The association between dietary energy intake and the risk of mortality in maintenance hemodialysis patients: a multicenter prospective cohort study

Yaya Yang¹, Xianhui Qin¹, Yan Li¹, Zihan Lei¹, Yumin Li¹, Shenglin Yang¹, Youbao Li¹, Yaozhong Kong², Yongxin Lu³, Yanhong Zhao³, Qijun Wan⁴, Qi Wang⁵, Sheng Huang⁶, Yan Liu⁷, Aiquin Liu⁸, Fanna Liu⁹, Fanfan Hou¹, and Min Liang¹

¹National Clinical Research Center for Kidney Disease, State Key Laboratory of Organ Failure Research, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China; ²the First People’s Hospital of Foshan, Foshan 528000, China ³People’s Hospital of Yuxi City, Yuxi 653100, China ⁴the Second People’s Hospital of Shenzhen, Shenzhen 518000, China ⁵Huadu District People’s Hospital of Guangzhou, Guangzhou 510515, China ⁶Nanhai District People’s Hospital of Foshan, Foshan 528000, China ⁷Guangzhou Red Cross Hospital, Guangzhou 510515, China ⁸the Third Affiliated Hospital of Southern Medical University, Guangzhou 510515, China ⁹Guangzhou Overseas Chinese Hospital, Guangzhou 510515, China

Correspondence and reprint requests should be addressed to:
Min Liang, M.D., Ph.D.
National Clinical Research Center for Kidney Disease, State Key Laboratory of Organ Failure Research, Nanfang Hospital, Southern Medical University, 1838 North Guangzhou Avenue, Guangzhou 510515, China.
Email: nfyylm@163.com
Phone: 86-020-61686217

Running head: dietary energy intake and mortality

Keywords: all-cause mortality; CVD mortality; dietary energy intake; maintenance hemodialysis patients

This peer-reviewed article has been accepted for publication but not yet copyedited or typeset, and so may be subject to change during the production process. The article is considered published and may be cited using its DOI

10.1017/S0007114519002861

The British Journal of Nutrition is published by Cambridge University Press on behalf of The Nutrition Society
Abstract

Maintenance hemodialysis (MHD) is the use of a machine to filter wastes, salts and fluid from blood for at least 3 months to prolong the life of patients with advanced kidney failure. Although low dietary energy intake (DEI) has been observed in MHD patients, few studies have related DEI to the risk of mortality. To explore this relationship, a study included 1039 MHD patients from 8 centers was conducted. DEI was assessed by three 24-hour diet recalls including one dialysis day and two non-dialysis days, and was normalized to ideal body weight (IBW). All-cause mortality and CVD mortality were the primary and secondary outcomes, respectively. During a median follow-up of 28 months, all-cause and CVD mortality occurred in 230 (22.1%) and 140 (13.5%) participants. Overall, a U-shaped relationship was observed between DEI and all-cause or CVD mortality. The risk of all-cause mortality decreased significantly with the increase of DEI in participants with DEI <40 kcal/kg IBW/d (HR, 0.98; 95% CI: 0.96-1.00) and increased significantly with the increase of DEI in those with DEI ≥40 kcal/kg IBW/d (HR, 1.12; 95% CI: 1.04-1.20). Similarly, the risk of CVD mortality decreased with the increase of DEI in participants with DEI <36.5 kcal/kg IBW/d (HR, 0.96; 95% CI: 0.93-0.99) and increased with the increase of DEI in participants with DEI ≥36.5 kcal/kg IBW/d (HR, 1.11; 95% CI: 1.04-1.18). In summary, there was a U-shaped association between DEI and all-cause or CVD mortality, with a turning point at about 40 and 36.5 kcal/kg IBW/d, respectively, in MHD patients.

Abbreviations: ABW: actual body weight; AMPM: Automated Multiple-Pass Method; BMI: body mass index; CI: confidence interval; CRP: C-reactive protein; CVD: cardiovascular disease; DEI: dietary energy intake; DPI: dietary protein intake; IBW: ideal body weight; MHD: maintenance hemodialysis patients; TC: total cholesterol
Introduction

Patients with end-stage renal disease often have extensive cardiovascular disease (CVD), with estimates of annual mortality as high as 20%\(^{(1)}\). This ongoing high mortality rate serves as an incentive to seek and establish more preventive strategies for dialysis-dependent patients.

