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Original article

Dietary fatty acids intake and all-cause and cardiovascular mortality in patients on peritoneal dialysis

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SUMMARY

Background & aims: The relationship between dietary fatty acids (FA) and clinical outcomes are relatively lacking in non-dialyzed and dialyzed chronic kidney disease (CKD) population, resulting in insufficient guide about the dietary FA intake in this population. In this study, we aimed to observe the association between the intake of total or different types of FA and all-cause and cardiovascular (CV) mortality in patients undergoing peritoneal dialysis (PD).

Methods: This is a prospective cohort study with data retrospectively analyzed in 881 patients undergoing PD. Dietary FA intake measured by 3-day dietary records. The outcomes were defined as all-cause and CV death. Baseline FA intake and time-averaged FA intake were categorized by tertiles based on the distribution among the study population. We used univariate and multivariate Cox proportional regression models to determine the association between amounts and types of FA and all-cause and CV mortality.

Results: During a median follow up of 45 months, 93 patients were still being maintained on PD, 467 had died, including 189 (40.5%) attributable to CV death. Compared to patients in the low tertile of total FA (TFA) intake at baseline group, the middle or/and high tertile groups were more likely to be male, younger, well-educated and better nutritional status ($P < 0.05$). At the baseline, no association was found between all-cause and CV death in either total or different types of FA after adjusting for nutritional variables. As for time-averaged analyses, the associations of TFA, saturated FA (SFA), monounsaturated FA (MUFA), ω-3 and ω-6 polyunsaturated FA (PUFA) and all-cause mortality were weakened after adjustment for laboratory and nutrients variables. However, PUFA independently reduced 5% of mortality even after adjustment for laboratory and nutrients variables [HR 0.95 (0.91, 0.99), $P = 0.023$], and the ratio of MUFA/PUFA was positively associated with the risk for all-cause mortality [HR 1.05 (1.01, 1.09), $P = 0.008$]. Furthermore, each 10% increase of the ratio of ω-6/ω-3 was only weakly associated with the risk for all-cause mortality [HR 1.02 (1.00, 1.04), $P = 0.034$]. As for CVD mortality, the impacts of total and each type of FA disappeared after adjustment for laboratory or nutrients variables.

Conclusions: Time-averaged PUFA intake was independently associated with a lower risk for all-cause mortality in our PD cohort, while the higher ratio of MUFA/PUFA and ω-6/ω-3 increased all-cause mortality. More observational and interventional researches are needed to determine these associations.

1. Introduction

Nutritional and metabolic abnormalities are pervasive in patients with chronic kidney disease (CKD), which partly contributes to the higher morbidities and mortalities [1]. Among them, lipid disorders are very common and worsens with the reduction of renal function, not being fully improved by lipid-lowering agents and dialysis treatment [2–5]. Dyslipidemia is also considered as a

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major risk factor for cardiovascular disease (CVD) and mortality in this population [6]. All the above attract increasing attention on patient-specific dietary patterns relevant to serum lipids and clinic prognosis.

Numerous studies and meta-analyses have investigated the association of dietary total fat, type of fatty acids (FA) intake and clinical prognosis in general population, which showed differential associations of total FA (TFA), monounsaturated FA (MUFA), polyunsaturated FA (PUFA), saturated FA (SFA) intake and all-cause death, cardiovascular (CV) events or CV death [7–11]. For different types of FA possibly exert varied influences on patient outcome, current recommendations mostly emphasize on restricting SFA, i.e. consuming less than 10 percent of total daily energy from SFA and replacing SFA with MUFA and PUFA [12–14]. However, evidences on the association of dietary FA and clinical outcomes are insufficient in both non-dialyzed and dialyzed CKD patients. Several interventional studies indicated an inconsistent efficacy of supplementation of ω-3 PUFA on the improvement of clinical outcomes in patients on hemodialysis or kidney transplant [15–18]. The 2020 update of Clinical Practice Guideline For Nutrition in CKD by the KDOQI guidelines thus did not recommend the target of total FA amounts and type of FA for CKD patients, and neither did suggest routinely prescribe ω-3 PUFA for lowering risk of mortality or CV events [19]. It is commonly recommended dietary fat intake in CKD should be the same as that in general population [20,21].

Therefore, in this study, we aimed to retrospectively analyze the data from a prospective cohort study to observe the association between the intake of total or different types of FA and all-cause and CV mortality in patients undergoing peritoneal dialysis (PD), so as to provide a real-world evidence for guiding the dietary FA intake in this population.

2. Materials and methods

2.1. Subjects and follow-up

This is a prospective cohort study with data retrospectively analyzed, carried out at the PD center of Peking University First Hospital. All incident PD patients between October 1, 2002, and August 31, 2014, were screened. Patients were excluded if they refused to complete the baseline test, denied the diagnosis of end-stage renal disease, or could not be regularly followed. All patients were followed until death, transfer to hemodialysis (HD), renal transplantation, loss to follow-up or the end of study (June 30, 2021) (Fig. 1). All patients were treated with continuous ambulatory peritoneal dialysis (CAPD) and visited by a physician at least once every 3 months. All patients began the PD program within 1 month after catheter implantation and were given lactate-buffered glucose dialysate with a twin-bag connection system (Baxter Healthcare, Guangzhou, China). This study was approved by the Medical Ethics Committee of Peking University. Written informed consent was obtained from each patient.

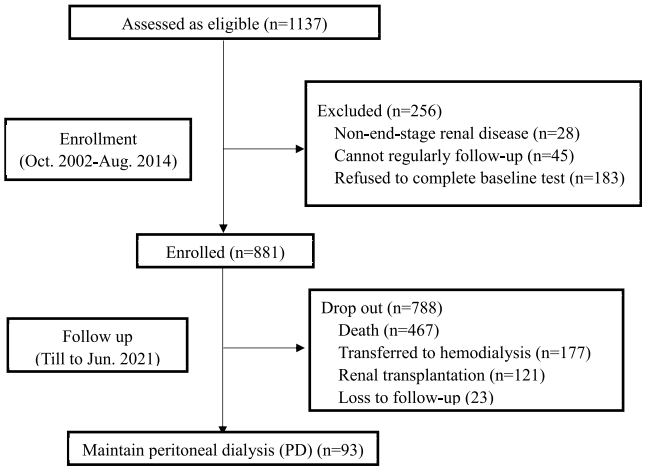


Fig. 1. Flow chart of the study.

