 registry data focusing on elderly patients. Kidney Res Clin Pract 35:204–211
6. Calder PC, Yaqoob P (2009) Omega-3 polyunsaturated fatty acids and human health outcomes. BioFactors (Oxford, England) 35:266–272
7. Baggio B, Musacchio E, Priante G (2005) Polyunsaturated fatty acids and renal fibrosis: pathophysiologic link and potential clinical implications. J Nephrol 18:362–367
8. He K (2009) Fish, long-chain omega-3 polyunsaturated fatty acids and prevention of cardiovascular disease—eat fish or take fish oil supplement? Prog Cardiovasc Dis 52:95–114
9. Xun P, Hou N, Daviglus M, Liu K, Morris JS, Shikany JM, Sidney S, Jacobs DR, He K (2011) Fish oil, selenium and mercury in relation to incidence of hypertension: a 20-year follow-up study. J Intern Med 270:175–186
10. de Roos B, Mavrommatis Y, Brouwer IA (2009) Long-chain n-3 polyunsaturated fatty acids: new insights into mechanisms relating to inflammation and coronary heart disease. Br J Pharmacol 158:413–428
11. Lee CC, Adler AI (2012) Recent findings on the effects of marine-derived n-3 polyunsaturated fatty acids on urinary albumin excretion and renal function. Curr Atheroscler Rep 14:535–541
12. Donadio JV, Grande JP (2004) The role of fish oil/omega-3 fatty acids in the treatment of IgA nephropathy. Semin Nephrol 24:225–243
13. Manson JE, Cook NR, Lee IM, Christen W, Bassuk SS, Mora S, Gibson H, Albert CM, Gordon D, Copeland T, D'Agostino D, Friedenberg G, Ridge C, Bubes V, Giovannucci EL, Willett WC, Buring JE, VITAL Research Group (2019) Marine n-3 fatty acids

and prevention of cardiovascular disease and cancer. N Engl J Med 380:23–32
14. Rizos EC, Ntzani EE, Bika E, Kostapanos MS, Elisaf MS (2012) Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis. JAMA 308:1024–1033
15. Aung T, Halsey J, Kromhout D, Gerstein HC, Marchioli R, Tavazzi L, Geleijnse JM, Rauch B, Ness A, Galan P, Chew EY, Bosch J, Collins R, Lewington S, Armitage J, Clarke R, Omega-3 Treatment Trialists' Collaboration (2018) Associations of omega-3 fatty acid supplement use with cardiovascular disease risks: meta-analysis of ten trials involving 77917 individuals. JAMA cardiology 3:225–234
16. Gribble MO, Karimi R, Feingold BJ, Nyland JF, O'Hara TM, Gladyshev MI, Chen CY (2016) Mercury, selenium and fish oils in marine food webs and implications for human health. J Mar Biol Assoc UK 96:43–59
17. Li YF, Dong Z, Chen C, Li B, Gao Y, Qu L, Wang T, Fu X, Zhao Y, Chai Z (2012) Organic selenium supplementation increases mercury excretion and decreases oxidative damage in long-term mercury-exposed residents from Wanshan, China. Environ Sci Technol 46:11313–11318
18. Ralston NV, Blackwell JL 3rd, Raymond LJ (2007) Importance of molar ratios in selenium-dependent protection against methylmercury toxicity. Biol Trace Elem Res 119:255–268
19. Lauretani F, Semba RD, Bandinelli S, Miller ER 3rd, Ruggiero C, Cherubini A, Guralnik JM, Ferrucci L (2008) Plasma polyunsaturated fatty acids and the decline of renal function. Clin Chem 54:475–481
20. Gopinath B, Harris DC, Flood VM, Burlutsky G, Mitchell P (2011) Consumption of long-chain n-3 PUFA, alpha-linolenic acid and fish is associated with the prevalence of chronic kidney disease. Br J Nutr 105:1361–1368
21. Lee CC, Howard BV, Mete M, Wang H, Jolly S, Adler AI (2012) Association between fish consumption and nephropathy in American Indians—the Strong Heart Study. J Renal Nutr Off J Council Renal Nutr Natl Kidney Found 22:221–227
