# Higher dietary fibre intake is associated with lower CVD mortality risk among maintenance haemodialysis patients: a multicentre prospective cohort study

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### **Abstract**

High fibre intake is associated with reduced mortality risk in both general and chronic kidney disease populations. However, in dialysis patients, such data are limited. Therefore, the association between dietary fibre intake (DFI) and the risk of all-cause and CVD mortality was examined in this study. A total of 1044 maintenance haemodialysis (MHD) patients from eight outpatient dialysis centres in China were included in this study. Data on DFI were collected using 24-h dietary recalls for 3 d in a week and were normalised to actual dry weight. The study outcomes included all-cause and CVD mortality. Over a median of 46 months of follow-up, 354 deaths were recorded, of which 210 (59 %) were due to CVD. On assessing DFI as tertiles, the CVD mortality risk was significantly lower in patients in tertiles 2-3 ( $\ge 0.13$  g/kg per d; hazard ratio (HR) 0.71; 95 % CI 0.51, 0.97) compared with those in tertile 1 (<0.13 g/kg per d). A similar but non-significant trend was found for the association between DFI (tertiles 2-3 v. tertile 1; HR 0.83; 95 % CI 0.64, 1.07) and all-cause mortality. In summary, higher DFI was associated with lower CVD mortality risk among Chinese MHD patients. This study emphasises the significance of DFI in MHD patients and provides information that is critical for the improvement of dietary guidelines for dialysis patients.

Keywords: All-cause mortality: CVD mortality: Dietary fibre intake: Maintenance haemodialysis patients

Patients with chronic kidney disease (CKD) have an increased risk of hospitalisation and mortality. This is especially so for patients with end-stage renal disease (ESRD)<sup>(1)</sup>. According to the 2018 annual report of the Renal Data System of the USA, nearly two-thirds (63%) of all existing patients of ESRD were receiving haemodialysis therapy. This number will keep rising due to an increase in the population of existing ESRD patients<sup>(2)</sup>. Over the years, the survival of patients on dialysis has improved.

However, only 57% of haemodialysis patients survive 3 years after the onset of ESRD. Notably, almost half of the deaths are related to CVD<sup>(2,3)</sup>. This high mortality provided an impetus to identify more modifiable risk factors to improve the survival of dialysis-dependent patients.

Dietary fibre comprises edible plant part of the diet that is difficult to digest and cannot be absorbed in the human small intestines<sup>(4)</sup>. Dietary fibre is considered to be an important

**Abbreviations:** BUN, blood urea nitrogen; CKD, chronic kidney disease; CRP, C-reactive protein; DEI, dietary energy intake; DFI, dietary fibre intake; DPI, dietary protein intake; HR, hazard ratio; MHD, maintenance haemodialysis.

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component of a healthy diet because it interacts with the gastrointestinal tract and positively affects the digestive system. Considerable epidemiological evidence has revealed that high dietary fibre intake (DFI) reduces the risk of several chronic diseases such as CVD, type 2 diabetes, cancer, obesity and  $CKD^{(5,6)}$ . Moreover, an inverse association between dietary fibre and mortality was reported in general and CKD populations<sup>(7,8)</sup>. It is noteworthy that dialysis population is special among CKD patients. This is because dialysis patients have a higher mortality rate and stricter dietary restriction compared with patients with other stages of CKD. Sometimes these patients have reverse epidemiological phenomena. There is a need to explore the effect of dietary fibre on mortality in dialysis patients. Notably, data on the association between dietary fibre and mortality, especially CVD mortality, in dialysis population are limited.

To address this gap in knowledge, the associations between DFI and all-cause and CVD mortality were evaluated. Potential effect modifications in patients undergoing maintenance haemodialysis (MHD) was assessed using data from a multicentre prospective cohort study in China.

#### Method

#### Study design and participants

The design of this study and some of the results have been reported previously (9,10). Briefly, this was a multicentre cohort study conducted prospectively from January 2014 to December 2015 in eight outpatient dialysis centres, namely Nanfang Hospital, The First People's Hospital of Foshan, Huadu District People's Hospital of Guangzhou, Guangzhou Red Cross Hospital, Jinan University First Affiliated Hospital, The Third Affiliated Hospital of Southern Medical University, Southern Medical University Affiliated Nanhai Hospital and Shenzhen Second People's Hospital. These centres are located in Guangdong province in China.

The inclusion criteria for participants were ≥18 years, undergone MHD for a minimum of 90 d (prevalent haemodialysis patients) and had a normal intake (not receiving enteral or parenteral nutrition). The exclusion criteria included history of physiciandiagnosed severe infection, serious gastrointestinal disease, hyperthyroidism, liver cirrhosis, multiple organ failure, cognitive disorder or malignant tumour at an advanced stage according to participants' previous medical records, because these conditions may influence dietary nutrient intake.