2.2. Data collection

Demographic and clinical data including age, gender, body mass index (BMI), education status, annual per capita income, the presence of CVD and diabetes mellitus (DM) was collected within the week preceding PD catheter implantation. CVD was recorded if one of the following conditions was present: angina, class III–IV congestive heart failure (as defined by the New York Heart Association), transient ischaemic attack, history of myocardial infarction or cerebrovascular accident and peripheral arterial disease [22]. Baseline values included all measurements of blood pressure, biochemistry tests, dialysis adequacy, dietary and nutrition parameters in the first 3 months. Baseline values of dietary nutrients were calculated in the first 6 months. All the above measurements during the study period were prospectively collected and averaged for each 6-month interval to calculate time-averaged values. The average of each 6-month period's FA intake is represented by the time-average FA intake [23].

2.3. Dietary variables

During the follow-up, patients completed 3-day dietary records before they visited the dietitian. A dedicated dietitian checked the diary by using food models. The dietary records would be invalid if they were recorded in less than 3 days or did not get checked successfully by the dietitian. Food models were used to estimate actual amounts of foods recorded in the diet diary. Daily fiber, protein, energy, carbohydrate, and fat including TFA, SFA, MUFA and PUFA were calculated by using a computer software program (PD information Management System, Peritoneal Dialysis Center, Peking University, Beijing, China). Oral nutrition supplements (ONS) including nutritionally complete food product such as Ensure and nutritionally incomplete food product such as protein powder were also recorded to calculate the total amount of protein and energy intake. The daily energy intake includes intakes from dietary and dialysate sources. Glucose absorption via dialysate was calculated by subtracting glucose amounts in drained dialysate from that in instilled dialysate, expressed as grams of glucose/day (g/d), and then dialysate energy absorption was calculated as kcal of energy/day (kcal/d).

2.4. Biochemical, dialysis adequacy

Biochemistry data including hemoglobin (Hb), serum albumin (Alb), lipids spectrum, urea nitrogen, creatinine, calcium, phosphate, intact parathyroid hormone (iPTH) and so on were examined using an automatic Hitachi chemistry analyzer (Hitachi Chemical, Tokyo, Japan). Serum high-sensitive C-reactive protein (hs-CRP) was measured by immune rate nephelometric analysis. Dialysis adequacy, residual renal function (RRF), and glucose absorption were measured by collecting 24-h urine and dialysate. Dialysis adequacy was defined as total urea nitrogen clearance (total Kt/V) and total creatinine clearance (total Ccr). RRF was estimated using the average renal clearance of urea nitrogen and creatinine.

2.5. Definition of outcome event

The outcomes were defined as all-cause and CVD death. The CVD death was defined as death due to myocardial infarction, congestive heart failure, cerebral bleeding, cerebral infarction, arrhythmia, peripheral arterial disease, and sudden death [22]. In all analysis, we censored follow-up at transferring to HD, renal transplantation, loss to follow-up, or the end of the study (June 30, 2021).

2.6. Statistical analysis

Statistical analyses were performed using the SPSS software package version 24.0 (SPSS, Chicago, IL, USA). Parametric data were presented as mean ± standard deviation. Nonparametric data were presented as median values with an inter-quartile range (IQR). Categorical variables were expressed as percentages or ratios. Baseline FA intake and time-averaged FA intake were categorized by tertile based on the distribution among the study population. One-way ANOVA, Kruskal Wallis, or the X^2 test were used to compare the differences of variables between groups and the variables with significant difference were adjusted in the later cox-proportional hazard regression analysis. In the prospective analysis, potential confounders combined with the baseline and time-averaged FA intakes as continuous or category variables respectively, were evaluated by Cox proportional regression models to determine the risk for CVD and all-cause mortality. Analysis for baseline FA were adjusted for age, gender, BMI, educational level, CVD, and diastolic blood pressure (Model 1), and additionally adjusted for variables which were different between groups categorized by baseline FA, such as hemoglobin, albumin, urea nitrogen, serum creatinine, serum calcium, serum phosphorus, serum potassium, serum sodium, triglycerides, and RRF (Model 2). Considering the possible impact of dietary nutrients, Model 3 was built with additional adjustment for total energy intake, total protein intake, and total fiber intake (Model 3). Analysis for time-averaged FA were adjusted for time-averaged variables accordingly. Changes in albumin, hs-CRP and serum lipid measurements over time were also compared among groups using a mixed model analysis of variance, with bootstrap covariance accounting for correlation among repeated measures within a patient. The baseline value of the outcome variables was adjusted as a model covariate.

We reported the multivariable-adjusted hazard ratios (HRs) with 95% confidence intervals. The calculation of time-averaged biochemistry, nutrition and dialysis parameters in the models used the half-yearly measurements. And we chose the 3-year period of observation here to calculate the total time-averaged values. All statistical tests were two-tailed, and the significance level was set at $P < 0.05$.

3. Results

3.1. Subject demographics and follow-up

We followed 881 incident PD patients (434 men, 447 women), mean age of 57.7 ± 14.8 years for 45.0 (21.5, 80.0) months; 42.1% had DM, and CVD was present in 42.6% (Table 1).

At the end of the study, 93 patients were still being maintained on PD, 467 had died, 177 had transferred to HD, 121 had undergone renal transplantation. A total of 189 of 467 (40.5%) of all deaths were due to cardiovascular causes, and 115 of 467 (24.6%) were due to infection (Table 2). According to the baseline TFA intake, patients in the high tertile had a much longer follow-up time ($P = 0.004$) and lower mortality rate ($P < 0.001$), majorly from severe malnutrition ($P = 0.005$). No difference in the rate of transfer to hemodialysis was found between groups. Patients in the high tertile were prone to receive renal transplantation ($P = 0.005$).

3.2. Dietary FA intake and clinical characteristics at baseline

The baseline TFA intake was 43.0 ± 12.2 g/d in our cohort. The baseline characteristics of the study population tertiled by baseline TFA intake were given in Table 1. Patients in the middle or/and high tertile groups were more likely to be male, younger, well-educated as compared to those in the low tertile group ($P < 0.05$). They also had better higher BMI, DBP and MAP, and lower prevalence of CVD ($P < 0.05$). The levels of blood urea nitrogen, serum creatinine, serum calcium, serum phosphorus, serum potassium, serum sodium and RRF in the middle or/and high tertile groups were significantly higher than those in the low tertile group ($P < 0.05$). All dietary parameters including total energy, protein, carbohydrate, fat, fiber intake, normalized daily protein and energy intake increased along with FA intake ($P < 0.001$). Higher intake of TFA was also consistent with higher intake of SFA, MUFA, PUFA, ω-3 and ω-6 PUFA ($P < 0.001$). There was significant difference in the ω-6/ω-3 PUFA Ratio ($P = 0.003$) rather than MUFA/PUFA Ratio ($P = 0.188$).