Maintenance hemodialysis (MHD) is the use of a machine to filter wastes, salts and fluid from blood for at least 3 months to prolong the life of patients with advanced kidney failure. Several previous studies have found that maintenance hemodialysis (MHD) patients tend to have low dietary energy intake (DEI) and to be underweight\(^{(2-5)}\). Inadequate energy intake is a frequent and important cause of protein-energy wasting which closely related to major adverse clinical outcomes in MHD patients\(^{(6,7)}\). Hence, ensuring the optimal amount of energy intake is very important to improve the clinical outcomes of MHD patients. A metabolic balance study on six MHD patients suggested that a mean energy intake of 35 kcal/kg/d was necessary to maintain both a neutral nitrogen balance and an unchanged body composition\(^{(8)}\). Mainly based on this study, the European Best Practice Guidelines on nutrition recommend a DEI of 30-40 kcal/kg of ideal body weight (IBW) per day in clinically stable MHD patients\(^{(9)}\). The guidelines from the Kidney Disease Outcome Quality Initiative recommend a daily DEI of 35 kcal/kg body weight/d for MHD patients who are less than 60 years of age and a DEI of 30 to 35 kcal/kg body weight/d for those 60 years of age or older\(^{(4)}\). And the International Society of Renal Nutrition and Metabolism consensus indicate that the minimum energy requirements for MHD patients are 30-35 kcal/kg of IBW/d based on physical activity level\(^{(6)}\).

However, few epidemiological studies have prospectively examined the association between DEI and risk of mortality in MHD patients, and the optimal energy intake for prevention of mortality in such patients is still unknown. Estimation of DEI can only be done by monitoring intake. The most common methods for estimating dietary intake are food frequency questionnaires, food intake records, and 24-h dietary recalls\(^{(10,11)}\). Given evidence from biomarker-based validation, the 24-h dietary recalls capture dietary intake with less bias than do food-frequency questionnaires\(^{(12,13)}\). Moreover, the US Department of Agriculture 5-step multiple-pass method for dietary recall has been validated by a lot of previous studies\(^{(14-17)}\). Therefore, we make the
assumption that the 24-h recalls used in this study reflected the DEI because of earlier validations. Our purpose was to explore the relationship of DEI with all-cause and CVD mortality, and to examine any possible effect modifies among MHD patients.

Methods

Study design and participants

This study was a multicenter, prospective cohort study conducted from January 2014 to December 2015, in eight outpatient dialysis centers (including Nanfang Hospital, the First People’s Hospital of Foshan, Huadu District People’s Hospital of Guangzhou, Guangzhou Red Cross Hospital, Guangzhou Overseas Chinese Hospital, the Third Affiliated Hospital of Southern Medical University, Nanhai District People’s Hospital of Foshan and the Second People’s Hospital of Shenzhen) in Guangdong province in China. Eligible participants were males and females aged more than 18 years who had received maintenance dialysis for at least 3 months and had a normal oral intake. We excluded those who had hyperthyroidism, acute infection, liver cirrhosis, multiple organ failure, serious gastrointestinal disease, cognitive disorder, and advanced malignant tumor.

Participants were followed up at each routine dialysis visit where vital signs and possible endpoint events were documented by trained research staff and physicians.

The study was approved by the Medical Ethics Committee of Nanfang Hospital and all the participants signed an informed consent.

Data collection and measurements

Baseline data were collected by trained research staff according to standard operating procedures. Interviews were conducted on each participant using a standardized questionnaire designed specifically for the present study.

Diabetes mellitus was defined as having a medical history of diabetes, or undergoing glucose-lowering therapy, including insulin or oral hypoglycemic agents. Patients who reported antihypertensive drugs use or had a medical history of hypertension were defined as having hypertension. The history of CVD was defined as history of angina, congestive heart failure, transient ischemic attack, history of myocardial infarction or cerebrovascular accident and peripheral arterial disease. The question about physical activity was phrased as follows, “How do you describe your daily physical activity level?” and a choice of three responses: low, moderate, and high was provided\(^ {18,19}\).

Anthropometric measures including weight and height were obtained during the
physical examination. All measurements were conducted post-dialysis when the patient was at dry weight. Body mass index (BMI) was calculated as weight/height squared (kg/m²).

