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CLINICAL RESEARCH

Associations of Dietary Protein and Energy Intakes With Protein-Energy Wasting Syndrome in Hemodialysis Patients

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Introduction: The associations of dietary protein and/or energy intakes with protein or energy wasting in patients on maintenance hemodialysis are controversial. We examined these in the Hemodialysis (HEMO) Study.

Methods: In 1487 participants in the HEMO Study, baseline dietary protein intake (grams per kilogram per day) and dietary energy intake (kilocalories per kilograms per day) were related to the presence of the protein-energy wasting (PEW) syndrome at month 12 (defined as the presence of at least 1 criteria in 2 of the 3 categories of low serum chemistry, low body mass, and low muscle mass) in logistic regression models. In additional separate models, protein intake estimated from equilibrated normalized protein catabolic rate (enPCR) was also related to the PEW syndrome.

Results: Compared with the lowest quartile, the highest quartile of baseline dietary protein intake was paradoxically associated with increased risk of the PEW syndrome at month 12 (odds ratio [OR]: 4.11; 95% confidence interval [CI]: 2.79–6.05). This relationship was completely attenuated (OR: 1.35; 95% CI: 0.88–2.06) with adjustment for baseline body weight, which suggested mathematical coupling. Results were similar for dietary energy intake. Compared with the lowest quartile of baseline enPCR, the highest quartile was not associated with the PEW syndrome at 12 months (OR: 0.78; 95% CI: 0.54–1.12).

Discussion: These data do not support the use of dietary protein intake or dietary energy intake criteria in the definition of the PEW syndrome in patients on maintenance hemodialysis.

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The 1- and 3-year survival probabilities of patients on incident hemodialysis are dismal at 74% and 50%, respectively.[1] Low body mass index (BMI),[2–7] muscle mass,[4,8,9] percentage of body fat,[9,10] history of weight loss,[11,12] serum albumin,[13,14] and total cholesterol levels[15] are some of the strongest predictors of mortality in the population on maintenance hemodialysis (MHD). It is theorized that the previously described indicators of protein or energy depletion are the result of a wasting syndrome.[16–18]

An expert panel of the International Society of Renal Nutrition and Metabolism (ISRNM) defined the protein-energy wasting (PEW) syndrome as "the state of decreased body stores of protein and energy fuels (that is, body protein and fat masses)."[19] They also developed objective criteria for the clinical definition of the PEW syndrome in patients on dialysis and patients with chronic kidney disease (CKD) (Table 1).[20] Although it has been considered that kidney disease, protein, or energy depletion is due to wasting and not decreased nutrient intake,[17,21] the ISRNM panel included dietary protein (<0.8 g/kg per day) and energy intakes (<25 kcal/kg per day) as criteria for the PEW syndrome definition in patients on MHD. To our knowledge, the validity of these dietary definitions as indicators of the PEW syndrome has not been examined; therefore, we analyzed these

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Table 1. International Society of Renal Nutrition and Metabolism Panel protein-energy wasting syndrome criteria

Low serum chemistry	Serum albumin <3.5 g/dl[a]
	Serum cholesterol <100 mg/dl
Low body mass	BMI <23 kg/m^2
	Unintentional weight loss over time: 10% over 6 months
	Body fat percentage <10%
Low muscle mass	Reduced mid-arm muscle circumference area (reduction >10% in relation to 50th percentile of reference population)
Low dietary intake	DPI <0.60 g/kg/d in stage 2–5 CKD patients or
	DPI <0.80 g/kg/d in MHD patients
	DEI <25 kcal/kg/d

BMI, body mass index; CKD, chronic kidney disease; DEI, dietary energy intake; DPI, dietary protein intake; MHD, maintenance hemodialysis.
[a]The International Society of Renal Nutrition and Metabolism serum albumin criterion was based on Bromocresol green (BCG) method measurement. In the HEMO study, serum albumin was measured by the nephelometry method, which is approximately 0.3 g/dl lower than that obtained with BCG method.[20]

in a retrospective analysis of the Hemodialysis (HEMO) study.[22,23]

MATERIALS AND METHODS

The details of the HEMO Study design were described elsewhere.[22,23] In brief, the HEMO study was a 2-by-2 factorial design randomized control trial of standard- or high-dose hemodialysis and high- or low-flux dialyzers. Eligibility criteria were patients aged 18 to 80 years old who underwent in-center hemodialysis 3 times per week for ≥3 months. A total of 1846 participants were randomized in 15 clinical centers from March 1995 to October 2000, and followed until December 2001.

Trained study coordinators following standardized protocols conducted study visits. Demographics and comorbidity data were obtained with standardized questionnaires. The heights of the patients, obtained at study entry, and postdialysis weight measurements, obtained monthly, were used to calculate BMI. mid-arm muscle circumference was calculated from mid-arm circumference, and triceps skinfold thicknesses were measured with previously published protocols.[24] Body fat percentage was calculated as: body fat percentage = (1.20 × BMI) + (0.23 × age) − (10.8 × sex) − 5.4, (sex: females = 0, males = 1). Details of dietary assessment in the HEMO study were published elsewhere.[25] Serum albumin was measured at a central laboratory by nephelometry. Equilibrated normalized protein catabolic rate (enPCR) were calculated from formal urea kinetic models using both single and double pool Kt/V urea. Total serum cholesterol was assessed locally at each clinical center laboratory.