3.3. Predictive value of FA intake for all-cause and CVD mortality

The relationship between baseline or time-averaged FA intake and outcomes was analyzed respectively. At the baseline, TFA, SFA, MUFA, and PUFA, as continuous variables, were all significantly associated with a lower all-cause mortality in model 1 ($P < 0.05$). These trends maintained after additional adjustment for laboratory variables ($P < 0.05$) but disappeared after adjustment for all dietary nutrients (Fig. 2–1). Similarly, although middle and/or high tertile of TFA, SFA, MUFA, and PUFA decreased the risk of all-cause mortality ($P < 0.05$), these trends did not maintain after additional adjustment for dietary nutrients (Supplement Table 1). Associations of ω-3 PUFA, ω-6 PUFA, ω-6/ω-3 Ratio and all-cause mortality were not observed through univariate analyzes or after multivariate adjustment for laboratory variables. With regards to the CVD mortality, any types of FA did not show their predicting roles except for ω-6 PUFA, the latter of which also weakened after adjustment for dietary nutrients (Fig. 2–2).

As for time-averaged analyses, TFA, SFA, MUFA and PUFA as continuous variables, or as middle and/or high tertile of categorical variables, also predicted a lower all-cause mortality in model 1 (Fig. 3–1, Supplement Table 2). Associations of TFA, SFA and MUFA were weakened after adjustment for laboratory and nutrients variables as baseline analyses indicated. However, the increase in each 1 g of PUFA independently reduced 5% of mortality even after adjustment for laboratory and nutrients variables [HR 0.95 (0.91, 0.99), $P = 0.023$]. The high tertile of PUFA (PUFA >13.9 g/d) decreased 32% of mortality compared with the low tertile [HR 0.68 (0.50, 0.94), $P = 0.019$]. Accordingly, each 1% increase of the ratio of MUFA/PUFA was positively associated with the risk for all-cause mortality [HR 1.05 (1.01, 1.09), $P = 0.008$]. And each 10% increase of the ratio of ω-6/ω-3 was only weakly associated with the risk for all-cause mortality [HR 1.02 (1.00, 1.04), $P = 0.034$]. As for CVD mortality, despite that TFA, SFA, MUFA, PUFA and ω-6 PUFA, as continuous variables or high tertile of categorical variable, indicated a decreased CVD mortality ($P < 0.05$) in model 1, these impacts disappeared after adjustment for laboratory or nutrients variables (Fig. 3–2).

Table 1
Baseline clinical characteristics of PD patients according to total fatty acids intake at baseline (n = 881).

Characteristic	Total	Tertile of total fatty acids intake			*P*
		Low (<37.7 g/d)	Middle (37.7–47.0 g/d)	High (>47.0 g/d)	
Age, years	57.7 ± 14.8	60.5 ± 14.6	58.5 ± 14.6[b]	54.2 ± 14.5[c]	<0.001
Male, n (%)	434 (49.3)	107 (36.5)	127 (43.1)[b]	200 (68.3)[c]	<0.001
BMI, kg/m^2	23.3 ± 3.7	22.7 ± 4.1[a]	23.4 ± 3.4	23.8 ± 3.6[c]	0.002
Educational level[b,c]					0.002
≤Elementary school, n (%)	149 (16.9)	57 (19.5)	63 (21.3)	29 (9.9)	
Middle school, n (%)	229 (26.0)	82 (28.0)	74 (25.1)	73 (24.9)	
High school, n (%)	244 (27.7)	71 (24.2)	84 (28.5)	89 (30.4)	
>High school, n (%)	259 (29.4)	83 (28.3)	74 (25.1)	102 (34.8)	
Annual per capita income, n (%)					0.464
Below ten thousand RMB	144 (16.5)	53 (18.2)	45 (15.5)	46 (15.8)	
Between ten to twenty thousand RMB	216 (24.7)	69 (23.7)	84 (29.0)	63 (21.6)	
Between twenty to thirty thousand RMB	170 (19.5)	56 (19.2)	53 (18.3)	61 (20.9)	
Between thirty to forty thousand RMB	114 (13.1)	41 (14.1)	31 (10.7)	42 (14.4)	
Between forty to fifty thousand RMB	73 (8.4)	26 (8.9)	27 (9.3)	20 (6.8)	
Above fifty thousand RMB	156 (17.9)	46 (15.8)	50 (17.2)	60 (20.5)	
DM, n (%)	371 (42.1)	120 (41.0)	127 (43.1)	124 (42.3)	0.878
CVD, n (%)	375 (42.6)	136 (46.4)	133 (45.1)[b]	106 (36.2)[c]	0.024
SBP, mmHg	135.8 ± 16.7	135.1 ± 18.0	135.9 ± 16.7	136.4 ± 15.4	0.665
DBP, mmHg	79.0 ± 11.2	78.1 ± 10.9	77.9 ± 11.4[b]	81.1 ± 11.0[c]	0.001
MAP, mmHg	98.0 ± 11.2	97.2 ± 11.7	97.3 ± 10.9[b]	99.7 ± 10.7[c]	0.013
Laboratory and nutritional data					
Albumin, g/L	35.4 ± 4.6	35.0 ± 4.7	35.8 ± 4.3	35.3 ± 4.7	0.077
Hemoglobin, g/L	102.8 ± 15.7	101.1 ± 16.0	103.7 ± 15.3	103.5 ± 15.7	0.089
Hs-CRP, mg/L	2.1 (0.7, 5.7)	2.2 (0.7, 7.2)	2.0 (0.8, 5.0)	2.2 (0.63, 5.6)	0.524
Urea nitrogen, mmol/L	22.5 ± 6.1	21.2 ± 6.1[a]	22.4 ± 5.7[b]	24.0 ± 6.3[c]	<0.001
Serum creatinine, μmol/L	689.2 ± 233.6	663.5 ± 235.4	687.8 ± 227.8	716.1 ± 235.5[c]	0.024
Serum calcium, mmol/L	2.2 ± 0.2	2.2 ± 0.2	2.2 ± 0.2	2.2 ± 0.2[c]	0.042
Serum phosphorus, mmol/L	1.6 ± 0.4	1.5 ± 0.4[a]	1.6 ± 0.3[b]	1.6 ± 0.4	0.005
Serum potassium, mmol/L	4.4 ± 0.6	4.3 ± 0.6[a]	4.4 ± 0.6	4.5 ± 0.6[c]	<0.001
Serum sodium, mmol/L	139.2 ± 3.0	138.7 ± 2.9[a]	139.3 ± 3.6	139.6 ± 2.2[c]	0.002
HDL-cholesterol, mmol/L	1.1 ± 0.3	1.1 ± 0.3	1.2 ± 0.4	1.1 ± 0.3	0.226
LDL-cholesterol, mmol/L	2.6 ± 0.8	2.6 ± 0.8	2.6 ± 0.8	2.6 ± 0.9	0.786
Total cholesterol, mmol/L	4.9 ± 1.1	4.9 ± 1.1	4.9 ± 1.1	4.8 ± 1.2	0.369
Triglycerides, mmol/L	1.5 (1.1, 2.0)	1.5 (1.2, 2.1)	1.6 (1.2, 2.1)	1.4 (1.1, 2.0)	0.069
iPTH, pg/mL	164.1 (77.4, 320.7)	159.7 (71.7, 322.1)	175.5 (69.5, 314.0)	167.4 (89.0, 324.3)	0.765
Total Ccr, L/w/1.73 m^2	72.8 ± 27.9	70.3 ± 29.0	73.7 ± 29.3	74.3 ± 25.2	0.198
Total Kt/V	1.9 ± 0.5	1.9 ± 0.6	2.0 ± 0.6[b]	1.9 ± 0.5	0.135
RRF, ml/min	3.7 (2.1, 5.6)	3.2 (1.8, 5.3)	3.8 (2.2, 5.4)	4.0 (2.5, 6.0)[c]	0.009
Total energy intake, kcal/day	1660.9 ± 334.3	1441.2 ± 269.8[a]	1625.3 ± 243.2[b]	1914.3 ± 301.1[c]	<0.001
Total protein intake, g/day	52.1 ± 13.9	43.5 ± 11.7[a]	51.0 ± 10.0[b]	62.0 ± 12.9[c]	<0.001
Total fat intake, g/day	54.0 ± 14.5	41.3 ± 9.8[a]	52.9 ± 7.0[b]	67.8 ± 11.6[c]	<0.001
Total carbohydrate intake, g/day	184.6 ± 49.2	167.8 ± 45.7[a]	179.9 ± 41.7[b]	206.3 ± 51.7[c]	<0.001
Total fiber intake, g/day	8.2 ± 3.4	7.3 ± 3.6[a]	8.0 ± 2.9[b]	9.2 ± 3.3[c]	<0.001
TFA, g/day	43.0 ± 12.2	30.5 ± 5.9[a]	42.3 ± 2.7[b]	56.3 ± 8.4[c]	<0.001
SFA, g/day	12.1 ± 3.7	8.7 ± 2.2[a]	11.8 ± 1.6[b]	15.8 ± 2.9[c]	<0.001
MUFA, g/day	17.3 ± 5.2	12.3 ± 2.7[a]	17.0 ± 2.0[b]	22.8 ± 4.1[c]	<0.001
PUFA, g/day	12.5 ± 4.4	8.8 ± 2.8[a]	12.5 ± 2.7[b]	16.3 ± 3.9[c]	<0.001
MUFA/PUFA Ratio	1.5 ± 0.4	1.5 ± 0.5	1.4 ± 0.4	1.5 ± 0.4	0.188
ω-3 PUFA, g/day	0.5 (0.3, 0.7)	0.4 (0.2, 0.6)[a]	0.5 (0.4, 0.7)[b]	0.7 (0.5, 1.0)[c]	<0.001
ω-6 PUFA, g/day	4.1 (2.9, 5.8)	2.7 (2.0, 3.5)[a]	4.2 (3.2, 5.2)[b]	6.0 (4.8, 7.0)[c]	<0.001
ω-6/ω-3 Ratio	7.6 (5.9, 11.1)	7.1 (5.3, 10.6)[a]	7.7 (6.1, 11.6)	8.2 (6.4, 11.3)[c]	0.003
nDEI, kcal/kg/d	28.5 ± 5.4	25.8 ± 5.1[a]	28.6 ± 4.9[b]	31.1 ± 5.0[c]	<0.001
nDPI, g/kg/d	0.85 ± 0.24	0.75 ± 0.23[a]	0.84 ± 0.20[b]	0.95 ± 0.24[c]	<0.001