Overall, the information of 1302 patients was collected and recorded in this cohort. However, we did not have a detailed number of cases for patients who were excluded due to the exclusion criteria. Furthermore, a total of 1044 patients were included in the final analysis, after further excluding participants who enrolled in the cohort twice (n 2), received peritoneal dialysis (n 8), haemodialysis duration <3 months (n 163) and lacked baseline biochemical parameters and Kt:V ratio data (n 85).

Possible events of endpoint and vital signs of participants were recorded by physicians and trained research staff during each follow-up visit. This study was approved by the medical ethics committee of Nanfang Hospital, and all participants signed informed consent before participating in the study.

### Data collection and measurements

Demographic data were collected by trained research staff as per standard operating procedures. Data on age, sex, co-morbidities (diabetes mellitus, hypertension, history of CVD), education level, smoking status, alcohol consumption and duration of dialysis were collected. Each participant was interviewed using a standardised questionnaire specifically designed for this study. Here the definition of diabetes mellitus was a past medical history of diabetes or the use of glucose-lowering medication, while that of hypertension was having a medical record of hypertension or using anti-hypertensive drugs. A history of CVD was defined as a previous history of myocardial infarction, congestive heart failure, angina, transient ischaemic attack or cerebrovascular accident and peripheral arterial disease. Patients who had a recent history of smoking or drinking were defined as having smoking status or alcohol consumption, respectively.

Physical examinations were carried out after dialysis when the dry weight of the patient could be estimated. The measurement of BMI was done using the formula: BMI = weight/height squared  $(kg/m^2)$ .

Blood samples were obtained from patients prior to an haemodialysis session in mid-week at baseline. Biochemical parameters, including serum albumin, Ca, phosphate, creatinine, TAG and C-reactive protein (CRP), were determined at each local dialysis centre as per the standard protocol. Total Kt:V ratio was calculated using the urea kinetic modelling (UKM) formula:

 $Kt:V = -\ln (post-BUN/pre-BUN - 0.008 \times t)$  $+(4-3.5 \times post-BUN/pre-BUN) \times UF/post-weight,$ 

where UF is ultrafiltration, BUN is serum blood urea nitrogen and t is effective dialysis time.

Dietary intakes were registered by trained interviewers using a 24-h dietary recall that is known as the automated multiple pass method. Data were collected on 3 d (2 non-dialysis days and 1 dialysis day) in 7 consecutive days. The 24-h dietary recall is a relatively quick and systematic evaluation method to acquire the recent information about the intake of food and is used widely in epidemiologic research<sup>(11)</sup>. The US Department of Agriculture developed the automated multiple pass method, which utilises a five-step, interviewer-administered, computerbased procedure for obtaining diet recalls. Details of this dietary assessment methodology have been published elsewhere (12,13). The calculation of nutrient intake was based on a dietary software, version 2.0 (Zhending). Nutrient models were sourced from the Chinese food consumption table developed in 2009 by the Center for Disease Control and Prevention of China. The dietary fibre intake was from foods (cereals, vegetables and fruits), not supplements. The intake of dietary fibre, protein and energy by the participants was normalised to the actual dry weight of the patient and presented in terms of g/kg per d and kJ/kg per d.

#### Study outcomes

All-cause mortality was defined as death from any cause, whereas CVD mortality was defined as death from myocardial infarction, heart failure, sudden cardiac death, stroke, cardiovascular haemorrhage and other vascular causes that are known.



Mortalities were confirmed either from hospital-provided death certificates or from a comprehensive consensus of the experts if death occurred out of hospital. All patients were followed up until death, transfer to kidney transplantation, peritoneal dialysis, end of the latest survey (July 2019) or censoring.

## Statistical analysis

We assumed that the annual mortality rate among the participants with lower DFI was about 35 %, with a type I error rate of 0·025; enrolled 300 participants in lower DFI group and 600 participants in higher DFI group; would provide >80 % power to observe a hazard ratio (HR) of  $\leq$ 0·75 for the comparison between lower v. higher DFI groups during a follow-up of about 3·5 years. Thus, given the possible rate of loss to follow-up, a sample size of about 1000 would be required.

Data are presented as means and standard deviations for continuous variables that are normally distributed, as medians and interquartile ranges for continuous variables that are skewed, and as frequencies and percentages for categorical variables. The difference among the tertiles of DFI levels was tested for categorical variables using the  $\chi^2$  test, and the Kruskal–Wallis test or ANOVA for continuous variables as suitable.