Definitions of PEW syndrome individual criteria and categories are summarized in Table 1. Because the goal of the present analyses was to examine the relationships of baseline dietary protein intake (DPI) and dietary energy intake (DEI) with the rest of the PEW

Table 2. Baseline characteristics by dietary protein intake and dietary energy intake groups (N = 1487)

	Low DPI <0.8 g/kg/d (*n* = 608)	High DPI ≥0.8 g/kg/d (*n* = 879)	*P* value	Low DEI <25 kcal/kg/d (*n* = 957)	High DEI ≥25 kcal/kg/d (*n* = 530)	*P* value
Age (yr)	59.1 ± 12.7	56.0 ± 14.8	<0.001	59.4 ± 12.6	53.4 ± 15.7	<0.001
Black (%)	66.4%	63.0%	0.18	67.2%	59.4%	0.003
Male (%)	35.4%	49.5%	<0.001	38.0%	54.0%	<0.001
ESRD duration (yr)	2.0 (1.0, 4.1)	2.3 (0.9, 5.2)	0.10	2.0 (0.9, 3.9)	2.7 (1.0, 6.5)	0.001
Fistula (%)	28.5%	38.7%	<0.001	28.4%	45.5%	<0.001
Kt/V group (%)	50.2%	50.2%	1.00	49.8%	50.8%	0.74
Flux group (%)	51.5%	49.9%	0.56	50.4%	50.9%	0.83
Smoking (%)	46.1%	51.1%	0.06	47.2%	52.3%	0.06
Alcohol use (%)	14.5%	16.8%	0.22	13.9%	19.4%	0.005
Diabetes (%)	51.5%	37.4%	<0.001	51.5%	28.1%	<0.001
Atherosclerotic conditions (%)	45.7%	39.1%	0.01	44.7%	36.6%	0.002
Cancer (%)	9.0%	7.8%	0.41	8.6%	7.9%	0.67
Congestive heart failure (%)	9.5%	11.5%	0.23	10.9%	10.4%	0.77
DPI (g/kg/d)	0.62 (0.51, 0.71)	1.10 (0.93, 1.36)	<0.001	0.74 (0.58, 0.92)	1.22 (1.02, 1.48)	<0.001
DEI (kcal/kg/d)	15.6 (12.4, 18.9)	26.4 (21.4, 32.7)	<0.001	17.6 (13.7, 21.2)	31.3 (27.5, 37.1)	<0.001
TPI (g/d)	44.7 (37.2, 52.7)	72.0 (62.2, 85.8)	<0.001	52.1 (41.6, 66.2)	74.4 (63.3, 89.6)	<0.001
TEI (kcal/d)	1162 (936, 1433)	1692 (1401, 2048)	<0.001	1225 (1012, 1497)	1962 (1697, 2308)	<0.001
enPCR (g/kg/d)	0.98 (0.83, 1.14)	1.04 (0.90, 1.22)	<0.001	1.01 (0.86, 1.17)	1.02 (0.88, 1.21)	0.38
Body weight (kg)	75.1 (65.8, 85.1)	63.8 (56.0, 72.3)	<0.001	72.0 (63.0, 83.1)	61.3 (54.0, 68.8)	<0.001

DEI, dietary energy intake; DPI, dietary protein intake; enPCR, equilibrated normalized protein catabolic rate; ESRD, end-stage renal disease; TEI, total energy intake; TPI, total protein intake.
Mean ± SD, % or median (25th, 75th percentiles) are presented.

Table 3. Month 12 distribution of PEW variables and the prevalence of PEW syndrome by baseline quartiles of DPI (g/kg/day) (N = 1487)

	Lowest quartile <0.67 (n = 372)	Second quartile 0.67–0.88 (n = 371)	Third quartile 0.89–1.16 (n = 373)	Highest quartile ≥1.16 (n = 371)	P value
Serum albumin (g/dl)	3.5 ± 0.4	3.6 ± 0.4	3.6 ± 0.4	3.6 ± 0.4	0.003
Serum cholesterol (mg/dl)	173.3 ± 40.9	169.5 ± 40.3	163.4 ± 40.0	159.0 ± 38.2	<0.001
BMI (kg/m^2)	28.7 ± 5.7	26.6 ± 5.0	25.0 ± 4.2	22.3 ± 3.7	<0.001
Weight change over 12 mo (%)	−0.1 (−4.8, 2.7)	−0.5 (−4.3, 3.7)	0.5 (−2.8, 4.2)	0.9 (−3.3, 5.1)	0.008
Body fat percentage	38.9 ± 10.1	35.9 ± 9.1	32.5 ± 8.9	27.5 ± 8.3	<0.001
MAMC (cm)	26.5 ± 4.0	25.1 ± 3.7	24.6 ± 3.3	23.2 ± 3.3	<0.001
Prevalence of PEW syndrome (%)	13.7	16.4	22.5	39.4	<0.001

BMI, body mass index; DPI, dietary protein intake; MAMC, mid-arm mass circumference; PEW, protein-wasting energy.
Mean ± SD, % or median (25th, 75th percentiles) are presented.

syndrome categories at month 12, the PEW syndrome at month 12 was defined as the presence of at least 1 criteria in 2 of the 3 nondietary categories (low serum chemistry, low body mass, or low muscle mass).

Statistical Methods

Descriptive statistics for baseline clinical characteristics and month 12 PEW variables were reported as means, SDs, or medians, 25th and 75th percentiles for numeric variables, and proportions for categorical variables. Numeric and categorical variables were compared between the 2 groups or between quartiles of DPI and total protein intake using t-tests, 1-way analysis of variance, or χ^2 tests as appropriate. Skewed variables were compared by a nonparametric equality-of-medians test.[26]

Associations of Baseline DPI and DEI With PEW Syndrome at Month 12

Using the lowest quartiles as the reference, in separate logistic models, the presence of the PEW syndrome at month 12 was related to the second to fourth quartiles of baseline DPI and DEI. These models were adjusted for baseline age, sex, race, duration of end-stage renal disease, dialysis access, Kt/V group, flux group, smoking, alcohol use, diabetes, atherosclerotic conditions, congestive heart failure, cancer, and clinical center. The relationships of baseline DPI and DEI with the presence of the PEW syndrome at month 12 might have been driven by mathematical coupling (body weight is in the denominator of DPI and DEI and lower body weight is an indicator of the PEW syndrome); therefore, these models were repeated with additional adjustment for baseline postdialysis weight.