22. Friedman GD, Cutter GR, Donahue RP, Hughes GH, Hulley SB, Jacobs DR Jr, Liu K, Savage PJ (1988) CARDIA: study design, recruitment, and some characteristics of the examined subjects. J Clin Epidemiol 41:1105–1116
23. McDonald A, Van Horn L, Slattery M, Hilner J, Bragg C, Caan B, Jacobs D Jr, Liu K, Hubert H, Gernhofer N, Betz E, Havlik D (1991) The CARDIA dietary history: development, implementation, and evaluation. J Am Diet Assoc 91:1104–1112
24. Liu K, Slattery M, Jacobs D Jr, Cutter G, McDonald A, Van Horn L, Hilner JE, Caan B, Bragg C, Dyer A (1994) A study of the reliability and comparative validity of the cardia dietary history. Ethn Dis 4:15–27
25. Echarte M, Zulet MA, Astiasaran I (2001) Oxidation process affecting fatty acids and cholesterol in fried and roasted salmon. J Agric Food Chem 49:5662–5667
26. Levey AS, Stevens LA (2010) Estimating GFR using the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation: more accurate GFR estimates, lower CKD prevalence estimates, and better risk predictions. Am J Kidney Dis 55:622–627
27. Jacobs DR Jr, Murtaugh MA, Steffes M, Yu X, Roseman J, Goetz FC (2002) Gender- and race-specific determination of albumin excretion rate using albumin-to-creatinine ratio in single, untimed urine specimens: the Coronary Artery Risk Development in Young Adults Study. Am J Epidemiol 155:1114–1119
28. Yaemsiri S, Hou N, Slining MM, He K (2010) Growth rate of human fingernails and toenails in healthy American young adults. J Eur Acad Dermatol Venereol JEADV 24:420–423
29. Garland M, Morris JS, Rosner BA, Stampfer MJ, Spate VL, Baskett CJ, Willett WC, Hunter DJ (1993) Toenail trace element levels as biomarkers: reproducibility over a 6-year period. Cancer Epidemiol Biomark Prevent Publ Am Assoc Cancer Res Cospons Am Soc Prevent Oncol 2:493–497
30. Longnecker MP, Stampfer MJ, Morris JS, Spate V, Baskett C, Mason M, Willett WC (1993) A 1-year trial of the effect of high-selenium bread on selenium concentrations in blood and toenails. Am J Clin Nutr 57:408–413
31. Pereira MA, FitzerGerald SJ, Gregg EW, Joswiak ML, Ryan WJ, Suminski RR, Utter AC, Zmuda JM (1997) A collection of Physical Activity Questionnaires for health-related research. Med Sci Sports Exerc 29:S1–S205
32. Grambsch PM, Therneau TM (1994) Proportional hazards tests and diagnostics based on weighted residuals. Biometrika 81:515–526
33. He K, Rimm EB, Merchant A, Rosner BA, Stampfer MJ, Willett WC, Ascherio A (2002) Fish consumption and risk of stroke in men. JAMA 288:3130–3136
34. He K, Merchant A, Rimm EB, Rosner BA, Stampfer MJ, Willett WC, Ascherio A (2003) Dietary fat intake and risk of stroke in male US healthcare professionals: 14 year prospective cohort study. BMJ 327:777–782
35. Graber R, Sumida C, Nunez EA (1994) Fatty acids and cell signal transduction. J Lipid Mediat Cell Signal 9:91–116
36. Di Marzo V (1995) Arachidonic acid and eicosanoids as targets and effectors in second messenger interactions. Prostaglandins Leukot Essent Fatty Acids 53:239–254
37. Miyazaki M, Takemura N, Watanabe S, Hata N, Misawa Y, Okuyama H (2000) Dietary docosahexaenoic acid ameliorates, but rapeseed oil and safflower oil accelerate renal injury in stroke-prone spontaneously hypertensive rats as compared with soybean oil, which is associated with expression for renal transforming growth factor-beta, fibronectin and renin. Biochem Biophys Acta 1483:101–110
38. Das UN (2004) Long-chain polyunsaturated fatty acids interact with nitric oxide, superoxide anion, and transforming growth factor-beta to prevent human essential hypertension. Eur J Clin Nutr 58:195–203