Variables that are known as traditional or suspected risk factors for the prognosis of haemodialysis patients (14,15) or variables that showed significant differences among different DFI levels were chosen as covariates in this study. We first explored the association between DFI and mortality using thin-plate regression splines in generalised additive models implemented by the R package mgcv. Then univariate and multivariate Cox proportional hazard regression models (HR (OR) and 95 % CI) were used to evaluate the relation of DFI (tertiles and categories: tertile 1 v. tertiles 2-3) with all-cause and CVD mortality risk with and without adjustment for age, sex, dialysis centres, education level, smoking status, alcohol consumption, co-morbidities (diabetes, hypertension, history of CVD), BMI, waist:hip ratio, Kt:V ratio, dialysis duration, serum albumin, cholesterol, creatinine, CRP, dietary energy intake (DEI) and dietary protein intake (DPI). In Cox proportional hazards, time at risk was from the entry of the study until death, transferring to kidney transplantation, peritoneal dialysis or the end of the latest survey, whichever came first. The proportional hazards' assumption was checked using statistical tests based on the scaled Schoenfeld residuals. Kaplan-Meier estimates were used to generate survival curves, and the log-rank test was applied to compare differences between DFI categories (tertile 1 v. tertiles 2-3) in survival. Furthermore, we added competing risk models to our analysis, treating non-CVD death as a competing event of CVD death. In competing risk models, cumulative incidence function was used to generate survival curves, and the differences among groups were recognised by Gray's test using the R package *cmprsk*. The Fine and Gray proportional sub-distribution hazard model was performed to determine the 95 % CI and HR for CVD mortality associated with DFI using the R package mstate.

As additional exploratory analyses, possible modifications on the association between DFI (tertile 1  $\nu$ . tertiles 2–3) and mortality risk were also evaluated by stratified analyses and interaction testing.

In all the analyses, a two-tailed P < 0.05 was regarded as statistically significant. All analyses were conducted using Empower (www.empowerstats.com) from X&Y Solutions Inc. and R software (http://www.R-project.org), version 3.5.3.

#### **Results**

#### Study participants and baseline characteristics

As illustrated in the flowchart (Fig. 1), a total of 1302 MHD patients participated in the survey, and 1044 patients were included in the final analysis. The baseline characteristics were similar among participants included and those not included in the current study (online Supplementary Table 1).

Supplementary Fig. 1 shows the distribution of DFI in the participants. Of the participants, 90 % consumed a value of DFI <14 g/d. The study population's baseline characteristics according to the tertiles of DFI are shown in Table 1. In this study, the average age of the participants was 54 (sp 15) years, and 58 % of them were males. The mean DFI in the total population was 0·16 (sp 0·07) g/kg per d. Participants with higher DFI levels tended to be younger, had lower BMI and waist:hip ratio and had higher DEI, DPI and Kt:V ratio.

# Association between dietary fibre intake and the risk of

During a median follow-up duration of 46 months, all-cause mortality occurred in 354 (34%) participants and 210 (59%) deaths were due to CVD.

The association between DFI levels and CVD mortality appeared to be non-linear (online Supplementary Fig. 2). Accordingly, in the multivariable Cox regression analysis (Table 2), when DFI was assessed as tertile, the adjusted HR and 95% CI of CVD mortality for participants in tertile 2 (0.13 to <0.18 g/kg per d) and tertile 3 ( $\ge 0.18$  g/kg per d) were 0.72 (95 % CI 0.51, 1.02) and 0.68 (95 % CI 0.45, 1.02), respectively, compared with those in tertile 1. Consistently, a remarkably lower CVD mortality risk was found in tertiles 2-3 (≥0.13 g/kg per d; adjusted HR 0.71; 95 % CI 0.51, 0.97) compared with participants in tertile 1. Similar results were found in the competing risk analysis (online Supplementary Fig. 3 and Table 2). In the Cox proportional hazard regression models for the association between DFI (tertial 1 v. tertiles 2–3) and CVD mortality, no clear evidence was found against the proportional hazards' assumption (P = 0.966).

Kaplan–Meier curves of the cumulative event rate of CVD mortality for DFI categories (tertial 1 v. tertiles 2–3) are shown in Fig. 2. Consistently, the participants in tertiles 2–3 had a remarkably lower risk of mortality due to CVD (HR 0.74; 95 % CI 0.56, 0.98) compared with those in tertile 1.

A similar but non-significant trend was found for all-cause mortality (Fig. 2 and Table 2).

### Stratified analysis of CVD mortality

Stratified analyses were conducted to assess the relationship between DFI and CVD mortality risk in various subgroups. As shown in Fig. 3, no variable significantly modified the correlation



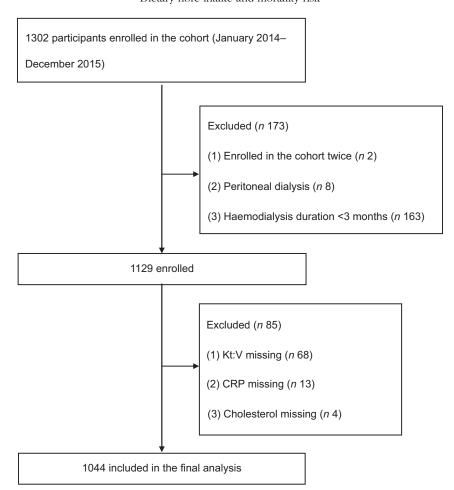


Fig. 1. Participant flowchart. CRP, C-reactive protein.

