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Abstract

Due to the anti-inflammatory properties of PUFA, it has been suggested that they may protect against kidney damage in adults. However, relatively few epidemiological studies have examined this hypothesis in human subjects. We investigated the association between dietary intakes of PUFA (n-3, n-6 and α -linolenic acid), fish and the prevalence of chronic kidney disease (CKD). A total of 2600 Blue Mountains Eye Study (1997-9) participants aged ≥ 50 years were analysed. Dietary data were collected using a semi-quantitative FFQ, and PUFA and fish intakes were calculated. Baseline biochemistry including serum creatinine was measured. Moderate CKD was defined as an estimated glomerular filtration rate of < 60 ml/min per 1.73 m². Participants in the highest quartile of long-chain n-3 PUFA intake had a significantly reduced likelihood of having CKD compared with those in the lowest quartile of intake (multivariable-adjusted OR 0.69, 95 % CI 0.49, 0.99). α -Linolenic acid intake was positively associated with CKD (OR, per standard deviation increase in α -linolenic acid, 1.18, 95 % CI 1.05, 1.32). Total n-3 PUFA or total n-6 PUFA were not significantly associated with CKD. The highest compared with the lowest quartile of fish consumption was associated with a reduced likelihood of CKD (OR 0.68, 95 % CI 0.48, 0.97; P for trend = 0.02). The present study shows that an increased dietary intake of long-chain n-3 PUFA and fish reduces the prevalence of CKD. Hence, a diet rich in n-3 PUFA and fish could have a role in maintaining healthy kidney function, in addition to roles of these nutrients in the prevention and modulation of other diseases.

Disciplines

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Consumption of long-chain *n*-3 PUFA, α -linolenic acid and fish is associated with the prevalence of chronic kidney disease

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Abstract

Due to the anti-inflammatory properties of PUFA, it has been suggested that they may protect against kidney damage in adults. However, relatively few epidemiological studies have examined this hypothesis in human subjects. We investigated the association between dietary intakes of PUFA (*n*-3, *n*-6 and α -linolenic acid), fish and the prevalence of chronic kidney disease (CKD). A total of 2600 Blue Mountains Eye Study (1997–9) participants aged ≥ 50 years were analysed. Dietary data were collected using a semi-quantitative FFQ, and PUFA and fish intakes were calculated. Baseline biochemistry including serum creatinine was measured. Moderate CKD was defined as an estimated glomerular filtration rate of < 60 ml/min per 1.73 m². Participants in the highest quartile of long-chain *n*-3 PUFA intake had a significantly reduced likelihood of having CKD compared with those in the lowest quartile of intake (multivariable-adjusted OR 0.69, 95% CI 0.49, 0.99). α -Linolenic acid intake was positively associated with CKD (OR, per standard deviation increase in α -linolenic acid, 1.18, 95% CI 1.05, 1.32). Total *n*-3 PUFA or total *n*-6 PUFA were not significantly associated with CKD. The highest compared with the lowest quartile of fish consumption was associated with a reduced likelihood of CKD (OR 0.68, 95% CI 0.48, 0.97; *P* for trend=0.02). The present study shows that an increased dietary intake of long-chain *n*-3 PUFA and fish reduces the prevalence of CKD. Hence, a diet rich in *n*-3 PUFA and fish could have a role in maintaining healthy kidney function, in addition to roles of these nutrients in the prevention and modulation of other diseases.

Key words: Chronic kidney disease: PUFA: *n*-3: Fish: Blue Mountains Eye Study

Chronic kidney disease (CKD) is an important health problem among older adults and can lead to end-stage renal disease with its need for dialysis or transplantation for survival^(1–3). Therefore, it is important to identify risk/protective factors associated with CKD at an early kidney disease stage in the continuum, at which prevention/control of disease progression is more applicable⁽⁴⁾. Many cohort studies have identified hypertension, diabetes, obesity, hyperlipidaemia and smoking as risk factors for the development of CKD. It is generally hypothesised that these risk factors exert their influence by increasing vascular pathology and by direct damage to kidney structures⁽¹⁾.

Due to the anti-inflammatory properties of PUFA, it has been suggested that these nutrients may protect the kidneys from damage in adults; however, very few studies have examined the putative association between PUFA and the

development of CKD^(5,6). PUFA supplementation was observed as reducing renal inflammation and fibrosis in animal models⁽⁶⁾. Recently, an Italian population-based cohort study of 931 adults aged ≥ 65 years old assessed the association between plasma PUFA levels and renal function. Baseline long-chain *n*-3 and *n*-6 PUFA were negatively associated with creatinine at the 3-year follow-up. Moreover, participants with higher plasma PUFA at enrollment had a lower risk of developing renal insufficiency (creatinine clearance < 60 ml/min) during the 3-year follow-up⁽⁵⁾.