Furthermore, the relationships of baseline DPI and DEI with the presence of the PEW syndrome at month 12 could be nonlinear, with an increase in the odds of the PEW syndrome below a given threshold for DPI and DEI. To investigate this further, natural cubic spline regressions[27,28] using 3 knots (placed as 0.48, 0.89, 1.50 g/kg per day for DPI and 11.7, 21.6, 36.3 kcal/kg per day for DEI) were performed to estimate odds ratio of the PEW syndrome at month 12 for continuous baseline values of DPI and DEI separately. These analyses included the same covariates as used in the analyses that compared DPI and DEI quartiles. Median values of DPI and DEI were used as reference values for expression of odds ratios. Although all available data were included in the spline regressions, we restricted graphic displays of the results of these analyses DPI and DEI values to between the 5th percentiles (0.38 g/kg per day for DPI and 9.6 kcal/kg per day for DEI) and the 95th percentiles (1.73 g/kg per day for DPI and 42.3 kcal/kg per day for DEI) in the respective baseline distributions, because spline regressions are unstable toward the extremes of the range of the predictor variable.

Table 4. Month 12 distribution of PEW variables and the prevalence of PEW syndrome by baseline quartiles of DEI (kcal/kg/day) (N = 1487)

	Lowest quartile <16.0 (n = 373)	Second quartile 16.0–21.7 (n = 371)	Third quartile 21.8–28.2 (n = 372)	Highest quartile ≥28.2 (n = 371)	P value
Serum albumin (g/dl)	3.5 ± 0.3	3.6 ± 0.4	3.6 ± 0.4	3.7 ± 0.4	<0.001
Serum cholesterol (mg/dl)	175.7 ± 41.7	166.8 ± 39.5	164.1 ± 38.4	158.6 ± 39.4	<0.001
BMI (kg/m^2)	29.3 ± 5.6	26.4 ± 4.8	24.8 ± 4.4	22.1 ± 3.3	<0.001
Weight change over 12 mo (%)	0 (−4.3, 3.0)	−0.6 (−4.2, 3.6)	0.2 (−3.2, 5.0)	0.9 (−3.0, 4.7)	0.005
Body fat percentage	40.2 ± 9.4	35.6 ± 9.0	32.4 ± 9.0	26.7 ± 7.7	<0.001
MAMC (cm)	26.4 ± 4.0	25.3 ± 3.8	24.4 ± 3.5	23.4 ± 3.1	<0.001
Prevalence of PEW (%)	12.3	19.7	22.3	37.7	<0.001

BMI, body mass index; DEI, dietary energy intake; MAMC, mid-arm mass circumference; PEW, protein-wasting energy.
Mean ± SD, % or median (25th, 75th percentiles) are presented.

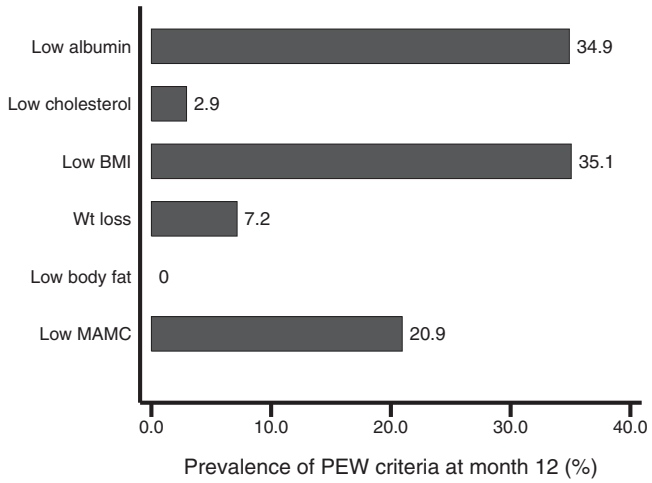

Figure 1. Prevalence of protein-energy wasting (PEW) criteria at month 12 in the entire cohort (N = 1487). BMI, body mass index; MAMC, mid-arm mass circumference; Wt, weight.

It could be argued that estimation of protein intake from diet might be unreliable. Therefore, in additional analyses, we used enPCR estimated from urea kinetics modeling as a measure of protein intake and repeated the preceding analyses. Urea kinetics modeling was carefully performed with a standardized protocol in the HEMO Study, and the details have been published elsewhere.[22,23]

RESULTS

The baseline clinical characteristics by DPI and DEI groups are presented in Table 2. At baseline, 40.9% had DPI <0.8 kg/kg per day and 64.4% had DEI <25 kcal/kg per day. Those with lower DPI or DEI were older and more likely to be women. At baseline, lower DPI and lower DEI were associated with higher body weight.

The aim of the study was to examine the longitudinal associations of baseline dietary variables with the presence of the PEW syndrome at month 12. Furthermore, weight loss variables for PEW syndrome were defined by the baseline and 12-month post-dialysis weights. Hence, the distribution of PEW variables at month 12 by DPI and DEI quartiles are