between DFI and CVD mortality for sex (male v. female), age ( $<60 \ v. \ge 60 \ \text{years}$ ), history of CVD (yes v. no), diabetes (yes v.no), BMI ( $<23 \ v. \ge 23 \ \text{kg/m}^2$ ), CRP ( $<3 \ v. \ge 3 \ \text{mg/l})^{(16)}$ , DPI  $(<1.2 \ v. \ge 1.2 \ g/kg \ per \ d)$ , DEI  $(<125.5 \ v. \ge 125.5 \ kJ/kg \ per \ d)$ , albumin (<35 v.  $\geq 35$  g/l) and dialysis duration (<24 v.  $\geq$ 24 months) (all values of P for interaction >0.05). Further stratified analysis based on age, BMI, DPI and DEI tertiles also found no interaction effect (online Supplementary Fig. 4).

#### Discussion

This multicentre prospective study was the first to show that high DFI correlated with a significantly decreased risk of CVD mortality after a follow-up of 46 months in MHD patients. Besides, the relation between DFI and CVD mortality was independent of sex, age, history of CVD, diabetes, BMI, CRP, DPI, DEI, albumin and dialysis duration.

Several previous reports have shown an inverse correlation between DFI and CVD mortality in general population. The NIH-AARP Diet and Health Study found that the multivariate relative risk for mortality due to CVD in the highest quintile were 0.76 (95 % CI 0.68, 0.85) for men and 0.66 (95 % CI 0.55, 0.79) for women compared to individuals in the lowest quintile of DFI<sup>(17)</sup>. A recent meta-analysis of twenty-two cohort studies examining the association of DFI with CVD mortality reported a 9% reduction in mortality from CVD for each 7 g/d increase in DFI<sup>(8)</sup>. The present study extends the existing evidence by demonstrating that the inverse association between DFI and CVD deaths is also existent in MHD patients. Consistently, a recent study in Hong Kong involving 127 peritoneal dialysis patients showed that an increase of dietary fibre by 1 g correlated with a reduced risk of major adverse cardiovascular events by 11 (95 % CI 0.81, 0.97) % after 18 months of follow-up<sup>(18)</sup>.

The inverse association between DFI and CVD mortality in MHD could be explained by different mechanisms. A part of the protective effect of fibre intake in CVD mortality may be attributed to its regulation of gut microbiota. Fibres could decrease the generation of colon-derived uraemic toxins such as p-cresol sulphate and indoxyl sulphate by modifying microbiota populations of the gut<sup>(19)</sup>. Through dialysis, it is difficult to get rid of these two uraemic toxins, which are related to CVD events in dialysis population<sup>(20-22)</sup>. Several small randomised trials involving haemodialysis patients had reported that supplementation with fibre correlates with reduced levels of indoxyl sulphate and p-cresol sulphate in the plasma(23-25). In addition, the well-proven health effects of dietary fibre, such as inflammation status amelioration<sup>(7,26)</sup>, blood lipid profile



Table 1. Baseline characteristics of study participants according to dietary fibre intake (DFI) levels\* (Numbers and percentages; mean values and standard deviations; medians and interquartile ranges (IQR))

	Tertile of DFI (g/kg per d)						
Variables	Tertile 1 (<0·13)		Tertile 2 (0·13–0·18)		Tertile 3 (>0·18)		
	Mean	SD	Mean	SD	Mean	SD	Р
n	34	18	34	.8	34	8	
Demographics							
Age (years)	55	15	55	15	52	15	0.02
Males							0.25
n	20		21		18		
%	5	9	60	)	54	ļ	
Education							0.14
Elementary school							
n	10		11		92		
%	3	0	32	2	26	5	
Secondary school				_		_	
n	19		19		19		
%	5	6	57	/	56	)	
University or equivalent	4	0	00	2	0.4		
n ov	4		39		61		
%	1	4	1.	I	18	3	0.61
Smoking status	5	1	54	4	45		0.61
n %	5 1		16		13		
Alcohol consumption	Į.	5	10	J	10	)	0.26
n	8	2	15	5	15		0.20
%		2	4		4		
Co-morbid conditions	2	_	7		4		
Diabetes							0.66
n	9	5	97	7	87	7	0 00
%	2		28		25		
Hypertension	_	•				,	0.74
n	29	94	30	1	29	9	•
%	8		86		86		
CVD	_		•		-		0.98
n	6	7	66	6	68	3	
%	1		19		20		
BMI (kg/m²)	22.4	3.8	21.1	3.1	20.2	2.9	< 0.001
WHR	0.91	0.07	0.90	0.07	0.89	0.07	< 0.001
Laboratory results							
Cholesterol (mmol/l)	4.1	1.1	4.2	1.2	4.1	1.1	0.89
Albumin (g/l)	37.8	3.7	38-1	3.9	38-4	3.7	0.06
CRP (mg/l)							0.09
Median	2-	-8	3.	0	2.0	3	
IQR	0.9-	-7·5	1.1-	-8-1	0.9-	6-0	
Creatinine (µmol/I)	1082⋅5	312.2	1100-5	310.7	1092-8	317.7	0.75
Dialysis duration (months)							0.52
Median	24		26		23		
IQR	13-		13–		12-		
Kt:V ratio*	1.3	0.4	1.3	0.5	1.4	0.4	0.05
Dietary parameters							
DEI (kJ/kg per d)	97.1	27.6	123.0	27.6	145-2	31.0	<0.001
DPI (g/kg per d)	0.9	0.3	1.1	0.3	1.3	0.4	<0.001
DFI (g/kg per d)	0.09	0.02	0.15	0.01	0.24	0.06	<0.001
DFI (g/d)	5⋅6	1.7	8.3	1.6	12.8	4.0	<0.001