Dietary intake was assessed by trained interviewers using the Automated Multiple-Pass Method (AMPM) where 24-hour diet recalls were administered on three days (including one dialysis day and two non-dialysis days) within one week. The 24-hour diet recalls are relatively quick assessment modalities to obtain the most recent information about food intake and are widely used in epidemiologic studies. Briefly, the AMPM was developed by the US Department of Agriculture and utilizes a five-step, multiple-pass, interviewer-administered, computerized process for obtaining diet recalls. The AMPM consists of five following steps: (a) the quick list, which is an uninterrupted listing by the subject of foods and beverages consumed; (b) the forgotten foods list, which queries the subject on categories of foods that have been documented as frequently forgotten; (c) a time and occasion at which foods were consumed; (d) the detail cycle, which elicits descriptions of foods and amounts eaten aided by the use of the Food Model Booklet; and finally (e) the final probe review. The energy intake of all food and drink items was sourced using a computer-aided dietary software (Zhending, Shanghai, China software version 2.0), in which nutrient models were based on the Chinese Food Composition Table developed by the Chinese Center for Disease Control and Prevention, 2009.

DEI was expressed in three units of measure: actual energy intake in kcal/d, energy intake normalized to actual body weight (ABW) in kcal/kg ABW/d, and energy intake normalized to ideal body weight in kcal/kg IBW/d. As guidelines recommended, we used ideal body weight instead of actual body weight, since normalizing energy intake to actual body weight would result in erroneously high or low energy requirements in overweight or underweight patients. In the main analysis of our current study, IBW was calculated using improved Broca formula adapted for Asian populations: IBW= (height (cm) – 100) ×0.9 (kg) for males; and (height (cm) – 100) ×0.9 (kg)-2.5(kg) for females. Moreover, IBW was also calculated by multiplying an ideal BMI of 22 kg/m² with a person’s actual height (m) squared in the sensitivity analysis.

Blood samples of all participants were obtained from each subject prior to the hemodialysis session at baseline. Serum lipids, albumin, calcium, phosphate levels and total CO₂ were measured using automatic clinical analyzers following the same
standard protocol at each local dialysis center.

**Study outcomes**

All-cause mortality was the primary outcome in this analysis and included death due to any reason. The secondary outcome was death from CVD, which included sudden cardiac death, myocardial infarction, heart failure, stroke, cardiovascular hemorrhage, and death due to other known vascular causes. Evidence for death included death certificates from hospitals or reports from investigator visits.

**Statistical analysis**

We assumed that the annual mortality rate of maintenance hemodialysis (MHD) patients is 20%\(^{(1)}\), the hazard ratio (HR) of the DEI between <25 vs. \(\geq 25\) kcal/kg IBW/d was about 1.67\(^{(23)}\), with an alpha of 0.05, 124 MHD patients followed-up for 2 years would have a power of 90%.

Baseline characteristics are presented as mean ± SD for normally distributed continuous variables, median (Q-Q3) for skewed continuous variables, and frequencies (percentages) for categorical variables. Differences in baseline characteristics according to DEI categories (<30, 30-35, 35-40, and \(\geq 40\) kcal/kg IBW/d) were compared using Chi-square tests or ANOVA tests as appropriate.

Cox proportional hazards models were used to estimate the HRs and 95% CIs for the risk of all-cause mortality and CVD mortality associated with DEI, without and with adjustments for dialysis center, age, sex, smoking, alcohol use, physical activity, BMI, albumin, triglycerides, total cholesterol (TC), C-reactive protein (CRP), calcium, phosphate, hemoglobin, dialysis vintage, Kt/V, diabetes, hypertension and history of CVD. We applied two-piecewise regression models to examine the threshold effect of DEI on the risk of all-cause mortality or CVD mortality using a smoothing function. The threshold level (turning point) was determined using likelihood-ratio tests and bootstrap resampling methods.

In a stratified analysis, possible modifications of the association between DEI and all-cause mortality were assessed for the variables, age (<60 vs. \(\geq 60\) years), sex, diabetes (yes vs. no), history of CVD (yes vs. no), CRP (<8 vs. \(\geq 8\) mg/L\(^{(24)}\)), TC (<200 vs. \(\geq 200\) mg/dL\(^{(25)}\)) and BMI (<23 vs. \(\geq 23\) kg/m\(^2\)\(^{(26)}\) levels at baseline.

A two-tailed \(P<0.05\) was considered statistically significant in all analyses. All analyses were performed using Empower (R) (www.empowerstats.com, X&Y Solutions, Inc. Boston MA) and R (http://www.R-project.org).
Results

Study participants and baseline characteristics

As illustrated in the flow chart (Supplemental Figure 1), 1039 MHD patients were included in the final analyses.