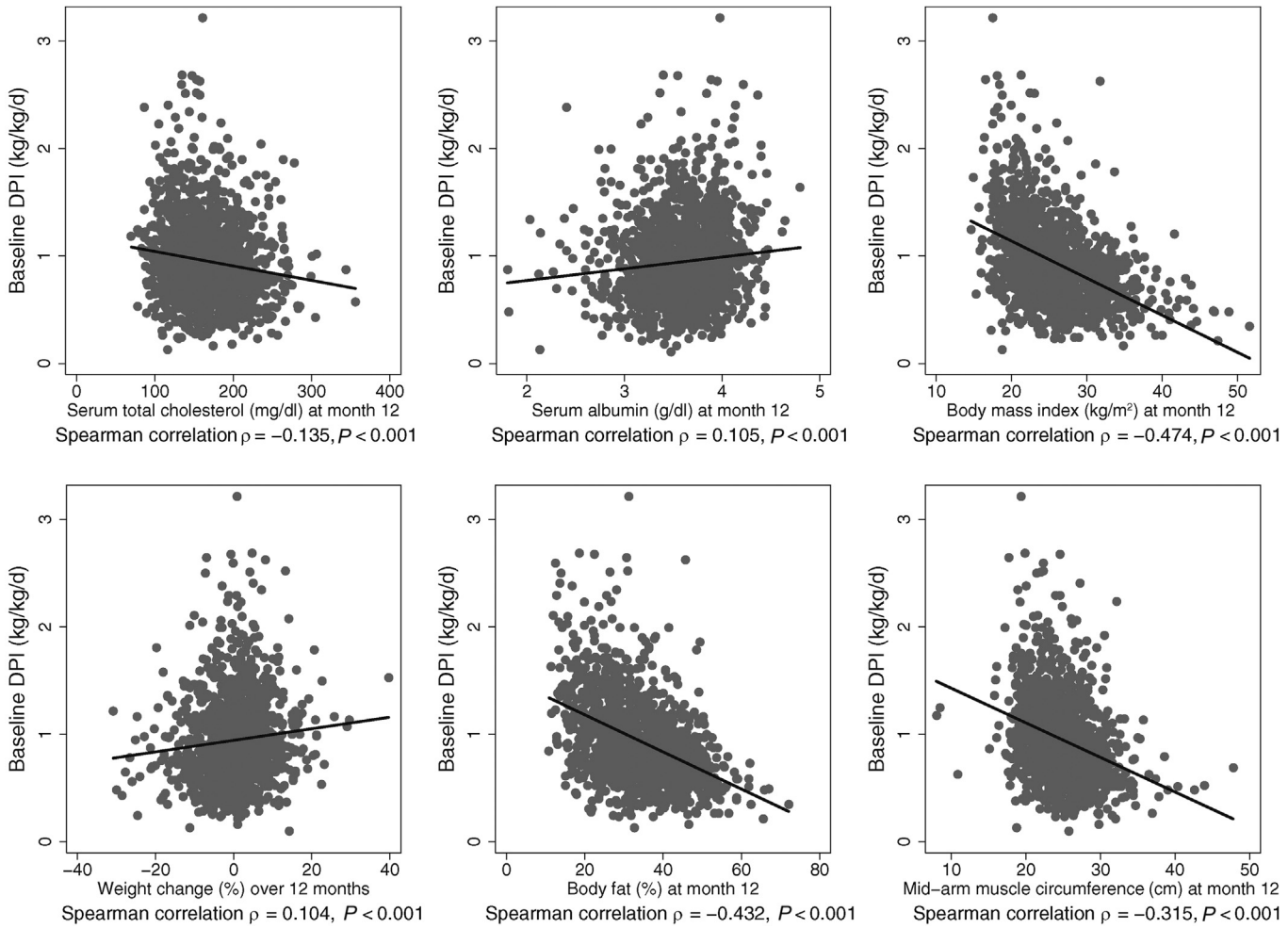

Figure 2. Scatterplots of baseline dietary protein intake (DPI) with month 12 protein-energy wasting variables.

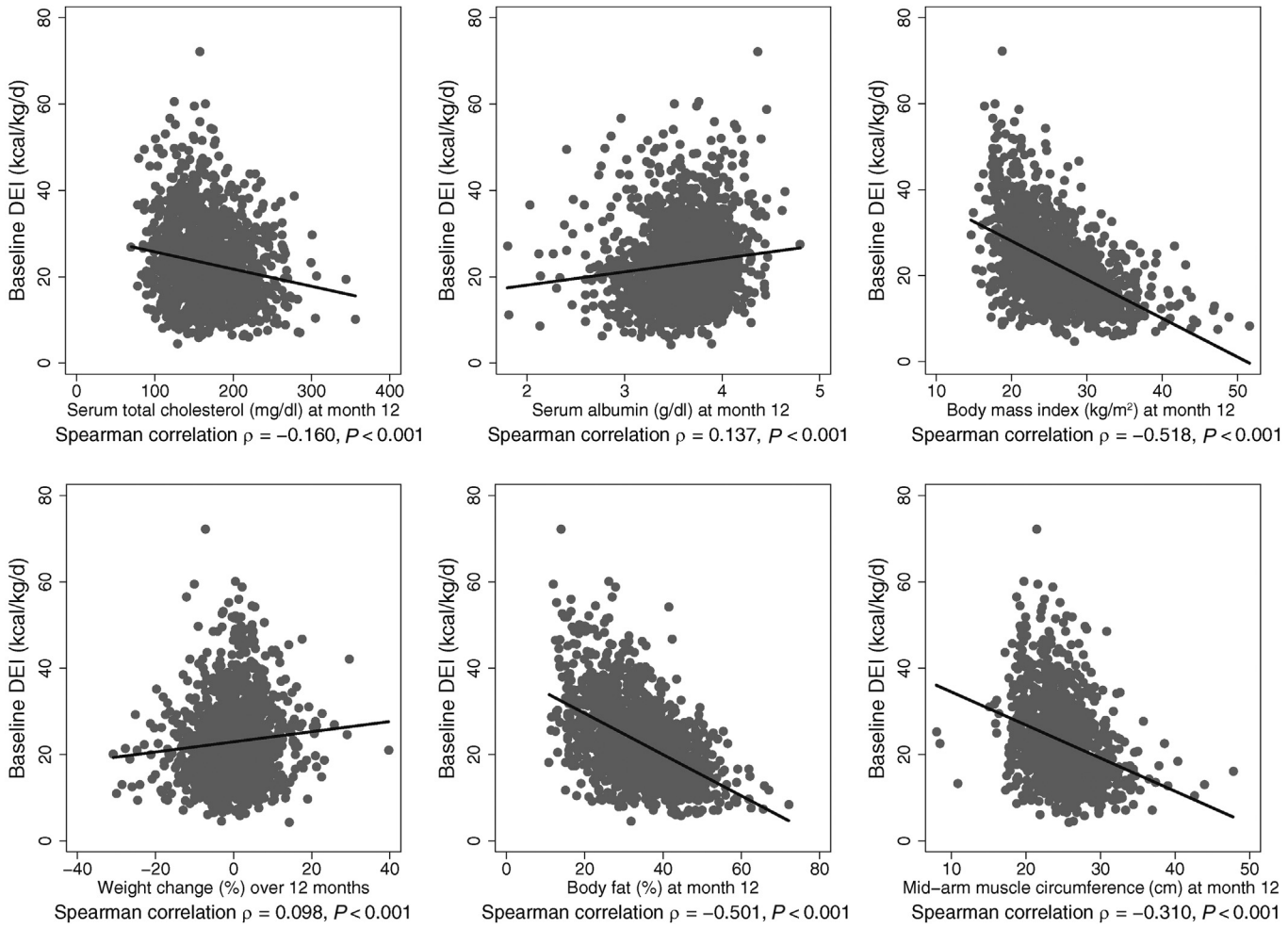

Figure 3. Scatterplots of baseline dietary energy intake (DEI) with month 12 protein-energy wasting variables.

listed in Tables 3 and 4. As shown in Figure 1, the prevalence of PEW variables at month 12 varied considerably. Although the prevalence of a low BMI was 35.1%, no patients had a low percentage of body fat (<10%).