WHR, waist:hip ratio; CRP, C-reactive protein; DEI, dietary energy intake; DPI, dietary protein intake; BUN, serum blood urea nitrogen; UF, ultrafiltration. \*Kt:V ratio, Kt represents the effective urea clearance and duration of dialysis, and V represents the volume of distribution of urea in the body, calculated as Kt:V = -In (post-BUN/ pre-BUN  $-0.008 \times t$ ) +  $(4-3.5 \times \text{post-BUN/pre-BUN}) \times \text{UF /post-weight}$ , where t is effective dialysis time.

improvement<sup>(27)</sup>, blood pressure regulation<sup>(28,29)</sup> and glycaemic control<sup>(30)</sup>, may contribute to reduced CVD mortality by slowing the progression of CVD.

Recommendations for fibre intake in the USA, Australia, New Zealand and most European countries are about 25-35 g/d for the general population (31). However, the recommendation for the CKD population is inconclusive (32–34). Only some guidelines recommend an exact value, such as that from the Italian Society of Nephrology, which recommends a DFI of 20-30 g/d based on a study that examined four different types of renal diets in the CKD population. Guideline from the National Health and Family Planning Commission of China recommends a DFI of 14 g/4184 kJ based on the recommended energy intake of CKD patients<sup>(35,36)</sup>. Current guidelines for dialysis patients lack



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Table 2. Univariate and multivariate Cox regression analyses of dietary fibre intake (DFI) in relation to mortality (Hazard ratios (HR) and 95 % confidence intervals)

				Crude			Adjusted*	
DFI (g/kg per d)	Events (no.)	%	HR	95 % CI	Р	HR	95 % CI	Р
All-cause mortality								
Tertiles								
T1 (< 0·13)	127	36	1.0 (Ref)		_	1.0 (Ref)		_
T2 (0·13-0·18)	117	34	0.90	0.70, 1.16	0.43	0.81	0.61, 1.07	0.13
T3 (>0·18)	110	32	0.82	0.64, 1.06	0.13	0.86	0.63, 1.18	0.35
Categories								
T1 (<0·13)	127	36	1.0 (Ref)		_	1.0 (Ref)		_
T2–T3 (≥0·13)	227	33	0.86	0.69, 1.07	0.18	0.83	0.64, 1.07	0.15
CVD mortality								
Tertiles								
T1 (<0·13)	83	24	1.0 (Ref)		_	1.0 (Ref)		_
T2 (0·13-0·18)	69	20	0.82	0.60, 1.13	0.22	0.72	0.51, 1.02	0.07
T3 (>0·18)	58	17	0.67	0.48, 0.93	0.02	0.68	0.45, 1.02	0.07
Categories				•				
T1 (< 0·13)	83	24	1.0 (Ref)		_	1.0 (Ref)		_
T2–T3 (≥ 0·13)	127	18	0·74 ´	0.56, 0.98	0.03	0·71 ´	0.51, 0.97	0.04

Ref, reference.

Adjusted for dialysis centre, age, sex, education level, smoking status, alcohol consumption, dietary energy intake, dietary protein intake, BMI, waist:hip ratio, albumin, cholesterol, C-reactive protein (log-transformed), creatinine, dialysis duration, Kt:V ratio and history of hypertension, diabetes and CVD.