At baseline, 577 (55.5%), 222 (21.4%), 154 (14.8%) and 86 (8.3%) participants had DEI<30, 30-<35, 35-<40 and ≥40 kcal/kg IBW/d, respectively. Mean (standard deviation) values of DEI in total population were 1600.3 (444.6) kcal/d and 29.3 (7.9) kcal/kg IBW/d, respectively.

Participant characteristics by DEI categories are listed in Table 1. Patients with lower DEI tended to be older, had lower TC, serum calcium, serum phosphate, CRP, dietary protein intake (DPI), and were more likely to be males.

The relationship of DEI with all-cause and CVD mortality

Over a median follow up of 28 months, 84 patients underwent kidney transplantation, 5 patients switched to peritoneal dialysis, and 55 patients were lost to follow-up. These patients were censored at the last date of follow-up. All-cause and CVD mortality occurred in 230 (22.1%) and 140 (13.5%) participants, respectively.

Overall, a U-shaped relationship was observed between DEI and all-cause mortality (Figure 1A). The two-piecewise regression models showed that a DEI value of 40 kcal/kg IBW/d was a turning point for all-cause mortality after multivariate adjustment. That is, the risk of all-cause mortality decreased significantly with the increase of DEI in participants with DEI <40 kcal/kg IBW/d (Hazard ratio (HR), 0.98; 95% confidence interval (CI): 0.96-1.00; \(P=0.027\)), but increased significantly with the increase of DEI in participants with DEI ≥40 kcal/kg IBW/d (HR, 1.12; 95%CI: 1.04-1.20; \(P=0.002\)) (Table 2). Consistently, when compared to participants with DEI of 35-<40 kcal/kg IBW/d, a significantly higher risk of all-cause mortality was observed in those with DEI <30 kcal/kg IBW/d (HR, 1.85; 95%CI: 1.20-2.85), and a higher but insignificant risk of all-cause mortality was also found in participants with DEI ≥40 kcal/kg IBW/d (HR, 1.83; 95%CI: 0.99-3.40) (Table 3).

Similarly, a U-shaped association was also found between DEI and CVD mortality (Figure 1B). The two-piecewise regression models showed that a DEI value of 36.5 kcal/kg IBW/d was a turning point for CVD mortality after multivariate adjustment. The risk of CVD mortality decreased significantly with the increase of DEI in participants with DEI <36.5 kcal/kg IBW/d (HR, 0.96; 95%CI: 0.93-0.99; \(P=0.006\)), but increased significantly with the increase of DEI in participants with DEI ≥36.5
kcal/kg IBW/d (HR, 1.11; 95%CI: 1.04-1.18; P=0.002) (Table 2). Consistently, when compared to participants with DEI of 35-<40 kcal/kg IBW/d, a significantly higher risk of CVD mortality was observed in those with DEI <30 kcal/kg IBW/d (HR, 1.94; 95%CI: 1.12-3.36) or ≥40 kcal/kg IBW/d (HR, 2.39; 95%CI: 1.14-5.03) (Table 3).

There was a similar trend in the relationship between DEI by actual body weight and all-cause or CVD mortality (Supplemental Figure 2). Moreover, DEI normalized to IBW calculated from BMI showed the similar relationship with mortality (Supplemental Figure 3). Further adjustment for dietary protein intake did not substantially changed the results (Supplemental Table 1).

**Stratified analyses by potential effect modifiers**

Stratified analyses were performed by age, sex, diabetes, history of cardiovascular disease, CRP, TC and BMI. The lowest risk of mortality was found in patients with DEI at 30-<40 kcal/kg IBW/d in all the subgroups. There were no significant interactions in any of the subgroups (P for interaction >0.05 for all comparisons; Figure 2).

**Discussion**

Our study is the first to demonstrate a U-shaped association between DEI and all-cause or CVD mortality in MHD patients. Participants with a DEI at 35-40 kcal/kg IBW/d had the lowest risk of all-cause and CVD mortality.

Hemodialysis patients are at increased risk of energy deficiency for several reasons, including inadequate energy intake, inflammation and multiple comorbidities, metabolic and hormonal derangements, hemodialysis-associated catabolism, and increased resting energy expenditure \(^{(6, 27-30)}\). A previous retrospective study including 344 incident hemodialysis patients, found that energy intake lower than 25 kcal/kg/d was related to worse survival \(^{(23)}\). Another retrospective observational study also reported that lower energy intake (<25 kcal/kg/d) was associated with all-cause mortality among 144 patients on maintenance hemodialysis \(^{(31)}\). Our findings are in agreement with these last two retrospective studies with small sample size, for we also found that DEI levels were inversely associated with all-cause mortality in participants with DEI < 40 kcal/kg IBW/d. The mechanisms linking lower energy intake and the risk of mortality are still unclear. When DEI is deficient, body fat and muscle mass are depleted to maintain basal metabolic rate and protein stores cannot be able to well preserved \(^{(6, 32)}\). In addition, pro-inflammatory cytokines, such as IL-6 or TNF-α, are higher in MHD patients with reduced nutrient intake \(^{(33-36)}\). Loss of muscle and fat stores and inflammation may increase the risk of all-cause mortality.
Moreover, patients with low energy intake might also have a higher prevalence of latent chronic disease\(^{(37)}\).