Scatterplots relating baseline DPI, DEI, and enPCR with month 12 PEW syndrome variables are presented in Figures 2 to 4. Both DPI and DEI had an inverse relationship with body size, percentage of body fat, and mid-arm muscle circumference, whereas enPCR had weak positive relationship with body size and mid-arm muscle circumference.

The prevalence of the PEW syndrome defined as the presence of at least 1 variable in 2 of the 3 categories (low serum chemistry, low body mass, and low muscle mass listed in Table 1) was 23.0% at the month 12 follow-up visit. The prevalence of the PEW syndrome at month 12 was 13.7% in the lowest baseline DPI quartile and the 39.4% in the highest baseline DPI quartile. In a multivariate logistic regression model, compared with those in the lowest baseline DPI quartile, those in the highest baseline DPI quartile had 4.11-fold (95% confidence interval: 2.79–6.05) higher odds of having the PEW syndrome at month 12 (Figure 5a). Similar relationships of the PEW syndrome with DEI quartiles were seen (Figure 5C).

This contrarian finding of lower risk of the PEW syndrome at month 12 in those with low baseline DPI and DEI could reflect mathematical coupling (because both DEI and DPI include body weight in the denominator and those with PEW have lower body weight). When the preceding logistic regression models were adjusted for baseline body weight, the previous associations were attenuated (Figures 5b and 5d).

Similar results were obtained using regression models with cubic splines that did not require categorizing participants into quartiles. In spline regression

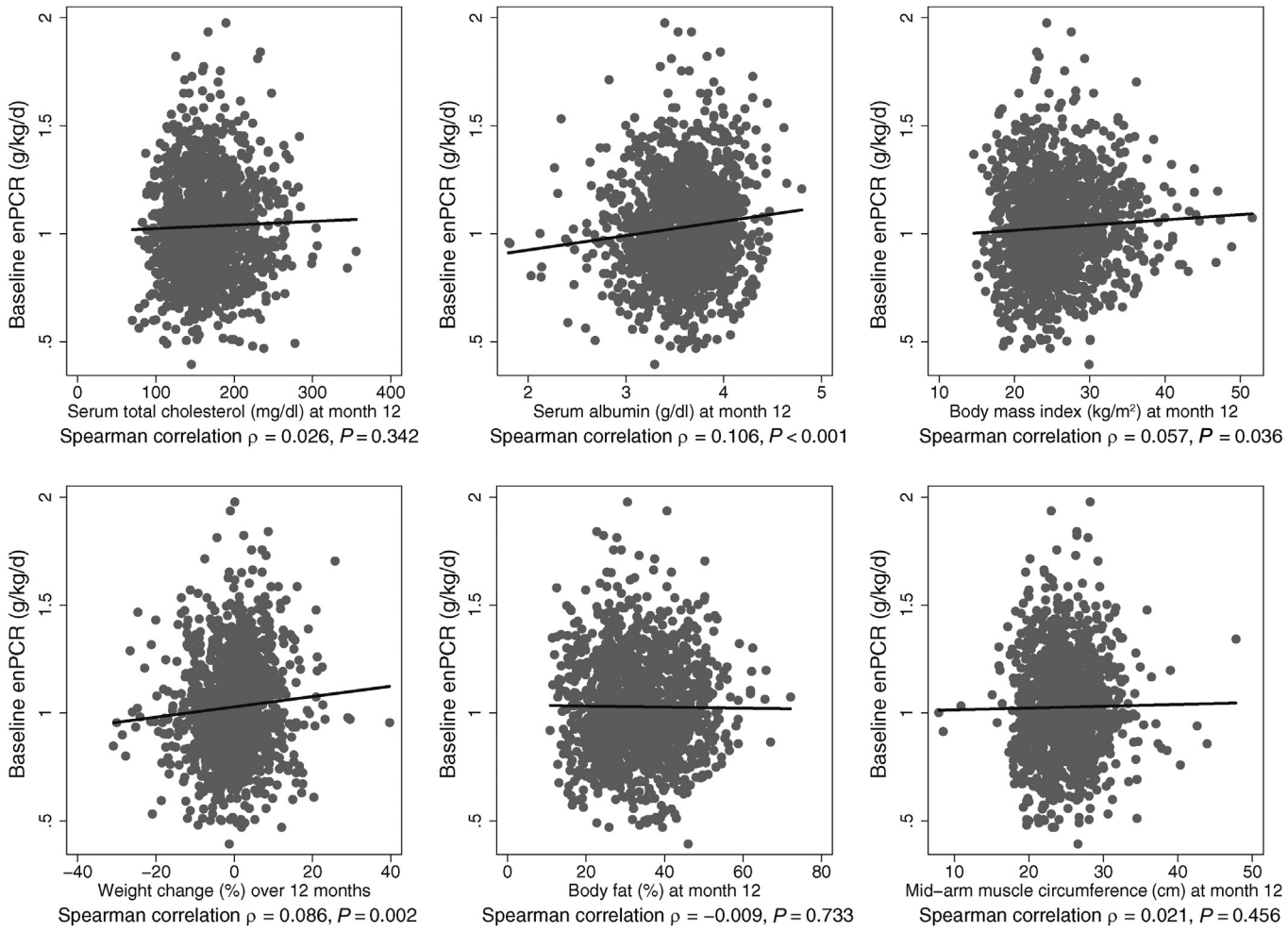

Figure 4. Scatterplots of baseline equilibrated normalized protein catabolic rate (enPCR) with month 12 protein-energy wasting variables.

models unadjusted for baseline body weight, there was an increase in the odds of having the PEW syndrome at month 12 with a higher baseline DPI or DEI (Figures 6a and 6c), which was markedly attenuated when adjusted for baseline body weight (Figures 6b and 6d).