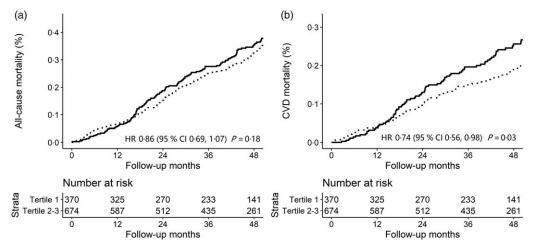


Fig. 2. Kaplan-Meier estimates of all-cause mortality (a) and CVD mortality (b) according to dietary fibre intake categories. — Tertile 1; • · tertile 2

specific recommendations for dietary fibre, and an optimal DFI value for dialysis patients still remains to be determined. It was notable that the mean fibre intake in our study was 8.9 g/d, which was relatively low compared with the recommendation from guidelines. Similarly, previous studies have found that patients receiving dialysis consume significantly lower amounts of dietary fibres compared with non-dialysis patients. These studies reported a daily fibre intake of 5-16 g/d in the haemodialysis population<sup>(37-40)</sup>. Several factors are involved in the reduced intake of fibre in dialysis population. One reason may be the dietary restriction on vegetables and fruits, as patients receiving dialysis were required to decrease K and phosphate intake in order to prevent (or correct) hyperkalaemia and hyperphosphatemia. This may lead to a simultaneous reduction in dietary fibre<sup>(41)</sup>. Besides, the loss of appetite due to side effects during

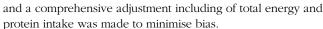
or after dialysis may also reduce fibre intake in these patients. Our current study further revelled the poor status of fibre intake and emphasised the significance of improving the intake of fibre in MHD patients. More studies are required to elucidate the suggested intake of fibre in dialysis and CKD populations.

Our study had several strengths that should be highlighted. First, this was the first multicentre cohort study conducted prospectively to explore whether the intake of dietary fibre correlated with CVD mortality in MHD patients and which had a comparatively long duration of follow-up with a large sample size. Second, detailed information, such as patients' characteristics, co-morbidities and laboratory data, was collected. Dietary nutrients were also quantified by a validated 24-h dietary recall thrice rather than a single assessment. Finally, the association between DFI and mortality (CVD and all-cause) was examined



Subgroup	Tertile 1	Tertile 2–3	HR (95 % CI)		P for interaction
	No. of events (%)	No. of events (%)		ī	
Age (years)					0.085
<60	22 (10.8)	45 (10-8)	0.91 (0.47, 1.76)	<b>├──</b>	
60+	61 (42·1)	82 (29-4)	0.62 (0.42, 0.91)	<b>⊢•</b>	
Sex					0.979
Male	47 (23.0)	76 (19.0)	0.68 (0.44, 1.05)	<b></b>	
Female	36 (25.0)	51 (17-2)	0.61 (0.36, 1.04)	<b></b>	
Diabetes					0.113
Yes	29 (30.5)	60 (32-6)	1.10 (0.64, 1.87)		0.113
No	54 (21.3)	67 (13·1)	0.61 (0.39, 0.94)		
	- ()	()	( 2 , 2 , 2 , 3	. • -	0.505
History of CVD Yes	21 (31.3)	42 (31-3)	0.84 (0.43, 1.65)		0.727
No	62 (22.1)	85 (15·1)	0.76 (0.51, 1.12)	<u> </u>	
	02 (22.1)	65 (15-1)	0.70 (0.31, 1.12)	<del></del>	
BMI (kg/m <sup>2</sup> )					0.527
<23	59 (26.8)	102 (18.7)	0.73 (0.51, 1.06)	<b>└</b>	
23+	24 (18.8)	25 (16·7)	0.52 (0.22, 1.21)	<del></del>	
CRP (mg/l)					0.932
<3	30 (16.4)	47 (12.7)	0.48 (0.27, 0.86)	<b></b>	
3+	53 (32·1)	80 (24.5)	0.79 (0.52, 1.21)	<b>⊢</b>	
DPI (g/kg per d)					0.308
<1·2	68 (22.4)	77 (19-5)	0.88 (0.60, 1.30)	<b>⊢</b>	(E), E, E, E
1.2+	15 (33.3)	50 (16.6)	0.56 (0.27, 1.19)	<b>——</b>	
DEI (kJ/kg per d	, ,			A	0.495
<125.5	68 (23.0)	66 (21-6)	0.74 (0.51, 1.08)		0.493
125.5+	15 (28.8)	61 (15.6)	0.56 (0.29, 1.11)		
	15 (20 0)	01 (13 0)	0 30 (0 2), 1 11)		
Albumin (g/l)	26 (40.0)	20 (22 6)	0.60.60.20.1.24)		0.56
<35 35+	26 (40.0)	38 (33.6)	0.69 (0.38, 1.24)		
	57 (20·1)	89 (15-3)	0.67 (0.45, 0.99)	—	
Dialysis duration					0.55
<24	41 (22.8)	57 (16·7)	0.76 (0.46, 1.23)	<b></b>	
24+	42 (25.0)	70 (19-7)	0.62 (0.39, 0.99)	<del></del>	
			<del> </del>		<u> </u>
			(	0 /	2

Fig. 3. Stratified analyses of the association between dietary fibre intake and the risk of CVD mortality. HR, hazard ratio; CRP, C-reactive protein; DPI, dietary protein intake; DEI, dietary energy intake.