Further epidemiological investigations are needed to confirm the role of PUFA in the renal inflammation and fibrosis pathways of CKD⁽⁶⁾. To the best of our knowledge, no population-based study has examined the association between dietary intakes of PUFA, fish and CKD in the general population. Therefore, we used a large representative,

Abbreviations: AA, arachidonic acid; BMES, Blue Mountains Eye Study; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

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community-based cohort of adults aged ≥ 50 years to pursue the following aims: (a) to establish whether a cross-sectional association exists between dietary intakes of PUFA and the prevalence of CKD; (b) to determine whether a diet high in fish reduces the likelihood of CKD.

Methods

Study population

The present study is based on the second Blue Mountains Eye Study (BMES), a population-based study of participants aged ≥ 49 years, living in two postcodes of the Blue Mountains region, west of Sydney, Australia, which has studied age-related eye diseases and other health outcomes in an urban Australian population. Details of the study methods have previously been described⁽⁷⁾. In brief, following a door-to-door census of the region, 4433 people were identified as eligible for the study. Of these, 3654 participants aged 49 years or older were examined (82.4% participation; BMES-1) during 1992–4. Surviving baseline participants were invited to attend 5-year follow-up examinations (1997–9, BMES-2), at which 2334 (75.1% of survivors) and an additional 1174 newly eligible residents were examined, i.e. those who had become eligible by moving into the area or into the age bracket of the original survey. At the 10-year follow-up (2002–4, BMES-3), 1952 participants (75.6% of survivors) were re-examined. The study was approved by the Human Research Ethics Committee of the University of Sydney and was conducted adhering to the tenets of the Declaration of Helsinki. Signed informed consent was obtained from all participants at each examination.

Dietary data

Dietary data were collected using a 145-item self-administered FFQ, modified for Australian diet and vernacular from an early Willett FFQ⁽⁸⁾, and included reference portion sizes. Participants used a nine-category frequency scale to indicate the usual frequency of consuming individual food items during the past year. The FFQ included details about frequency estimates and fatty acid supplements in order to permit a more detailed analysis of fatty acids.

We extracted separate data on the frequency of consuming fish (any species plus method of preparation) and oily fish (specifically salmon, tuna and sardines). Fish consumption was converted into g/d by multiplying the food consumption frequency by fixed portion sizes. The FFQ was validated on seventy-nine participants on three occasions during 1 year by using 4 d weighed food records⁽⁹⁾. The FFQ showed moderate to good agreement for ranking individuals according to their fat intakes (total fat, r 0.68; SFA, r 0.67; MUFA, r 0.54; PUFA, r 0.44) and correctly classified more than 70% of people within 1 quintile for all types of fat^(9,10).

Dietary intakes were estimated using the Australian Tables of Food Composition (NUTTAB95)⁽¹⁰⁾ and its fatty acid supplement. Additional fatty acid food composition data were added from the Royal Melbourne Institute of Technology database (Melbourne, VIC, Australia)⁽¹¹⁾, available on

FoodWorks, version 3 (Xyris Software Private Limited, Highgate Hill, QLD, Australia). Long-chain n -3 PUFA were calculated from the sum of EPA (20:5 n -3), docosapentaenoic acid (22:5 n -3) and DHA (22:6 n -3). Total n -3 PUFA consumption was calculated by adding the intakes of long-chain n -3 PUFA and α -linolenic acid. Total n -6 PUFA consumption was calculated by adding the intakes of linoleic and arachidonic acid (AA).

Assessment of chronic kidney disease

Serum creatinine was measured within 4 h of fasting venous blood collection using a Hitachi 747 biochemistry analyser (Roche Diagnostics, Castle Hill, Sydney, NSW, Australia). Estimated glomerular filtration rate (eGFR) was the preferred measure of kidney function in the present study. Glomerular filtration rate was indirectly estimated using the four-variable Modification of Diet in Renal Disease Study equation⁽¹²⁾:

$$\begin{aligned} \text{Glomerular filtration rate (ml/min per } 1.73 \text{ m}^2) \\ = 186 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \\ \times (0.742 \text{ if female}) \text{ (conventional units).} \end{aligned}$$

The main outcome of interest was CKD of stage 3 or greater, defined as an eGFR of < 60 ml/min per 1.73 m^2 . For the purposes of the present study, this was defined as CKD of moderate severity.