In additional analyses, we used enPCR as another measure of protein intake. Month 12 distribution of PEW variables and the prevalence of PEW syndrome by baseline quartiles of enPCR are presented in Table 5. Results of logistic regression models relating baseline enPCR quartiles and spline regression models relating enPCR as a continuous variable with the presence of the PEW syndrome at month 12 are shown in Figure 7. These results suggested that there was no relationship of baseline enPCR with PEW syndrome at month 12.

DISCUSSION

The current national guidelines recommend a DPI of 0.8 g/kg per day in the general population and 1.2 g/kg per day in patients on hemodialysis.[29] The ISRNM panel used a conservative definition of <0.8 g/kg per day as a PEW criterion for patients on MHD, with the expectation that for most patients on hemodialysis, the dietary protein requirements could be even higher. Hence, in this study we examined the relationships of baseline DPI and DEI with the PEW syndrome at month 12 using the quartiles of these variables at baseline. Interestingly, those in the highest quartile of DPI or DEI had a higher risk of the PEW syndrome. This was the result of mathematical coupling induced by the use of body weight as the denominator in the definition of DPI and DEI. However, when adjusted for baseline body weight, we still did not observe lower risk of PEW with higher baseline DPI or DEI (Figure 5). Similarly, we did not observe a relationship of low DPI or low DEI with increased odds of the PEW syndrome (Figure 6) in the spline regression models.

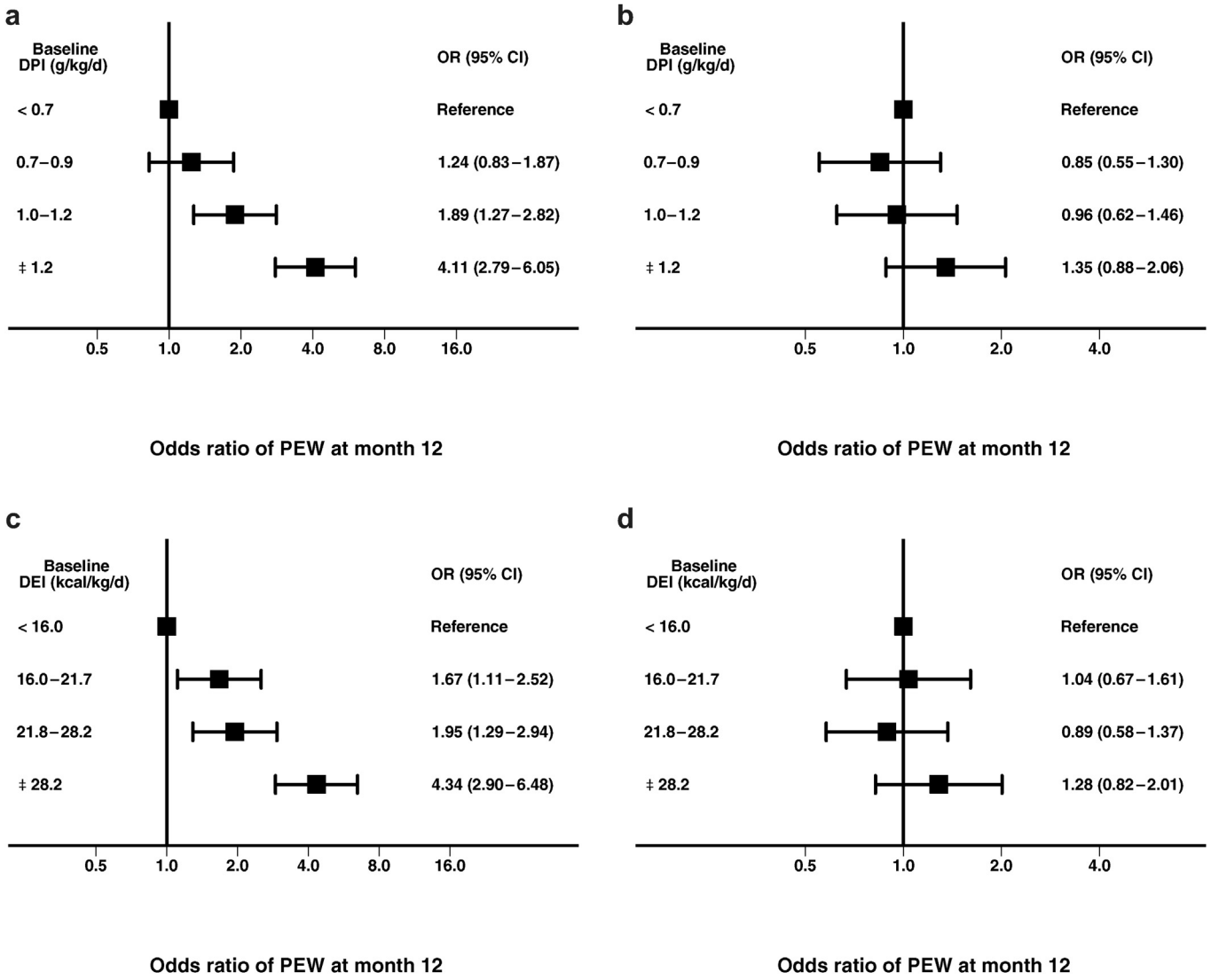

Figure 5. Logistic regression models relating baseline dietary protein intake (DPI) and dietary energy intake (DEI) quartiles to the presence of the protein-wasting energy (PEW) syndrome at month 12 without (panels a and c) and with (panels b and d) adjustment for baseline body weight (N = 1487). (a,c) Model adjusted for baseline age, sex, race, duration of end-stage renal disease, dialysis access, Kt/V, flux group, smoking, alcohol use, diabetes, IHD, cerebrovascular disease, pulmonary vascular disease, congestive heart failure, cancer, and clinical center. (b,d) Model with additional adjustment for baseline postdialysis weight. CI = confidence interval; IHD = ischemic heart disease; OR = odds ratio.