Our study had a relatively higher DEI compared to some studies. In our study, the mean (SD) DEI were 29.1(8.3) kcal/kg of actual body weight/d and 29.3(7.9) kcal/kg IBW/d, respectively. In comparison, the mean DEI by actual body weight in hemodialysis patients was 22.9 (8.4) kcal/kg/d in the Hemodialysis (HEMO) Study cohort\(^{(38)}\), 25.8 kcal/kg/d in a Korean cohort\(^{(31)}\), and 26.2 kcal/kg/d in a Brazilian cohort\(^{(23)}\). The differences in mean DEI across these different studies may be due to several reasons. First, dietary habits vary greatly across different countries and cultures. Second, the nutritional status of a population is known to improve with its economic development; the living standards for these populations may have improved considerably since each study was conducted. The HEMO study\(^{(38)}\) was conducted between May 1995 and March 1997, the study from Korea\(^{(31)}\) was conducted during April 2006, and the study from Brazil\(^{(23)}\) was conducted from January 1992 to December 2002. By contrast, our study was conducted more recently, from January 2014 to December 2015. Third, each study used a different method to assess DEI thereby potentially over or under estimating the true energy intake. DEI in the HEMO study was assessed using a 2-day dietary intake diary on one dialysis day and one non-dialysis day, and was recorded by patients. However, in our study, DEI was assessed through face to face or telephone interview by trained staff on two non-dialysis days and one dialysis day. Fourth, at each follow-up visit, all patients in the present study received information on how to improve their protein and energy intake, and may be a major contributor to the relatively high DEI observed in our study. Still, some studies observed similar results compared to our study. In a French study, Chauveau et al. found results with a DEI of 29.8 kcal/kg/d\(^{(39)}\). On the other hand, Arslan and Kiziltan assessed a higher DEI of 34.2 kcal/kg/d in 93 MHD patients\(^{(40)}\).

The relatively high DEI level and large sample size of the current study offers an exceptional opportunity to examine the relationship of higher DEI levels with all-cause and CVD mortality in MHD patients. Our study further indicated that all-cause mortality risk increased significantly with the increase of DEI in participants with DEI $\geq$ 40 kcal/kg IBW/d. Consistently, previous studies reported that high energy intake was associated with increased risks of cancer, incident diabetes, all-cause mortality and CVD mortality in general populations\(^{(41-43)}\). Iff S et al\(^{(44)}\) found that higher relative energy intake increases mortality in patients with eGFRs
<60mL/min/1.73m². The biological mechanisms linking higher DEI to mortality risk are not well known. It has been suggested that excessive energy exposure may increase oxidative stress, leading to diminished mitochondrial function, decreased ATP productive capacity, cell death and multiple organ failure \(^{(45)}\). However, more studies are needed to further investigate our findings, and examine the underlying mechanisms.

Due to the exclusion of patients with acute infection, CRP was at a relatively low level in our current study. Furthermore, our study showed that patients with higher DEI tended to have higher CRP levels in our current study. At the same time, participants with higher DEI also had higher TC levels, and there was a positive association between CRP and TC \((P=0.038)\). It has been reported that cholesterol accumulation in macrophages and other immune cells may promote inflammatory responses, including augmentation of Toll-like receptor (TLR) signaling, inflammasome activation, and the production of monocytes and neutrophils \(^{(46)}\). Although the underlying mechanisms still need to be further investigated in future studies, we speculated that elevated TC associated with higher DEI may partly explain the increased CRP levels in this population. More importantly, the stratified analysis indicated that both TC and CRP levels did not significantly modify the association between DEI and the mortality risk.