Values are expressed as mean ± standard deviation, percentage or median with upper and lower quartile or percentage.
Abbreviation: CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; HDL, high density lipoprotein; Hs-CRP, high-sensitive C-reactive protein; iPTH, intact parathyroid hormone; LDL, low density lipoprotein; MAP, mean arterial pressure; RRF, residual renal function; SBP, systolic blood pressure; Total CCr, total creatinine clearance; Total Kt/V, total urea clearance; TFA: Total fatty acids; SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid, nDEI, normalized energy intake; nDPI, normalized protein intake.
[a] P < 0.05 low-tertile group compared to middle-tertile group.
[b] P < 0.05 middle-tertile group compared to high-tertile group.
[c] P < 0.05 high-tertile group compared to low-tertile group.

3.4. Longitudinal changes in serum lipids and inflammation in the tertiles of PUFA and ω-6/ω-3 PUFA

The trends of serum albumin, total cholesterol, HDL-cholesterol and LDL-cholesterol values were significantly different between the tertiles of time-averaged dietary PUFA ($P \leq 0.01$ for all). The high and middle PUFA intake group had significantly increasing trend of albumin values compared with low group during the whole 36-month observation period ($P < 0.001$) (Fig. 4–1). And the total cholesterol, HDL-cholesterol, and LDL-cholesterol values significantly decreased in the high or/and middle PUFA intake group after 6–12 months of observation period ($P < 0.05$) (Fig. 4–3, 5, 6).

Besides, the trends of serum total cholesterol and HDL-cholesterol values were significantly different between the

Table 2
Outcomes among PD patients based on total fatty acids intake at baseline (n = 881).