It could be argued that estimation of protein intake from 24-hour dietary recall is limited by reliance on memory and that the responses may be less accurate or unrepresentative of typical intakes.[30] The accuracy of diet recalls can be questioned. For instance, the mean DEI of those who reported DEI of <25 kcal/kg per day was only 17.3 ± 4.6 kcal/kg per day. The contradiction of stable body mass despite low reported DEI in patients on long-term hemodialysis has been previously studied; those who are overweight tend to under-report their calorie intake.[31] Therefore, we also examined the associations of protein intake as estimated from urea kinetics with enPCR. Urea kinetics was carefully performed following a standardized protocol in the HEMO study because the dialysis dose intervention was based on Kt/V.[22,23] However, we did not observe an association of low enPCR with an increased risk of PEW syndrome (Figure 7).

The ISRNM panel noted that depletion of protein or energy stores in kidney disease is not related to nutrient intake but rather is the result of wasting induced by hypercatabolism from multiple factors, including uremic toxins, inflammation, oxidative

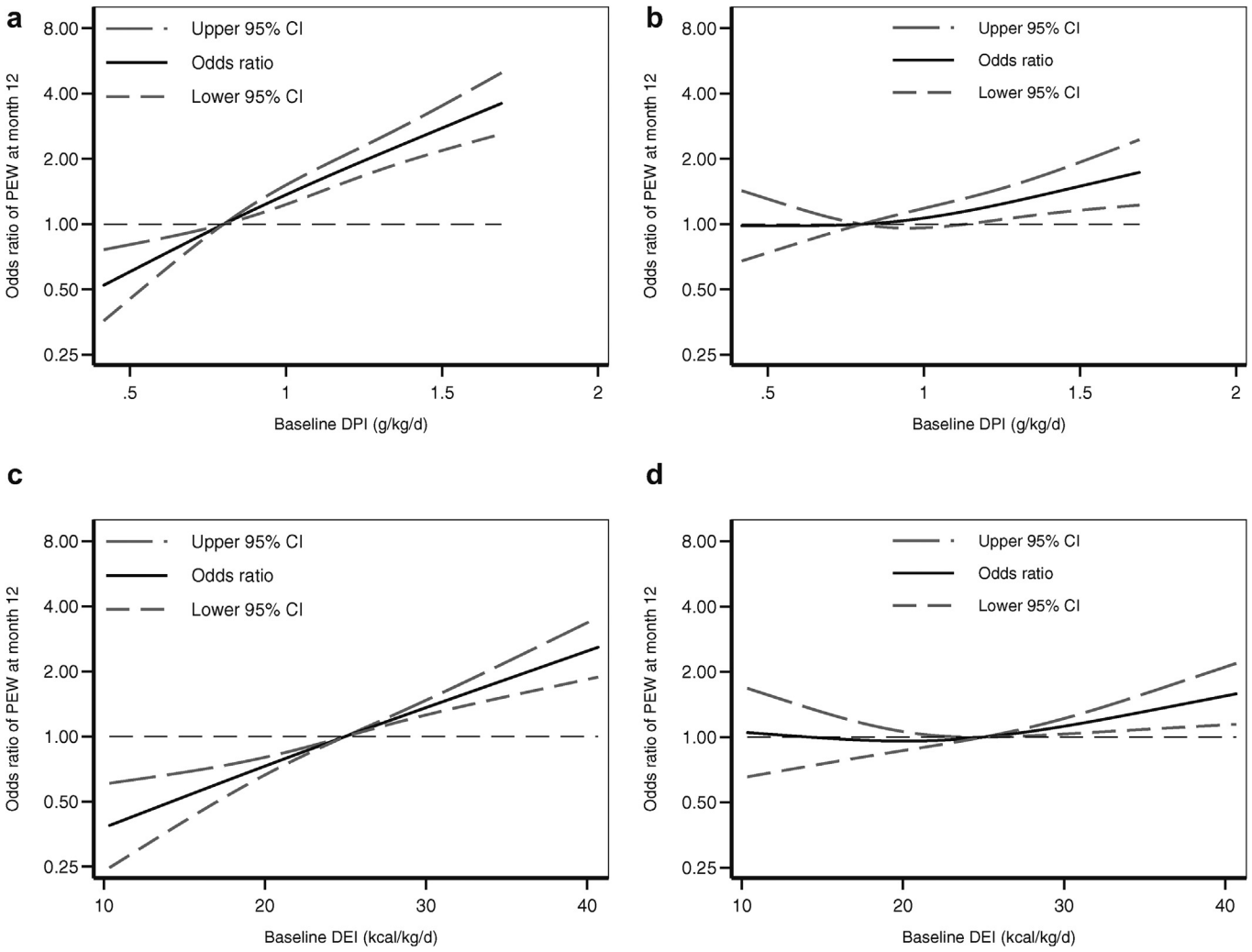

Figure 6. Natural cubic spline regression models relating baseline dietary protein intake (DPI) and dietary energy intake (DEI) as continuous variables with the presence of the protein-wasting energy (PEW) syndrome at month 12 without and with adjusting for baseline body weight (N = 1487). (a,c) Model adjusted for baseline age, sex, race, duration of end-stage renal disease, dialysis access, Kt/V, flux group, smoking, alcohol use, diabetes, IHD, cerebrovascular disease, pulmonary vascular disease, congestive heart failure, cancer, and clinical center. (b,d) Model with additional adjustment for baseline postdialysis weight. CI = confidence interval; IHD = ischemic heart disease.

stress, and metabolic acidosis.[19] The present analyses supported the concept that depleted protein and energy stores in patients on MHD might not be related to dietary intake.[16–18]

The strengths of this study included the careful collection of data in the HEMO study and the detailed examination of protein and energy intakes as continuous and categorical variables, as well as different methodologies of protein intake assessment (dietary and urea kinetic modeling methods). The limitations of the study included the observational analysis of the existing trial data.