Our findings should be interpreted in the context of several limitations. First, the DEI was assessed using the 24-hour diet recalls which was dependent on reporting by patients \(^{(10)}\). However, it’s one of the most common methods for obtaining dietary intake data as there are no alternatives to calculate accurate nutrient intake \(^{(4)}\). To minimize the potential errors, we used extensive quality control procedures and three 24-hour diet recalls including one dialysis day and two non-dialysis days to yield more accurate data. More importantly, AMPM approach to 24-hour diet recalls that was used in this study has been validated by a lot of previous studies \(^{(14, 16, 17, 47, 48)}\). Although the determination of DEI may possibly be unreliable in both obese and very thin \(^{(49)}\), the exclusion of patients with BMI<18.5 or \(\geq 30\)kg/m² did not substantially change our results (Supplemental Table 2). Second, dietary intake was assessed at only a single time which did not take into consideration the changing pattern of eating and physical behavior over the follow-up period. Third, this was an observational study. Despite extensive adjustment for known confounders in our analysis, we cannot exclude the possibility that unrecorded factors may explain some of our findings. Fourth, the study was carried out in China. Whether the results can be extrapolated to
other populations requires further verification. Therefore, further confirmation of our findings in an independent trial is greatly needed.

In conclusion, our study suggests a U-shaped association between DEI and all-cause or CVD mortality, with a turning point at about 40 and 36.5 kcal/kg IBW/d, respectively, in MHD patients. Our findings provide new insights with respect to the benefit-risk ratio of energy supplementation in MHD patients.

**Acknowledgements**

We thank the participants, investigators, and staff for their contribution to this study.

**Financial Support**

This study was supported by the National Key Technology Support Program of China (grant number 2015BAI12B00), the High-level Matching Funds of Nanfang Hospital (2014070).

**Conflict of Interest**

Dr. Xianhui Qin reports grants from the National Natural Science Foundation of China [81730019] and Outstanding Youths Development Scheme of Nanfang Hospital, Southern Medical University [2017J009].

Dr. Fanfan Hou reports grants from the Science and Technology Planning Project of Guangzhou and the National Key Research and Development Program.

Research idea and study design: ML, SLY, YML, YYY; data acquisition: SLY, YML, YYY, YL, ZHL, YZK, YL, QW, FNL, SH, AQL, QJW; data analysis/interpretation: YML, YYY, YZK, YL, QW, FNL, SH, AQL, QJW; statistical analysis: YYY, XHQ; supervision or mentorship: ML, XHQ. Each author contributed important intellectual content during manuscript drafting or revision and 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.
References


22. Daiki Watanabe, Shinji Machida, Naoki Matsumoto et al. (2018) Age Modifies the Association of Dietary Protein Intake with All-Cause Mortality in Patients with Chronic Kidney Disease. *Nutrients* 10, 1744


Accepted manuscript

*Intern Med* 256(6), 499-509.


Table 1. Baseline Characteristics of the Maintenance Hemodialysis Patients*

<table>
<thead>
<tr>
<th></th>
<th>DEI, kcal/kg IBW/d</th>
<th></th>
<th></th>
<th></th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;30</td>
<td>30&lt;~&lt;35</td>
<td>35&lt;~&lt;40</td>
<td>≥40</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>577</td>
<td>222</td>
<td>154</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>55.3 ± 15.3</td>
<td>52.5 ± 15.3</td>
<td>51.7 ± 14.7</td>
<td>53.2 ± 13.8</td>
<td>0.02</td>
</tr>
<tr>
<td>Males, N (%)</td>
<td>367 (63.6)</td>
<td>116 (52.3)</td>
<td>74 (48.1)</td>
<td>43 (50.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes, N (%)</td>
<td>167 (28.9)</td>
<td>57 (25.7)</td>
<td>34 (22.1)</td>
<td>19 (22.1)</td>
<td>0.24</td>
</tr>
<tr>
<td>Hypertension, N (%)</td>
<td>493 (85.4)</td>
<td>190 (85.6)</td>
<td>138 (89.6)</td>
<td>71 (82.6)</td>
<td>0.45</td>
</tr>
<tr>
<td>CVD, N (%)</td>
<td>120 (20.8)</td>
<td>40 (18.0)</td>
<td>31 (20.1)</td>
<td>10 (11.6)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Physical examination

|                        |          |          |          |          |
| BMI, kg/m²             | 21.1 ± 3.4 | 21.2 ± 3.2 | 21.6 ± 3.5 | 21.9 ± 3.1 | 0.07     |
| Weight, kg             | 56.8 ± 10.9 | 55.2 ± 10.6 | 55.9 ± 10.3 | 55.1 ± 11.1 | 0.21     |