Outcomes, no. of events (event rate/100 person-years)	total	Tertile of total fatty acids intake			*P*
		Low (< 37.7 g/d)	Middle (37.7–47.0 g/d)	High (> 47.0 g/d)	
Follow-up, months	45.0 (21.5, 80.0)	38.0 (16.5, 65.5)[a]	49.0 (24.0, 84.0)	50.0 (23.0, 82.5)[c]	0.004
Maintain PD	93 (2.30)	17 (1.44)	47 (3.20)	29 (2.08)	0.824
Death	467 (11.54)	186 (15.75)[a]	147 (12.45)	134 (9.59)[c]	<0.001
Cardiovascular events[d]	189 (4.67)	74 (6.27)	60 (4.09)	55 (3.94)	0.328
Infection	115 (2.84)	42 (3.56)	36 (2.45)	37 (2.65)	0.895
Severe malnutrition	20 (0.50)	13 (1.10)[a]	5 (0.34)	2 (0.14)[c]	0.005
Gastrointestinal haemorrhage	22 (0.54)	8 (0.68)	8 (0.54)	6 (0.43)	0.763
Tumor	44 (1.09)	17 (1.44)	16 (1.09)	11 (0.79)	0.514
Others	76 (1.88)	32 (2.71)	22 (1.50)	22 (1.57)	0.362
Transfer to hemodialysis	177 (4.37)	49 (4.15)	62 (4.22)	66 (4.72)	0.598
PD-related infection	105 (2.59)	28 (2.37)	31 (2.11)	46 (3.29)	0.467
Fluid overload	17 (0.42)	9 (0.76)	6 (0.41)	2 (0.14)[c]	0.016
Inadequate solute clearance	13 (0.32)	2 (0.17)	9 (0.61)	2 (0.14)	0.548
Catheter dysfunction	2 (0.05)	0 (0.00)	1 (0.07)	1 (0.07)	0.589
Socioeconomic causes	22 (0.54)	7 (0.59)	10 (0.68)	5 (0.36)	0.200
Renal transplantation	121 (2.99)	34 (2.88)	31 (2.11)[b]	56 (4.01)	0.045

[a] P < 0.05 low-tertile group compared to middle-tertile group.
[b] P < 0.05 middle-tertile group compared to high-tertile group.
[c] P < 0.05 high-tertile group compared to low-tertile group.
[d] Cardiovascular events include cardiovascular events, cerebrovascular events, and sudden death.

Figure 2-1

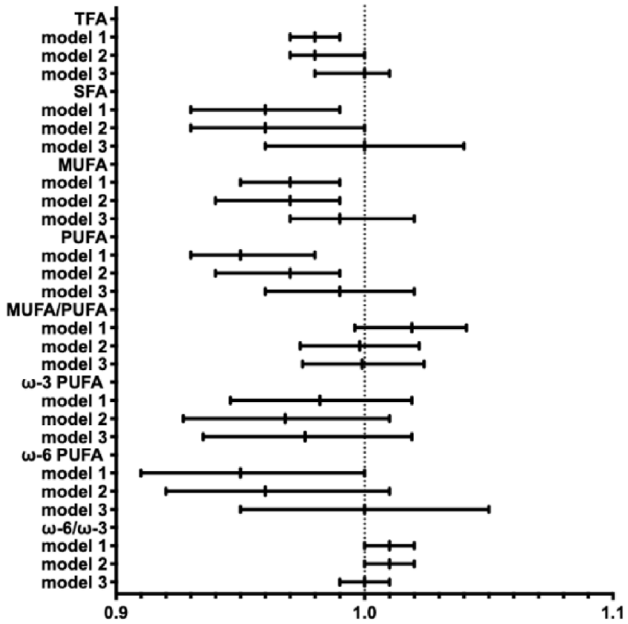


Figure 2-2

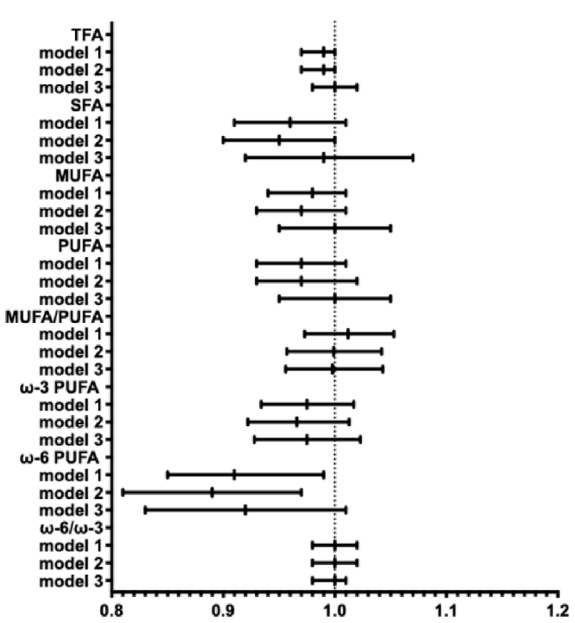


Fig. 2. The prognostic value of total and different types of fatty acids intake for all-cause mortality (Fig. 2–1) and CVD mortality (Fig. 2–2) at baseline. Model 1: Adjusted for age, gender, BMI, educational level, CVD, DBP; Model 2: Adjusted for Model 1 plus hemoglobin, albumin, urea nitrogen, serum creatinine, serum calcium, serum phosphorus, serum potassium, serum sodium, triglycerides, RRF; Model 3: Adjusted for Model 2 plus total energy intake, total protein intake, total fiber intake. Abbreviation: BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; RRF, residual renal function. *ω-3 PUFA, HR associated with each 10g increase.

tertiles of time-averaged dietary ω-6/ω-3 PUFA ($P = 0.003$ and $P = 0.031$, respectively). Total cholesterol values in the low dietary ω-6/ω-3 PUFA intake group were significantly higher than those in the high group at 36th month ($P = 0.009$) (Fig. 5–3). And the middle ω-6/ω-3 PUFA intake group had decreased HDL-cholesterol values than the low group ($P < 0.05$) (Fig. 5–5).

There were no differences in the change trend of Hs-CRP and triglyceride between groups (Fig. 4–2 and 4, Fig. 5–2 and 4). Also, other laboratory measurements such as serum calcium, phosphorus, potassium, sodium and iPTH did not show significant differences during the follow up between groups (data not shown).

4. Discussion

To our knowledge, this is the first study to explore the association of dietary FA and all-cause and CV mortality in PD patients