Collection of other information

At face-to-face interviews with trained interviewers, a comprehensive medical history that included information about hearing, demographic factors, socio-economic characteristics and lifestyle factors such as smoking was obtained from all participants. History of smoking was defined as never, past or current smoking. Current smokers included those who had stopped smoking within the past year. Alcohol intake was assessed by questions about the frequency of consuming alcoholic drinks (d/week), and consumption was split into three groups (no alcohol, 0–20 and > 20 g/d). Physical inactivity (yes and no) was categorised as answering negatively to 'have you participated in any recreational exercise/walk in the last 2 weeks?' Diabetes was defined either from history or by fasting blood glucose ≥ 7.0 mmol/l. Subjects were defined as having hypertension if they had a systolic blood pressure greater than 140 mmHg or a diastolic blood pressure more than 90 mmHg or were on anti-hypertensive medications⁽¹³⁾. Serum total homocysteine was determined from blood using the fluorescent polarization immunoassay method on an IMx analyser. BMI was calculated as weight divided by height squared (kg/m^2). Serum total cholesterol and TAG were measured on a Reflotron reflectance photometric analyser (Roche Diagnostics).

Statistical analysis

Analyses including t tests, χ^2 tests and logistic regression were performed using the SAS statistical software package version

9.1 (SAS Institute, Cary, NC, USA). Associations between dietary intakes of PUFA, fish and the prevalence of CKD were examined in logistic regression models, adjusting first for age and sex, and then for confounders that were found to be significantly associated with CKD (i.e. smoking, alcohol intake, BMI, physically inactive, diabetes mellitus, hypertension, serum total homocysteine, serum total cholesterol and serum TAG). Dietary fatty acid intakes were energy adjusted using the residual method described by Willett & Stampfer⁽¹⁴⁾. Results of the logistic regression analysis are expressed as adjusted OR with 95% CI. We assessed dietary intakes of PUFA and fish both as categorised (quartiles; with the lowest quartile as the reference group) and continuous (per standard deviation) variables. Statistical significance was defined as $P < 0.05$.

Results

Data for the cross-sectional analyses were obtained from 3508 participants at BMES-2. Of these, 2600 participants had their fasting blood collected at BMES-2 including serum creatinine measures. In addition, at the same time, these 2600 subjects also had complete dietary data collected at BMES-2. Among these subjects, 504 (19.4%) had CKD of at least stage 3 (moderate CKD) and 2096 (80.6%) did not. Table 1 shows the characteristics of participants with and without moderate CKD. Participants with moderate CKD were more likely to be older, be physically inactive and have hypertension, diabetes, stroke, higher Hb, haematocrit and serum homocysteine, total cholesterol and TAG than participants with mild or no CKD. On the other hand, participants with moderate

CKD were less likely to be male, current smokers and less likely to heavily consume alcohol (Table 1).

Table 2 shows a significant inverse association between long-chain *n*-3 PUFA intake (assessed as a continuous variable) and the prevalence of CKD; each standard deviation increase in energy-adjusted long-chain *n*-3 PUFA intake was associated with a 13% decrease in the prevalence of CKD (multivariable-adjusted OR 0.87, 95% CI 0.76, 0.99). In contrast, each standard deviation increase in energy-adjusted α -linolenic acid intake was associated with an 18% increased likelihood of having CKD. Significant associations were not observed with total *n*-3 PUFA or total *n*-6 PUFA intake (Table 2). A non-significant association was observed between fish consumption and moderate CKD (multivariable-adjusted OR 0.89, 95% CI 0.78, 1.03). We observed a significant linear relationship between dietary intake of α -linolenic acid, fish and eGFR (Fig. 1(a) and (b)); however, a linear relationship was not observed with the other dietary PUFA and eGFR (data not shown).

We also analysed the different components of dietary PUFA as quartiles, and observed that participants in the highest quartile of long-chain *n*-3 PUFA intake had a 31% reduced likelihood of having moderate CKD compared with those in the lowest quartile (P for trend=0.052; Table 3). However, participants in the highest quartile of α -linolenic acid intake had an 73% increased likelihood of having moderate CKD compared with those in the lowest quartile of intake (P for trend=0.004).