39. Rudkowska I, Paradis AM, Thifault E, Julien P, Tchernof A, Couture P, Lemieux S, Barbier O, Vohl MC (2013) Transcriptomic and metabolomic signatures of an n-3 polyunsaturated fatty acids supplementation in a normolipidemic/normocholesterolemic Caucasian population. J Nutr Biochem 24:54–61
40. Mueller BA, Talbert BL, Tegeler CH (1989) Comparative effects of omega-3 fatty acids in men and women. Clin Pharm 8:328–329
41. Thifault E, Cormier H, Bouchard-Mercier A, Rudkowska I, Paradis AM, Garneau V, Ouellette C, Lemieux S, Couture P, Vohl MC (2013) Effects of age, sex, body mass index and APOE genotype on cardiovascular biomarker response to an n-3 polyunsaturated fatty acid supplementation. J Nutrigenet Nutrigenom 6:73–82
42. Moorhead JF, Chan MK, El-Nahas M, Varghese Z (1982) Lipid nephrotoxicity in chronic progressive glomerular and tubulointerstitial disease. Lancet (London, England) 2:1309–1311
43. Abrass CK (2004) Cellular lipid metabolism and the role of lipids in progressive renal disease. Am J Nephrol 24:46–53
44. Robbesyn F, Auge N, Vindis C, Cantero AV, Barbaras R, Negre-Salvayre A, Salvayre R (2005) High-density lipoproteins prevent the oxidized low-density lipoprotein-induced epidermal [corrected] growth factor receptor activation and subsequent matrix metalloproteinase-2 upregulation. Arterioscler Thromb Vasc Biol 25:1206–1212
45. Ishikado A, Nishio Y, Morino K, Ugi S, Kondo H, Makino T, Kashiwagi A, Maegawa H (2010) Low concentration of 4-hydroxy hexenal increases heme oxygenase-1 expression through activation of Nrf2 and antioxidative activity in vascular endothelial cells. Biochem Biophys Res Commun 402:99–104

46. Abbott KA, Burrows TL, Thota RN, Acharya S, Garg ML (2016) Do omega-3 PUFAs affect insulin resistance in a sex-specific manner? A systematic review and meta-analysis of randomized controlled trials. Am J Clin Nutr 104:1470–1484
47. Wright JA, Cavanaugh KL (2010) Dietary sodium in chronic kidney disease: a comprehensive approach. Semin Dial 23:415–421
48. Jain N, Reilly RF (2014) Effects of dietary interventions on incidence and progression of CKD. Nat Rev Nephrol 10:712–724
49. Mozaffarian D, Lemaitre RN, Kuller LH, Burke GL, Tracy RP, Siscovick DS (2003) Cardiac benefits of fish consumption may depend on the type of fish meal consumed: the Cardiovascular Health Study. Circulation 107:1372–1377
50. Phang M, Sinclair AJ, Lincz LF, Garg ML (2012) Gender-specific inhibition of platelet aggregation following omega-3 fatty acid supplementation. Nutr Metab Cardiovasc Dis NMCD 22:109–114
51. Bates CJ, Prentice A, Birch MC, Delves HT, Sinclair KA (2006) Blood indices of selenium and mercury, and their correlations with fish intake, in young people living in Britain. Br J Nutr 96:523–531
52. Buettner C (2003) Mercury and the risk of myocardial infarction. N Engl J Med 348:2151–2154 **(author reply 2151–2154)**
53. Anna S, Sofia B, Christina R, Magnus B (2016) The dilemma in prioritizing chemicals for environmental analysis: known versus unknown hazards. Environ Sci Process Impacts 18:1042–1049
54. He K (2011) Trace elements in nails as biomarkers in clinical research. Eur J Clin Invest 41:98–102
55. Parsa A, Kao WH, Xie D, Astor BC, Li M, Hsu CY, Feldman HI, Parekh RS, Kusek JW, Greene TH, Fink JC, Anderson AH, Choi MJ, Wright JT Jr, Lash JP, Freedman BI, Ojo A, Winkler CA, Raj DS, Kopp JB, He J, Jensvold NG, Tao K, Lipkowitz MS, Appel LJ (2013) APOL1 risk variants, race, and progression of chronic kidney disease. N Engl J Med 369:2183–2196