Figure 3-1

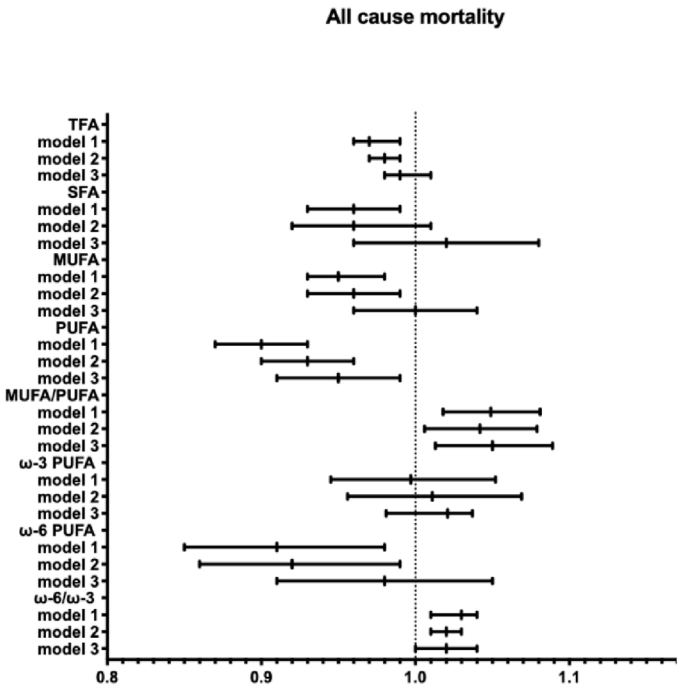


Figure 3-2

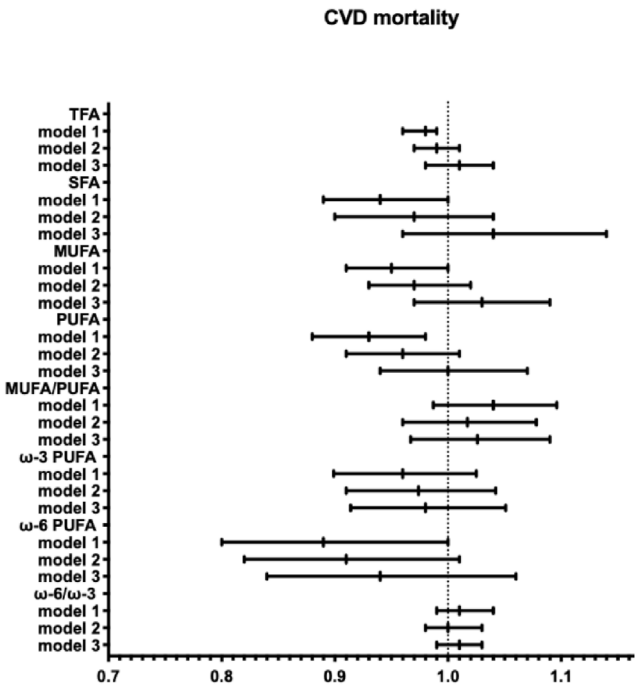


Fig. 3. The prognostic value of time-averaged total and different types of fatty acids intake for all-cause mortality (Fig. 3–1) and CVD mortality (Fig. 3–2). Model 1: Adjusted for age, gender, BMI, educational level, CVD, time-averaged DBP; Model 2: Adjusted for Model 1 plus time-averaged hemoglobin, time-averaged albumin, time-averaged urea nitrogen, time-averaged serum creatinine, time-averaged serum calcium, time-averaged serum phosphorus, time-averaged serum potassium, time-averaged serum sodium, time-averaged triglycerides, time-averaged RRF; Model 3: Adjusted for Model 2 plus time-averaged total energy intake, time-averaged total protein intake, time-averaged total fiber intake. Abbreviation: BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; RRF, residual renal function. *ω-3 PUFA, HR associated with each 10g increase.

through a prospective cohort. Our data thus provide a real-world clue to guide FA intake, accounting for one-third energy requirement or so, to maintain nutrition and metabolic balance in this population.

We observed that higher intake of TFA is in tandem with being younger, male, better RRF, general nutrients intake and nutritional status. There was significant difference in the death rate by severe malnutrition among tertiles of baseline TFA intake. These clues are in line with protective impacts of TFA and each type of FA on all-cause and CVD mortality. However, all these trends weakened after adjustment for laboratory and nutrients variables, except that the association of time-averaged PUFA and MUFA/PUFA ratio and all-cause mortality maintained. These findings again support that protein and energy intake is the key confounder for the association of dietary components and clinical outcomes, as indicated by our researches on dietary fiber, plant protein ratio in PD patients [24,25]. In other words, total amounts of protein and energy intake rather than dietary pattern are the most important determinants for nutritional preservation in dialyzed individuals in whom protein energy wasting is such a common phenomenon due to complex mechanisms [19,26].

Our data showed that a higher time-averaged PUFA rather than baseline PUFA negatively correlated with all-cause mortality, and time-averaged MUFA to PUFA ratio positively correlated with all-cause mortality accordingly even adjustment for laboratory and nutrients variable. The longitudinal trends of serum lipides did differ across the tertiles of PUFA, indicating a potential cause for benefits of high dietary PUFA intake in our subjects. Till to date, dietary guidelines have recommended to replacement of dietary SFA with unsaturated FA, especially PUFA, owing to its broad cardioprotective effects in general population [27,28], although these guidelines have been challenged due to contrary findings from interventional trials [29–31]. Among CKD patients, relevant data on the type of FA and clinical outcomes are limited. One study indicated that participants with higher plasma PUFAs at enrollment had a lower risk of developing renal insufficiency during 3-year follow-up in older adults [32]. A systematic review demonstrated replacement of SFA by MUFA and PUFA has been associated with a decrease in metabolic syndrome components [33]. Mika et al. reported the potential contribution of serum MUFA to various risk factors of CVD in all stages of CKD but no association of serum MUFA or dietary MUFA intake and CVD outcome was explored [34]. Therefore, our finding on the protective impact of PUFA needs to be verified in large-scale cohorts and interventional studies, to provide more robust evidences for dietary guidelines in CKD in the near future. In addition, the intake of MUFA and PUFA was low, at 9.4% and 6.7% of calories per day, respectively, below the requirements of current guidelines for general population [28] and specific individuals with diabetes [35]. The mostly intake of PUFA was derived from edible oils in our subjects as there were limitations to dietary supplementation of seafood in dialysis patients. If benefits of PUFA are verified, more researches should focus on dietary pattern and appropriate food sources to increase the PUFA for these individuals.

It is worth noting that the time-averaged dietary ω-6 PUFA and ω-3 PUFA ratio correlated with the increased all-cause mortality in our PD cohort, similar to Noori et al.'s report in HD patients [36]. Patients with low ω-6/ω-3 PUFA also showed the increasing total cholesterol and lower HDL-cholesterol values. However, the direct benefits of ω-3 PUFA were not observed in this study. The beneficial effect of ω-3 PUFA, mainly marine-derived, has been demonstrated in numerous studies, by decreasing blood lipids and inflammatory cytokines [17,18,37]. However, due to inconsistent findings from heterogeneous study design in different study population [16,19,38–40], the 2020 update of the KDOQI guidelines only