Table 4 shows the association between consumption of fish (in quartiles) and moderate CKD. Participants in the highest quartile of fish consumption had a 32% reduced likelihood

Table 1. Characteristics of participants with and without chronic kidney disease (CKD)
(Mean values and standard deviations or number of participants and percentages)

| | Moderate CKD (eGFR < 60 ml/min per 1.73 m ² , n 504) | | | | Without moderate CKD (eGFR \geq 60 ml/min per 1.73 m ² , n 2096) | | | | <i>P</i> |
|---|---|------|----------|------|---|------|----------|------|----------|
| | Mean | SD | <i>n</i> | % | Mean | SD | <i>n</i> | % | |
| Age (years) | 73.2 | 8.4 | | | 64.9 | 8.5 | | | <0.0001 |
| Male | | | 145 | 28.8 | | | 977 | 46.6 | <0.0001 |
| Current smokers | | | 33 | 6.7 | | | 205 | 9.9 | 0.03 |
| Alcohol consumption (g/d) | | | | | | | | | |
| No alcohol | | | 137 | 27.2 | | | 380 | 18.1 | <0.0001 |
| 0–20 | | | 310 | 61.5 | | | 1284 | 61.3 | |
| > 20 | | | 57 | 11.3 | | | 432 | 20.6 | |
| BMI (kg/m ²) | 27.3 | 4.6 | | | 27.6 | 4.7 | | | 0.25 |
| Physically inactive | | | 104 | 21.8 | | | 265 | 13.5 | <0.0001 |
| Systolic BP (mmHg) | 151.8 | 22.4 | | | 146.1 | 38.6 | | | <0.0001 |
| Diastolic BP (mmHg) | 83.9 | 10.4 | | | 86.2 | 36.2 | | | 0.01 |
| Serum total homocysteine (μ mol/l) | 15.6 | 6.0 | | | 11.2 | 3.8 | | | <0.0001 |
| Serum cholesterol (mmol/l) | 6.0 | 1.1 | | | 5.8 | 1.0 | | | <0.0001 |
| Serum TAG (mmol/l) | 1.6 | 0.8 | | | 1.5 | 0.9 | | | 0.03 |
| Albumin (g/l) | 41.5 | 2.7 | | | 41.7 | 2.4 | | | 0.27 |
| Hb (g/l) | 143.5 | 13.5 | | | 148.4 | 12.1 | | | <0.0001 |
| Haematocrit | 0.43 | 0.04 | | | 0.44 | 0.03 | | | <0.0001 |
| Diuretics | | | 103 | 20.4 | | | 148 | 7.1 | <0.0001 |
| Hypertension* | | | 323 | 64.3 | | | 1012 | 48.4 | <0.0001 |
| Diabetes | | | 71 | 14.1 | | | 198 | 9.5 | 0.002 |
| Stroke† | | | 42 | 8.4 | | | 66 | 3.2 | <0.0001 |

eGFR, estimated glomerular filtration rate (in ml/min per 1.73 m²) using the four-variable Modification of Diet in Renal Disease Study formula; BP, blood pressure.

* Defined as a systolic BP greater than 140 mmHg or a diastolic BP more than 90 mmHg or using anti-hypertensive medications⁽¹³⁾.

† History of previously diagnosed stroke.

Table 2. Associations between dietary intake of PUFA, fish and the prevalence of chronic kidney disease (CKD) (Mean values, ranges, odds ratios per standard deviation and 95 % confidence intervals)

| Energy-adjusted fatty acid intake | Mean | Range | eGFR <60 (moderate CKD; <i>n</i> 504 (19.4 %)) | | | |
|---|------|------------|--|------------|------------------------|------------|
| | | | Age-sex adjusted | | Multivariate adjusted* | |
| | | | OR | 95 % CI | OR | 95 % CI |
| Total <i>n</i> -3 PUFA (1 SD = 0.58) | 1.10 | 0.07–5.91 | 1.10 | 0.99, 1.22 | 1.07 | 0.95, 1.20 |
| Long-chain <i>n</i> -3 PUFA (1 SD = 0.30) | 0.25 | 0.00–4.44 | 0.89 | 0.79, 1.01 | 0.87 | 0.76, 0.99 |
| α -Linolenic acid (1 SD = 0.46) | 0.84 | 0.07–3.31 | 1.19 | 1.08, 1.32 | 1.18 | 1.05, 1.32 |
| Total <i>n</i> -6 PUFA (1 SD = 4.7) | 9.0 | 0.90–39.23 | 1.08 | 0.97, 1.20 | 1.03 | 0.91, 1.17 |
| Fish (1 SD = 30.3) | 31.7 | 0.00–396.5 | 0.90 | 0.80, 1.01 | 0.89 | 0.78, 1.03 |

eGFR, estimated glomerular filtration rate (in ml/min per 1.73 m²) using the four-variable Modification of Diet in Renal Disease Study formula.