Laboratory results

|                        |          |          |          |          |
| TC, mg/dL              | 157.0 ± 42.7 | 160.3 ± 42.1 | 173.8 ± 44.6 | 156.4 ± 47.0 | <0.001   |
| Triglycerides, mmol/L  | 1.8 ± 1.3 | 1.9 ± 1.4 | 2.0 ± 1.6 | 1.9 ± 1.3 | 0.28     |
| Calcium, mmol/L        | 2.1 ± 0.3 | 2.2 ± 0.3 | 2.2 ± 0.3 | 2.2 ± 0.2 | 0.01     |
| Phosphate, mmol/L      | 2.1 ± 0.7 | 2.2 ± 0.6 | 2.3 ± 0.7 | 2.2 ± 0.6 | <0.001   |
| Albumin, g/L           | 37.9 ± 3.6 | 38.5 ± 3.5 | 38.2 ± 4.5 | 38.2 ± 4.4 | 0.28     |
| CRP, mg/L              | 2.3 (0.8-7.0) | 2.6 (1.0-6.3) | 3.7 (1.2-10.2) | 3.1 (1.6-8.9) | 0.005    |
| Dialysis duration, months | 23.1 (12.4-45.3) | 25.6 (11.1-50.8) | 29.6 (12.4-54.3) | 28.1 (13.9-56.6) | 0.23     |
| Kt/V† ratio            | 1.3 ± 0.4 | 1.3 ± 0.4 | 1.4 ± 0.5 | 1.4 ± 0.4 | 0.45     |

Dietary parameters

|                        |          |          |          |          |
| DEI, kcal/kg IBW/d     | 23.7 ± 4.6 | 32.3 ± 1.4 | 37.3 ± 1.5 | 44.6 ± 4.0 | <0.001   |
| DEI, kcal/kg IBW/d‡    | 22.6 ± 4.5 | 30.2 ± 2.0 | 34.8 ± 2.1 | 41 ± 4.3  | <0.001   |
| DEI, kcal/kg ABW/d     | 23.4 ± 4.8 | 32.5 ± 1.4 | 37.4 ± 1.5 | 44.5 ± 3.6 | <0.001   |
| DEI, kcal/d            | 1344.3 ± 319.7 | 1738.7 ± 255.8 | 1987.3 ± 287.1 | 2275.3 ± 422.4 | <0.001   |
| DPI, g/kg IBW/d        | 0.9 ± 0.2 | 1.2 ± 0.2 | 1.4 ± 0.3 | 1.6 ± 0.4 | <0.001   |

Abbreviations: DEI, dietary energy intake; IBW, ideal body weight; CVD, cardiovascular diseases; BMI, body mass index; TC, total cholesterol; CRP, C-reactive protein; ABW, actual body weight; DPI, dietary protein intake;

*Continuous variables are expressed as the mean (SD) or median (25th-75th); and categorical variables are given as N (%).

†Kt/V, Kt showed effective urea clearance and duration of dialysis, and V represents the volume of distribution of urea in the body, calculated as Kt/V = -ln (post BUN/pre BUN– 0.008xt) + (4-3.5 ×post BUN/pre BUN) ×UF /post weight where t is effective dialysis time, BUN is serum blood urea nitrogen and UF is ultrafiltration.

‡Ideal body weight was defined as a body mass index of 22 kg/m².
Table 2. Threshold Effect Analyses of DEI Levels on the Risk of All-cause Mortality and CVD Mortality Using Two-piecewise Regression Models

<table>
<thead>
<tr>
<th>DEI, Kcal/kg IBW/d</th>
<th>No. of events (%)</th>
<th>Crude HR(95%CI)</th>
<th>P</th>
<th>DEI, Kcal/kg IBW/d</th>
<th>No. of events (%)</th>
<th>Adjusted* HR(95%CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;42.8</td>
<td>219(22.2)</td>
<td>0.98(0.97,1.00)</td>
<td>0.084</td>
<td>&lt;42.8</td>
<td>213(22.4)</td>
<td>0.98(0.96,1.00)</td>
<td>0.027</td>
</tr>
<tr>
<td>≥42.8</td>
<td>11(20.8)</td>
<td>1.09(0.96,1.19)</td>
<td>0.077</td>
<td>≥40</td>
<td>17(19.8)</td>
<td>1.12(1.04,1.20)</td>
<td>0.002</td>
</tr>
<tr>
<td>CVD-related mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;33.9</td>
<td>105(13.8)</td>
<td>0.96(0.94,0.99)</td>
<td>0.013</td>
<td>&lt;36.5</td>
<td>115(13.4)</td>
<td>0.96(0.93,0.99)</td>
<td>0.006</td>
</tr>
<tr>
<td>≥33.9</td>
<td>35(12.5)</td>
<td>1.05(1.00,1.11)</td>
<td>0.072</td>
<td>≥36.5</td>
<td>25(13.8)</td>
<td>1.11(1.04,1.18)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Abbreviations: DEI, dietary energy intake; IBW, ideal body weight; HR, hazard ratio; CI, confidence interval; CVD, cardiovascular diseases.