Figure 4-1

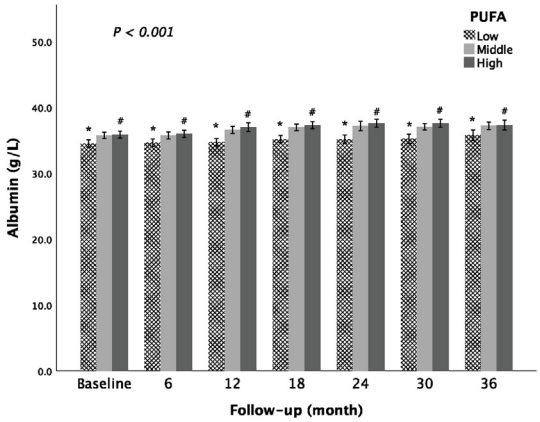
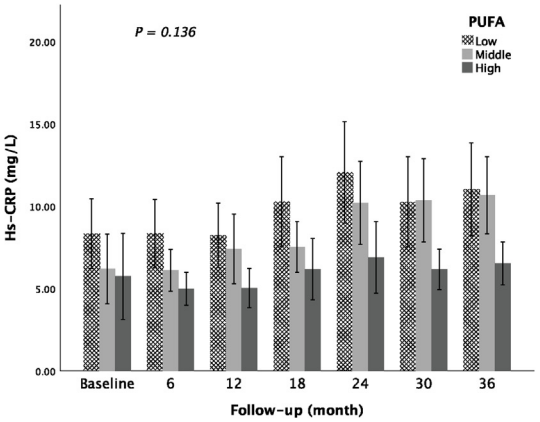


Figure 4-2



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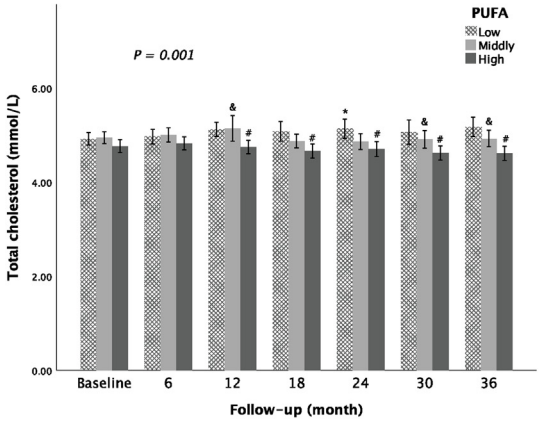

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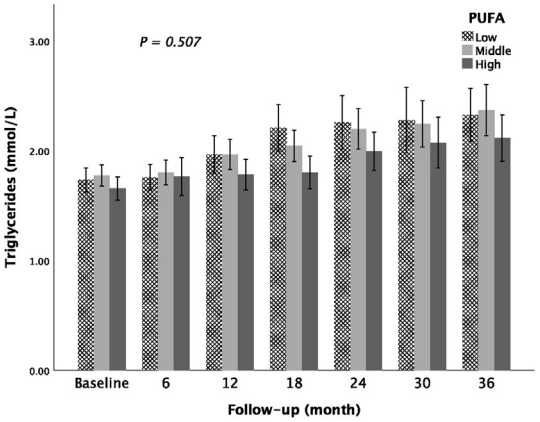


Figure 4-5

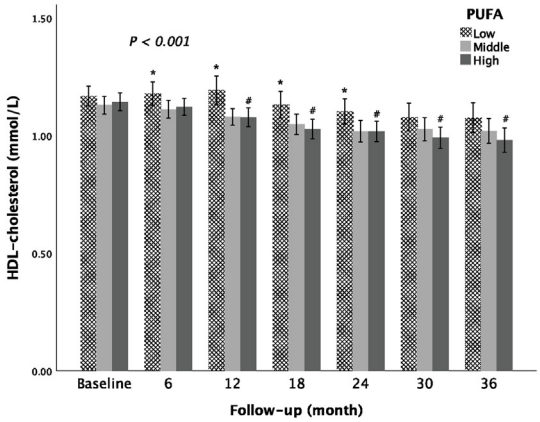


Figure 4-6

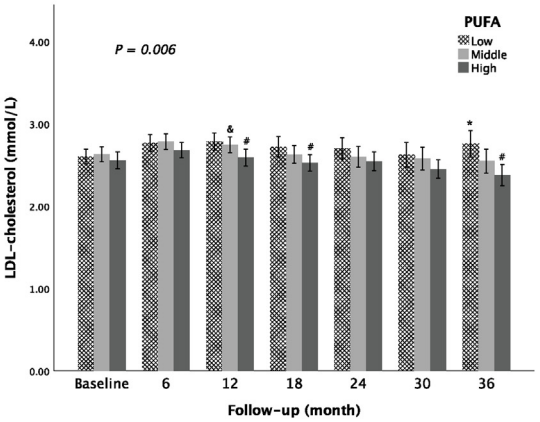
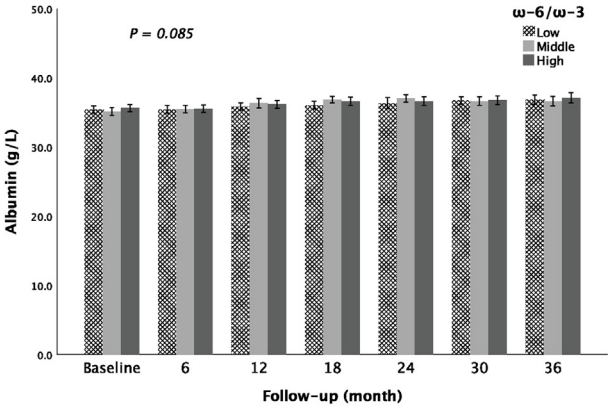


Fig. 4. Albumin, hs-CRP and serum lipid measurements in 36-month observation period in PD patients with different tertile of time-averaged polyunsaturated fatty acid (PUFA) intake. Bars represent the mean, and error bars are 95% CI; P value comparing the 3 groups over time was obtained from the linear mixed model with bootstrap covariance accounting for correlation among repeated measures within a patient. The baseline value of the outcome variables was adjusted as a model covariate. *, P < 0.05 low-tertile group compared to middle-tertile group in the same timepoint; &, P < 0.05 middle-tertile group compared to high-tertile group in the same timepoint; #, P < 0.05 high-tertile group compared to low-tertile group in the same timepoint.

recommend to prescribe long-chain ω-3 PUFA for the improvement of serum lipids rather than lowering risk of mortality of CV events in patients with CKD 5D on HD, PD and posttransplantation [19]. In regards to the source of supplementation, apart from oily fish and vegetable oils, nuts, flaxseed, and chia seeds are also particularly valuable sources of ω-3 PUFA but have some limitations for CKD patients due to their potassium and phosphorus-rich feature [41]. Given that it is difficult for CKD patients to obtain sufficient marine-derived ω-3 PUFA through dietary source, whether exogenous supplementation should be prescribed in clinical practice still