* Adjusted for age, sex, BMI, smoking, alcohol consumption, physical activity, serum total homocysteine, serum total cholesterol, serum TAG, hypertension and history of diagnosed diabetes.

of having an eGFR <60 ml/min per 1.73 m² (multivariable-adjusted OR 0.68, 95 % CI 0.48, 0.97). A significant trend was also observed with increasing consumption of fish, i.e. from the first to the fourth quartile (*P* for trend=0.001).

We also assessed the association between dietary intake of PUFA and fish and the different eGFR categories, using eGFR \geq 90 ml/min per 1.73 m² as the reference group (Table 5). The association between long-chain *n*-3 PUFA and fish (as continuous variables) was particularly marked in participants with an eGFR of 45 to <60 ml/min per 1.73 m²; compared with those with an eGFR of \geq 90 ml/min per 1.73 m² (OR 0.66, 95 % CI 0.49, 0.89; OR 0.68, 95 % CI 0.53, 0.87,

respectively). Significant positive associations were observed with dietary intake of α -linolenic acid in participants with an eGFR of 60 to <75 ml/min per 1.73 m² and an eGFR of 45 to <60 ml/min per 1.73 m². Significant associations with dietary intakes of PUFA and fish were not observed among subjects with an eGFR of <45 ml/min per 1.73 m², possibly due to reduced statistical power.

Discussion

To the best of our knowledge, the putative association between dietary intakes of PUFA and fish with renal function has not been investigated in a community-based setting. Data from this sample of adults show that increased dietary intake of long-chain *n*-3 PUFA is inversely associated with the prevalence of CKD. Similarly, high consumption of fish reduced the odds of having moderate CKD by 32%. In contrast, a higher intake of α -linolenic acid was associated with a 73 % increased likelihood of having prevalent CKD.

The prevalence of moderate CKD in the BMES was 19.4%, which is relatively similar to the data from the Third National Health and Nutrition Examination Survey⁽¹⁵⁾, which demonstrated a prevalence of 20.6% in adults aged \geq 65 years, and also concurs with a Norwegian study that observed a prevalence of 18.7% in adults aged 70 years and over⁽¹⁶⁾. The inverse association between dietary intake of long-chain *n*-3 PUFA and the prevalence of CKD concurs with findings of a negative association between plasma *n*-3 PUFA levels and renal function in a cohort of Italians⁽⁵⁾. These data are also in agreement with animal models that show that PUFA supplementation reduces the progression of renal disease⁽⁶⁾. The underlying mechanism for our observation is unknown. We hypothesise that long-chain *n*-3 PUFA may protect kidney function by exerting an anti-inflammatory influence through the down-regulation of pro-inflammatory cytokine production, reduction of NO and expression of endothelial leukocyte adhesion molecules^(5,17,18). Furthermore, Cicero *et al.*⁽¹⁹⁾ showed that highly purified *n*-3 PUFA long-term supplementation is associated with a significant reduction in systolic and diastolic blood pressure. Hypertension is a risk factor for CKD; hence, the influence of long-chain *n*-3 PUFA on blood pressure may be a potential mechanism by which

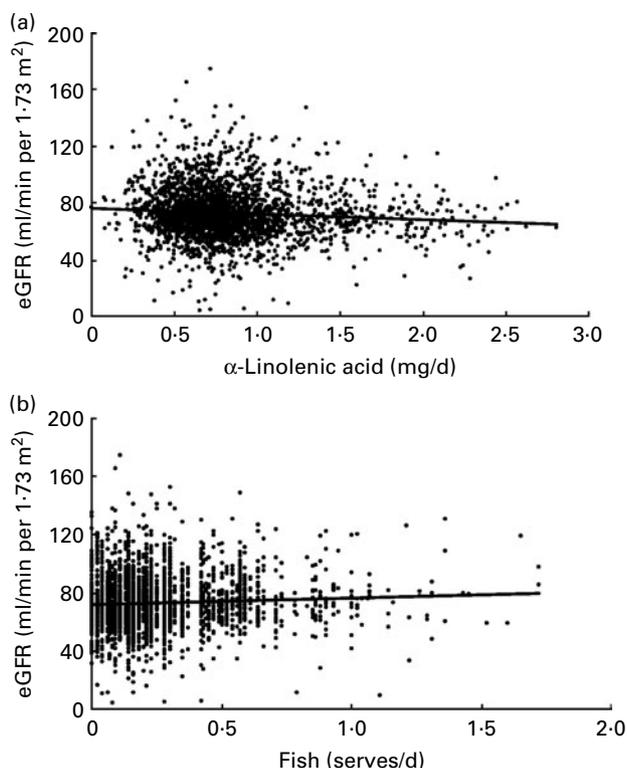


Fig. 1. Linear relationship between dietary intakes of (a) energy-adjusted α -linolenic acid (mg/d; $\beta = -3.97$, $P=0.003$) and (b) fish (serves/d; $\beta = 4.53$, $P\leq 0.001$), with estimated glomerular filtration rate (eGFR) as determined by the four-variable Modification of Diet in Renal Disease Study formula.