This study also had some limitations that should be addressed. First, as an observational study, residual confounding cannot be ruled out due to interference from factors that we did not determine, such as race/ethnicity, genetic factors and trimethylamine-N-oxide. However, our current study only included the Chinese and did not have detailed genetic information. Moreover, the relation between trimethylamine-N-oxide and mortality risk in MHD patients is inconclusive(42,43) and remains to be studied. Second, only patients with normal intake were included in this study; the results may not be applicable to patients receiving enteral or parenteral nutrition. The association between DFI and mortality in these patients needed to be further examined. Third, the assessment of each parameter was done at baseline, only once. More frequent measurements would have allowed a more accurate assessment of the DFI and mortality association. Fourth, our study could not distinguish dietary fibre into insoluble and soluble fibre and could not determine the respective food source. Different types and sources of fibre may have different effects on the prognosis of patients with

MHD, which still needs to be verified. Finally, participants in our study had relatively lower fibre intake levels. Due to these limitations, confirmation of our findings through further studies is assential

In conclusion, we first demonstrated that a higher intake of dietary fibre significantly correlated with a reduced risk of CVD mortality in MHD patients. These results provide new insights into the benefits of DFI in MHD patients. Future randomised clinical trials are needed to further explore this association.

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# Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114521000210

#### References

- Wang F, Yang C, Long J, et al. (2019) Executive summary for the 2015 Annual Data Report of the China Kidney Disease Network (CK-NET). Kidney Int 95, 501-505.
- Saran R, Robinson B, Abbott KC, et al. (2019) US Renal Data System 2018 annual data report: epidemiology of kidney disease in the United States. Am J Kidney Dis 73, A7-A8.
- Thomas B, Wulf S, Bikbov B, et al. (2015) Maintenance dialysis throughout the World in years 1990 and 2010. J Am Soc Nephrol **26**, 2621–2633.
- Turner ND & Lupton JR (2011) Dietary fiber. Adv Nutr 2, 151 - 152.
- Anderson JW, Baird P, Davis RH, et al. (2009) Health benefits of dietary fiber. Nutr Rev 67, 188-205.
- Mirmiran P, Yuzbashian E, Asghari G, et al. (2018) Dietary fibre intake in relation to the risk of incident chronic kidney disease. Br J Nutr 119, 479-485.
- Krishnamurthy VM, Wei G, Baird BC, et al. (2012) High dietary fiber intake is associated with decreased inflammation and allcause mortality in patients with chronic kidney disease. Kidney Int 81, 300-306.
- Threapleton DE, Greenwood DC, Evans CE, et al. (2013) Dietary fibre intake and risk of cardiovascular disease: systematic review and meta-analysis. BMJ 347, f6879.
- Yang Y, Qin X, Li Y, et al. (2020) The association between dietary energy intake and the risk of mortality in maintenance hemodialysis patients: a multicenter prospective cohort study. Br J Nutr 123, 437-445.
- Chen J, Qin X, Li Y, et al. (2019) Comparison of three nutritional screening tools for predicting mortality in maintenance hemodialysis patients. Nutrition 25, 67–68.
- 11. Bross R, Noori N, Kovesdy CP, et al. (2010) Dietary assessment of individuals with chronic kidney disease. Semin Dial 23 359-364
- 12. Burrows TL, Martin RJ & Collins CE (2010) A systematic review of the validity of dietary assessment methods in children when compared with the method of doubly labeled water. J Am Diet Assoc **110**, 1501–1510.
- 13. Conway JM, Ingwersen LA & Moshfegh AJ (2004) Accuracy of dietary recall using the USDA five-step multiple-pass method in men: an observational validation study. J Am Diet Assoc 104, 595-603.