Figure 5-1



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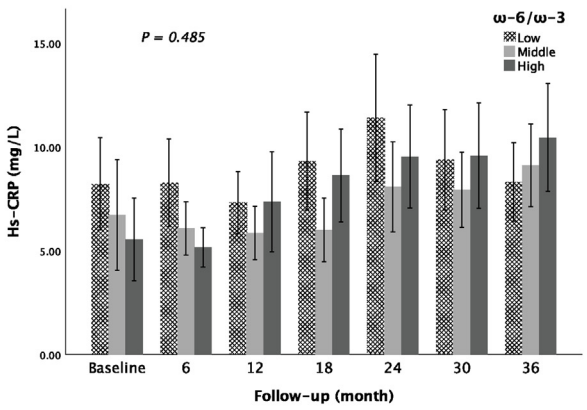
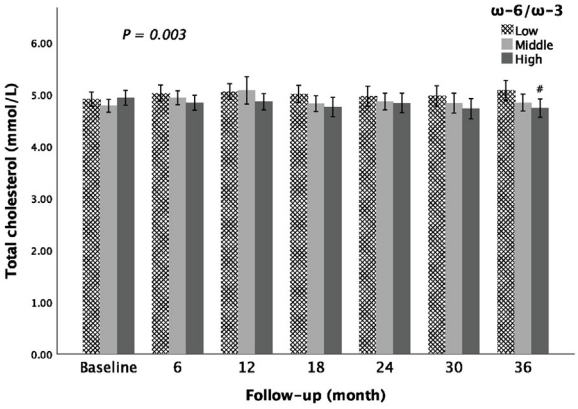


Figure 5-3



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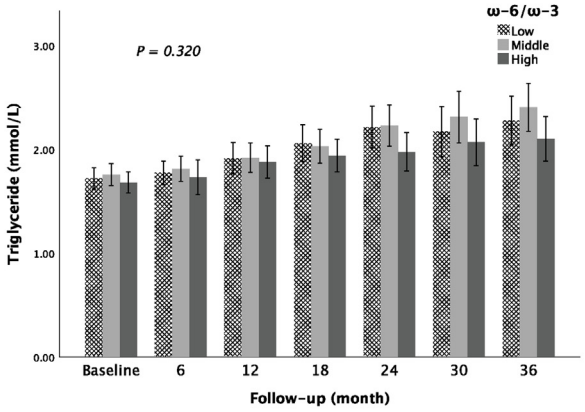
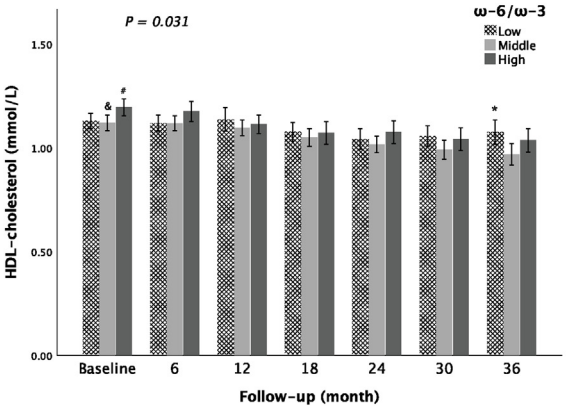


Figure 5-5



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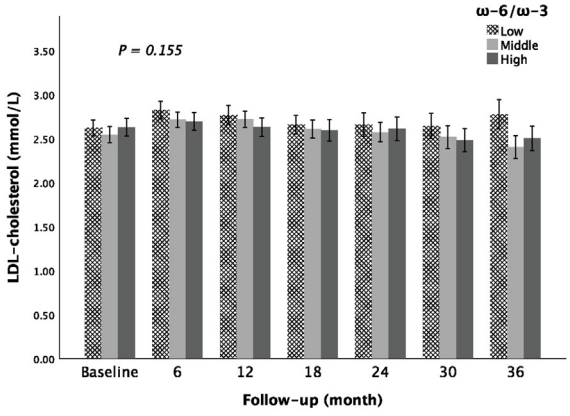

Fig. 5. Albumin, hs-CRP and serum lipid measurements in 36-month observation period in PD patients with different tertile of time-averaged ω-6/ω-3 PUFA intake. Bars represent the mean, and error bars are 95% CI; P value comparing the 3 groups over time was obtained from the linear mixed model with bootstrap covariance accounting for correlation among repeated measures within a patient. The baseline value of the outcome variables was adjusted as a model covariate. *, $P < 0.05$ low-tertile group compared to middle-tertile group in the same timepoint; &, $P < 0.05$ middle-tertile group compared to high-tertile group in the same timepoint; #, $P < 0.05$ high-tertile group compared to low-tertile group in the same timepoint.

needs to be explored, taking the evidences of advantages and feasibilities into account.

The present study has several strengths. We have a relatively large sample size of the patients, with a long follow-up time. i.e. 45-months, and enough number of endpoints. The prognostic value of different types and ratios of FA both at baseline and time-averaged level for all-cause and CVD mortality were explored. In spite of the above strengths, the study also has potential limitations. First, we used 3-day diet diary rather than measurement of erythrocyte membrane FA composition that has been proved very well correlated with dietary intake as the standard compliance measurement [42]. But to maximize the accuracy of the assessment, we used food models to assist patients in visualizing foods and portions consumed over the past 3 days, while face-to-face training of subjects enhances validity. Since the study was observational, we can't draw any conclusions of causality from our results. Although most-recognized risk factors were adjusted, we cannot completely exclude the possibility of residual or unmeasured confounding, because of observational nature of the study. In addition, this is a single-center study, the results may not be generalizable.

In conclusion, we, for the first time, found that the increased time-averaged PUFA intake was independently associated with a lower risk for all-cause mortality, while the increased ratio of MUFA to PUFA and ω-6 to ω-3 has inverse effect in our PD cohort. These findings are partly explained by the improvement of serum lipids in the longitudinal observation period. For the current nutrition guidelines in CKD population did not provide specific recommendations on total amounts and type of fatty acids based on inconsistent data, more strength studies are needed to explore the relationship between PUFA, the ratio of ω-6 to ω-3 PUFA, and prognosis of patients undergoing PD. Interventions on the amounts and type of dietary fatty acids, or the exogenous supplementation of specific type of fatty acids also need to be investigated in terms of clinical outcomes.

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Conflict of interest

None declared.

Author contributions

JD, research idea and study design; YLZ, LLJ, data curation; XX, LLJ, statistical analysis; YLZ, LLJ, Writing - original draft; TTM, JD, Writing - review & editing; JD, supervision or mentorship; Each author accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. JD takes responsibility that this study has been reported honestly, accurately and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained. All authors read and approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2023.09.002.

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