Table 3. Associations between dietary intake of PUFA (in quartiles) and the prevalence of chronic kidney disease (CKD) (Ranges, odds ratios and 95 % confidence intervals)

| Energy-adjusted fatty acid intake (range) | No. of cases/no. at risk | eGFR < 60 (moderate CKD) | | | |
|---|--------------------------|--------------------------|------------|------------------------|------------|
| | | Age–sex adjusted | | Multivariate adjusted* | |
| | | OR | 95 % CI | OR | 95 % CI |
| Total <i>n</i>-3 PUFA | | | | | |
| 1 (0.04–0.79) | 109/651 | 1.0 | Reference | 1.0 | Reference |
| 2 (0.79–1.01) | 126/651 | 1.33 | 0.97, 1.81 | 1.21 | 0.85, 1.72 |
| 3 (1.01–1.29) | 131/647 | 1.44 | 1.06, 1.96 | 1.29 | 0.91, 1.84 |
| 4 (1.29–4.76) | 138/651 | 1.39 | 1.02, 1.89 | 1.28 | 0.91, 1.81 |
| <i>P</i> for trend | | | 0.06 | | 0.21 |
| Long-chain <i>n</i>-3 PUFA | | | | | |
| 1 (0.00–0.10) | 131/651 | 1.0 | Reference | 1.0 | Reference |
| 2 (0.10–0.18) | 122/649 | 0.92 | 0.68, 1.24 | 0.88 | 0.63, 1.24 |
| 3 (0.18–0.31) | 141/650 | 1.13 | 0.84, 1.51 | 1.04 | 0.74, 1.46 |
| 4 (0.31–4.18) | 110/650 | 0.77 | 0.56, 1.04 | 0.69 | 0.49, 0.99 |
| <i>P</i> for trend | | | 0.09 | | 0.05 |
| α-Linolenic acid | | | | | |
| 1 (0.04–0.59) | 92/651 | 1.0 | Reference | 1.0 | Reference |
| 2 (0.60–0.76) | 130/650 | 1.67 | 1.21, 2.30 | 1.38 | 0.96, 1.99 |
| 3 (0.76–0.99) | 134/650 | 1.65 | 1.20, 2.26 | 1.50 | 1.05, 2.16 |
| 4 (0.99–2.80) | 148/649 | 1.93 | 1.41, 2.64 | 1.73 | 1.22, 2.47 |
| <i>P</i> for trend | | | 0.0003 | | 0.004 |

eGFR, estimated glomerular filtration rate (in ml/min per 1.73 m²) using the four-variable Modification of Diet in Renal Disease Study formula.

* Adjusted for age, sex, BMI, smoking, alcohol consumption, physical activity, serum total homocysteine, serum total cholesterol, serum TAG, hypertension and history of diagnosed diabetes.

it protects the kidneys. However, the association between *n*-3 PUFA and CKD in BMES subjects was independent of the presence of hypertension.

Our finding of a significant negative association between consumption of fish and CKD is novel, but not surprising, given that there is little doubt that long-chain *n*-3 PUFA in fish are the key nutrients responsible for the health benefits and cardiovascular disease prevention^(17,20–22). It has been suggested that regular consumption of fish attenuates inflammatory processes by antagonising pro-inflammatory cytokines that increase the risk of conditions such as cardiovascular disease and possibly CKD^(5,23). Additionally, the hypocholesterolaemic effects of fish proteins have been reported both in animals and humans, together with lower TAG concentrations^(24–26). These

properties of fish may also account for the observed association with renal function, as hyperlipidaemia is a risk factor for CKD and is thought to cause direct damage to kidney structures and/or increases vascular pathology⁽¹⁾.