* Adjusted for dialysis center, age, sex, smoking, alcohol use, physical activity, BMI, albumin, triglycerides, total cholesterol, C-reactive protein, calcium, phosphate, hemoglobin, dialysis vintage, Kt/V, systolic blood pressure, diabetes, and history of CVD.
Table 3. Univariate and Multivariate Cox Regression Models of All-cause Mortality and CVD-related Mortality for DEI Groups

<table>
<thead>
<tr>
<th>DEI, Kcal/kg IBW/d</th>
<th>No. of events (%)</th>
<th>Crude HR (95%CI)</th>
<th>P</th>
<th>Adjusted* HR (95%CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality Categories</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>146(25.3)</td>
<td>1.31(0.88,1.95)</td>
<td>0.187</td>
<td>1.85 (1.20,2.85)</td>
<td>0.005</td>
</tr>
<tr>
<td>30-35</td>
<td>38(17.1)</td>
<td>0.88(0.54,1.42)</td>
<td>0.591</td>
<td>1.31(0.79,2.17)</td>
<td>0.301</td>
</tr>
<tr>
<td>35-40</td>
<td>29(18.8)</td>
<td>1.0(Ref)</td>
<td>--</td>
<td>1.0(Ref)</td>
<td>--</td>
</tr>
<tr>
<td>≥40</td>
<td>17(19.8)</td>
<td>1.12(0.61,2.03)</td>
<td>0.719</td>
<td>1.83 (0.99,3.40)</td>
<td>0.056</td>
</tr>
<tr>
<td>CVD-related mortality Categories</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>146(25.3)</td>
<td>1.41(1.06,1.89)</td>
<td>0.019</td>
<td>1.59(1.17,2.16)</td>
<td>0.003</td>
</tr>
<tr>
<td>30-40</td>
<td>67(17.8)</td>
<td>1.0(Ref)</td>
<td>--</td>
<td>1.0(Ref)</td>
<td>--</td>
</tr>
<tr>
<td>≥40</td>
<td>17(19.8)</td>
<td>1.21(0.71,2.05)</td>
<td>0.491</td>
<td>1.58 (0.92,2.73)</td>
<td>0.099</td>
</tr>
</tbody>
</table>

Abbreviations: DEI, dietary energy intake; IBW, ideal body weight; HR, hazard ratio; CI, confidence interval; CVD, cardiovascular diseases.

* Adjusted for dialysis center, age, sex, smoking, alcohol use, physical activity, BMI, albumin, triglycerides, total cholesterol, C-reactive protein, calcium, phosphate, hemoglobin, dialysis vintage, Kt/V, systolic blood pressure, diabetes, and history of CVD.
Figure legends

Figure 1. The association between DEI normalized to IBW and risk for all-cause mortality (A) and CVD-related mortality (B)*

* Adjusted for dialysis center, age, sex, smoking, alcohol use, physical activity, BMI, albumin, triglycerides, total cholesterol, C-reactive protein, calcium, phosphate, hemoglobin, dialysis vintage, Kt/V, systolic blood pressure, diabetes, and history of CVD.

Abbreviations: CI, confidence interval; CVD, cardiovascular diseases; DEI, dietary energy intake; HR, hazard ratio; IBW, ideal body weight.
Figure 2: Subgroup analysis of the relationship of DEI (A: <30 vs. 30-<40 kcal/kg IBW/d and B: ≥40 vs. 30-<40 kcal/kg IBW/d) with all-cause mortality

* Adjusted for dialysis center, age, sex, smoking, alcohol use, physical activity, BMI, albumin, triglycerides, total cholesterol, C-reactive protein, calcium, phosphate, hemoglobin, dialysis vintage, Kt/V, systolic blood pressure, diabetes, and history of CVD.

Abbreviations: CI, confidence interval; CVD, cardiovascular diseases; DEI, dietary energy intake; DM, diabetes mellitus; HR, hazard ratio; IBW, ideal body weight; TC, total cholesterol.