- 14. Ma LJ & Zhao SM (2017) Risk factors for mortality in patients undergoing hemodialysis: a systematic review and metaanalysis. Int J Cardiol 238, 151-158.
- 15. Pifer TB, Mccullough KP, Port FK, et al. (2002) Mortality risk in hemodialysis patients and changes in nutritional indicators: DOPPS. Kidney Int 62, 2238–2345.
- 16. Pearson TA, Mensah GA, Alexander RW, et al. (2003) American Heart Association: markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 107, 499-511.
- 17. Park Y, Subar AF, Hollenbeck A, et al. (2011) Dietary fiber intake and mortality in the NIH-AARP Diet and Health Study. Arch Intern Med 171, 1061–1068.
- Wang AY, Sea MM, Ng K, et al. (2019) Dietary fiber intake, myocardial injury, and major adverse cardiovascular events among end-stage kidney disease patients: a prospective cohort study. Kidney Int Rep 4, 814-823.
- 19. Kieffer DA, Martin RJ & Adams SH (2016) Impact of dietary fibers on nutrient management and detoxification organs: gut, liver, and kidneys. Adv Nutr 7, 1111-1121.
- Meijers BK, Bammens B, De Moor B, et al. (2008) Free p-cresol is associated with cardiovascular disease in hemodialysis patients. Kidney Int 73, 1174-1180.
- 21. Niwa T (2010) Indoxyl sulfate is a nephro-vascular toxin. J Ren Nutr 20, 2-6.
- 22. Poesen R, Viaene L, Verbeke K, et al. (2013) Renal clearance and intestinal generation of p-cresyl sulfate and indoxyl sulfate in CKD. Clin J Am Soc Nephrol 8, 1508-1514.
- 23. Khosroshahi HT, Abedi B, Ghojazadeh M, et al. (2019) Effects of fermentable high fiber diet supplementation on gut derived and conventional nitrogenous product in patients on maintenance hemodialysis: a randomized controlled trial. Nutr Metab 16, 18.
- 24. Esgalhado M, Kemp JA, Azevedo R, et al. (2018) Could resistant starch supplementation improve inflammatory and oxidative stress biomarkers and uremic toxins levels in hemodialysis patients? A pilot randomized controlled trial. Food Funct 9, 6508-6516.
- 25. Sirich TL, Plummer NS, Gardner CD, et al. (2014) Effect of increasing dietary fiber on plasma levels of colon-derived solutes in hemodialysis patients. Clin J Am Soc Nephrol 9, 1603-1610.
- 26. Xie LM, Ge YY, Huang X, et al. (2015) Effects of fermentable dietary fiber supplementation on oxidative and inflammatory status in hemodialysis patients. Int J Clin Exp Med 8, 1363-1369.
- 27. Whitehead A, Beck EJ, Tosh S, et al. (2014) Cholesterollowering effects of oat  $\beta$ -glucan: a meta-analysis of randomized controlled trials. Am J Clin Nutr 100, 1413-1421.
- 28. Khan K, Jovanovski E, Ho HVT, et al. (2018) The effect of viscous soluble fiber on blood pressure: A systematic review and meta-analysis of randomized controlled trials. Nutr Metab Cardiovasc Dis 28, 3-13.
- 29. Sun B, Shi X, Wang T, et al. (2018) Exploration of the association between dietary fiber intake and hypertension among U.S. adults using 2017 American College of Cardiology/American Heart Association Blood Pressure Guidelines: NHANES 2007-2014. Nutrients 10, 1091.
- 30. Weickert MO & Pfeiffer AF (2018) Impact of dietary fiber consumption on insulin resistance and the prevention of type 2 diabetes. J Nutr 148, 7-12.
- 31. Stephen AM, Champ MM, Cloran SJ, et al. (2017) Dietary fibre in Europe: current state of knowledge on definitions, sources,



- recommendations, intakes and relationships to health. Nutr Res Rev 30, 149-190.
- 32. Andrassy KM (2013) Comments on 'KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease'. Kidney Int 84, 622-623.
- Japanese Society of Nephrology (2014) Evidence-based clinical practice guideline for CKD 2013. Clin Exp Nephrol 18, 346-423.
- Fouque D, Vennegoor M, ter Wee P, et al. (2007) EBPG Guideline on Nutrition. Nephrol Dial Transplant
- 35. Cupisti A, Brunori G, Di Iorio BR, et al. (2018) Nutritional treatment of advanced CKD: twenty consensus statements. J Nephrol **31**, 457–473.
- National Health and Family Planning Commission of PRC (2017) Dietary guide for chronic kidney disease patients. http://www.nhc.gov.cn/wjw/yingyang/201708/b966bb821 a014ab893325541e2e93785.shtml (accessed May 2019).
- Therrien M, Byham-Gray L, Denmark R, et al. (2014) Comparison of dietary intake among women on maintenance dialysis to a women's health initiative cohort: results from the

- NKF-CRN second national research question collaborative study. J Ren Nutr 24, 72-80.
- 38. Khoueiry G, Waked A, Goldman M, et al. (2011) Dietary intake in hemodialysis patients does not reflect a heart healthy diet. J Ren Nutr 21, 438-447.
- 39. Luis D, Zlatkis K, Comenge B, et al. (2016) Dietary quality and adherence to dietary recommendations in patients undergoing hemodialysis. J Ren Nutr 26, 190–195.
- 40. As'habi A, Tabibi H, Houshiar Rad A, et al. (2011) Dietary assessment of hemodialysis patients in Tehran, Iran. Hemodial Int 15, 530-537.
- 41. Kalantar-Zade K & Fouque D (2017) Nutritional management of chronic kidney disease. N Engl J Med 377, 1765-1776.
- Zhang P, Zou JZ, Chen J, et al. (2020) Association of trimethylamine N-Oxide with cardiovascular and all-cause mortality in hemodialysis patients. Renal Fail 42, 1004-1014.
- 43. Stubbs JR, Stedman MR, Liu S, et al. (2019) Trimethylamine N-oxide and cardiovascular outcomes in patients with endstage kidney disease receiving maintenance hemodialysis. Clin J Am Soc Nephrol **14**, 261–267.