Alternatively, the anti-proteinuric effects of *n*-3 PUFA and fish could explain its relationship with moderate CKD, as reductions in proteinuria correlate with the preservation of renal function⁽²⁷⁾. Previously, Weise *et al.*⁽²⁸⁾ used a rat model of membranous nephropathy to demonstrate that rats fed with fish oil had a 25–50 % decline in proteinuria than those fed safflower oil. Hobbs *et al.*⁽²⁹⁾ also demonstrated that supplementation of the diet with fish oil prevented the development of proteinuria in hypertensive rats. Additionally, in patients with chronic glomerular disease (an important

Table 4. Associations between dietary intake of fish (in quartiles) and the prevalence of chronic kidney disease (CKD) (Ranges, odds ratios and 95 % confidence intervals)

| Energy-adjusted fish intake | No. of cases/no. at risk | eGFR < 60 (moderate CKD) | | | |
|-----------------------------|--------------------------|--------------------------|------------|------------------------|------------|
| | | Age–sex adjusted | | Multivariate adjusted* | |
| | | OR | 95 % CI | OR | 95 % CI |
| Fish (g/d) | | | | | |
| 1 (0.00–14.2) | 140/651 | 1.0 | Reference | 1.0 | Reference |
| 2 (14.2–24.3) | 134/649 | 1.03 | 0.77, 1.38 | 1.02 | 0.73, 1.43 |
| 3 (24.3–39.7) | 137/650 | 1.05 | 0.78, 1.41 | 1.04 | 0.74, 1.45 |
| 4 (39.8–373.5) | 93/650 | 0.64 | 0.47, 0.88 | 0.68 | 0.48, 0.97 |
| <i>P</i> for trend | | | 0.002 | | 0.02 |

eGFR, estimated glomerular filtration rate (in ml/min per 1.73 m²) using the four-variable Modification of Diet in Renal Disease Study formula.

* Adjusted for age, sex, BMI, smoking, alcohol consumption, physical activity, serum total homocysteine, serum total cholesterol, serum TAG, hypertension and history of diagnosed diabetes.

Table 5. Associations between dietary intakes of PUFA, fish and the estimated glomerular filtration rate (eGFR) category* (Odds ratios and 95 % confidence intervals)

| | eGFR category† | | | | | | | |
|---|------------------------------|------------|-------------------------------|------------|------------------------------|------------|---------------------|------------|
| | 75 to <90 (n 628, 61.5 %) | | 60 to <75 (n 1075, 73.2 %) | | 45 to <60 (n 398, 50.2 %) | | <45 (n 106, 21.2 %) | |
| Energy-adjusted fatty acid intake | OR ‡ | 95 % CI | OR ‡ | 95 % CI | OR ‡ | 95 % CI | OR ‡ | 95 % CI |
| Total <i>n</i> -3 PUFA (1 SD = 0.58) | 1.07 | 0.92, 1.24 | 1.19 | 1.02, 1.40 | 1.23 | 0.96, 1.57 | 1.13 | 0.73, 1.73 |
| Long-chain <i>n</i> -3 PUFA (1 SD = 0.30) | 0.99 | 0.86, 1.15 | 0.99 | 0.85, 1.15 | 0.66 | 0.49, 0.89 | 0.83 | 0.59, 1.18 |
| α -Linolenic acid (1 SD = 0.46) | 1.10 | 0.95, 1.28 | 1.25 | 1.07, 1.46 | 1.51 | 1.19, 1.91 | 1.42 | 0.93, 2.18 |
| Total <i>n</i> -6 PUFA (1 SD = 4.7) | 1.03 | 0.90, 1.18 | 1.06 | 0.92, 1.23 | 1.17 | 0.94, 1.47 | 1.06 | 0.69, 1.62 |
| Fish (1 SD = 30.3) | 0.94 | 0.83, 1.08 | 0.88 | 0.76, 1.01 | 0.68 | 0.53, 0.87 | 0.69 | 0.46, 1.05 |

* eGFR (ml/min per 1.73 m²) using the four-variable Modification of Diet in Renal Disease Study formula.

† Compared with participants with eGFR \geq 90 ml/min per 1.73 m² i.e. the reference group.

‡ Adjusted for age, sex, BMI, smoking, alcohol consumption, physical activity, serum total homocysteine, serum total cholesterol, serum TAG, hypertension and history of diagnosed diabetes.

cause of CKD), a high-dose *n*-3 PUFA supplementation over 12 weeks reduced proteinuria⁽³⁰⁾. Finally, Hogg *et al.*⁽³¹⁾ demonstrated that in IgA nephropathy patients, a dose-dependent relationship existed between *n*-3 PUFA and reductions in proteinuria.

The role of α -linolenic acid on cardiovascular function and cardiometabolic risk remains a matter of debate⁽³²⁾. The positive association between α -linolenic acid and moderate CKD observed in the present study was not expected. The specific mechanisms underlying why *n*-3 fatty acids mainly from terrestrial sources and those from mainly marine sources⁽³³⁾ have differing effects on the prevalence of CKD are unclear. One possibility is that α -linolenic acid is a plant *n*-3 fatty acid which is poorly converted (less than 5%) to EPA and DHA, which have been shown to be cardioprotective⁽³⁴⁾. Thus, increased dietary availability of α -linolenic acid does not necessarily enhance DHA synthesis and may even decrease tissue DHA concentrations⁽³⁵⁾, since DHA synthesis appears to be tightly regulated by feedback inhibition⁽³⁶⁾. Additionally, while EPA and DHA have numerous anti-inflammatory properties, α -linolenic acid exerts little influence on inflammatory cytokine production at feasible dietary intakes^(18,33,37). Finally, α -linolenic acid is present in some vegetable oils and nuts, and animal fats⁽³⁸⁾; hence, we cannot rule out the possibility that α -linolenic acid from both non-animal and animal sources represents a marker of a correlated component of fat or fat-containing food, such as red meat⁽³³⁾, which could lead to, for example, hyperlipidaemia and in turn increase the prevalence of CKD.

In the present study, a non-significant increase in the prevalence of moderate CKD was observed with increasing consumption of *n*-6 PUFA. This observation is not surprising as the *n*-6 PUFA AA gives rise to eicosanoid mediators that have established roles in inflammation and AA metabolism, and is a long recognised target for anti-inflammatory therapies⁽³⁹⁾. The *n*-3 fatty acids EPA and DHA are incorporated into inflammatory cell phospholipids in a time- and dose-dependent manner, and are partly incorporated at the expense of AA. EPA and DHA inhibit AA metabolism. Hence, the production of AA-derived eicosanoids is decreased by *n*-3 PUFA and occurs in a dose-dependent manner⁽³⁹⁾.

Ageing population trends in Western countries emphasise the need for the identification and development of potential protective strategies for CKD. Hence, the findings presented in this investigation are important as they demonstrate that a diet rich in long-chain *n*-3 PUFA and fish could have a protective influence against the decline in kidney function that is common with ageing⁽⁵⁾. Ideally, the diet best designed to preserve renal function would be similar to what has also been proposed for cardiovascular disease, i.e. low in SFA and high in long-chain *n*-3 PUFA from fish and fish oils, for example, a Mediterranean-style diet^(17,40).

Key strengths of the present study include its representative population-based sample with relatively high participation, minimising selection bias, availability of rich covariate/confounder information and the use of standardised protocols for exposure and outcome assessment. However, there are some caveats such as the lack of longitudinal data, which precludes conclusions regarding the prospective nature of the association between dietary intakes of *n*-3 PUFA and fish, and eGFR. Nevertheless, it is unlikely that moderate CKD is an independent predictor of high consumption of PUFA and fish. Second, dietary assessment by the FFQ in which respondents have to estimate typical intake frequencies of food items and their portion sizes can potentially introduce measurement error and bias. We cannot rule this possibility out, but, overall, the validity of fatty acid categories compared with weighed food records was moderately good^(9,10,41). Finally, the BMES was not designed to examine the issues of kidney function *per se*, but rather to examine the issues of sensory loss. Hence, we do not have urinalysis results, although we have estimated renal function in our subjects using a widely accepted method. Nonetheless, limitations of such estimated measures of kidney function exist, specifically serum creatinine is an insensitive marker of glomerular filtration rate in older adults; hence, it is not surprising that the Modification of Diet in Renal Disease formula based predominantly on it is imperfect. The use of this formula cannot circumvent the very significant spectral interferences affecting serum creatinine measurement, e.g. haemolysis⁽⁴²⁾; as such, eGFR should not be accepted without reservation as a reliable substitute for the direct measurement of renal function.

In conclusion, higher dietary intake of long-chain *n*-3 PUFA was associated with a reduced prevalence of moderate CKD. Additionally, increased consumption of fish was associated with a reduced likelihood of CKD in adults aged ≥ 50 years. These data suggest that long-chain *n*-3 PUFA and fish could have a role in maintaining healthy kidney function, in addition to the roles of these nutrients in the prevention and modulation of other diseases (e.g. autoimmune disorders, coronary heart disease and stroke)^(17,18). However, to fully determine the effects of *n*-3 dietary fats and fish on renal function, there is a need for further high-quality population-based studies and randomised controlled trials of long duration.

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