Table 5. Month 12 distribution of PEW variables and the prevalence of PEW syndrome by baseline quartiles of enPCR (g/kg/d) (N = 1487)

	Lowest quartile <0.87 (*n* = 372)	2nd quartile 0.87–1.01 (*n* = 371)	3rd quartile 1.02–1.18 (*n* = 371)	Highest quartile ≥1.18 (n = 373)	*P* value
Serum albumin (g/dl)	3.6 ± 0.4	3.6 ± 0.4	3.6 ± 0.4	3.7 ± 0.4	0.001
Serum cholesterol (mg/dl)	163.2 ± 40.8	168.1 ± 41.7	167.4 ± 39.4	166.1 ± 38.9	0.41
BMI (kg/m^2)	25.1 ± 5.0	25.7 ± 5.2	25.9 ± 5.6	25.9 ± 5.4	0.13
Weight change over 12 mo (%)	–0.3 (–4.1, 3.4)	0 (–4.0, 3.9)	0 (–3.5, 4.0)	1.0 (–3.0, 5.0)	0.15
Body fat percentage	33.6 ± 9.9	34.1 ± 9.6	34.2 ± 10.5	33.1 ± 10.3	0.54
MAMC (cm)	24.7 ± 3.9	25.0 ± 3.9	24.8 ± 3.5	24.9 ± 3.8	0.74
Prevalence of PEW (%)	24.5 ± 43.0	24.5 ± 43.1	20.8 ± 40.6	22.3 ± 41.6	0.55

BMI, body mass index; enPCR, equilibrated normalized protein catabolic rate; MAMC, mid-arm mass circumference; PEW, protein-wasting energy.
Mean ± SD, % or median (25th, 75th percentiles) are presented.

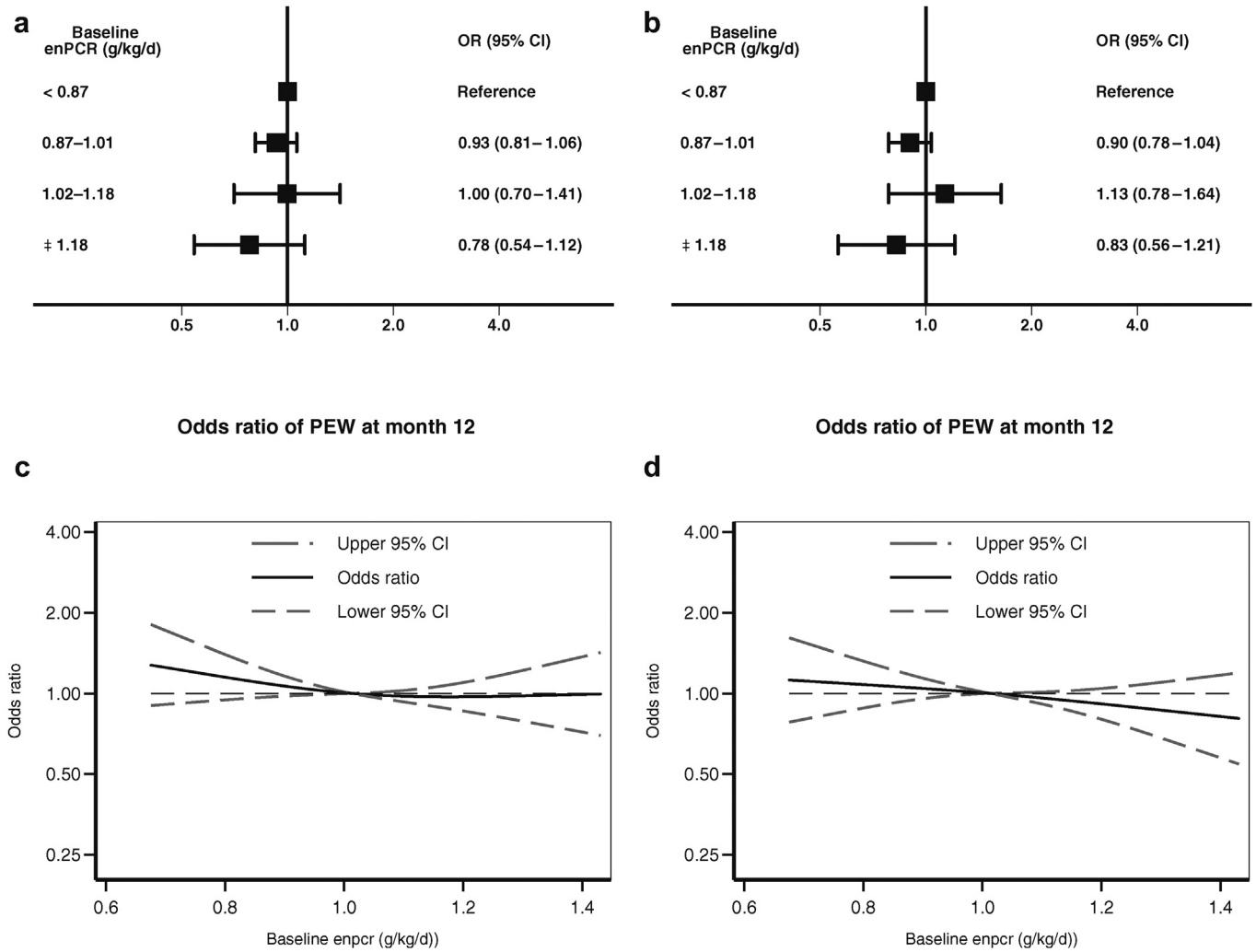

Figure 7. Logistic and spline regression models relating baseline equilibrated normalized protein catabolic rate (enPCR) to the presence of the protein-wasting energy (PEW) syndrome at month 12 without and with adjustment for baseline body weight (N = 1487). (a,c) Model adjusted for baseline age, sex, race, duration of end-stage renal disease, dialysis access, Kt/V, flux group, smoking, alcohol use, diabetes, IHD, cerebrovascular disease, pulmonary vascular disease, congestive heart failure, cancer, and clinical center. (b,d) Model with additional adjustment for baseline postdialysis weight. CI = confidence interval; IHD = ischemic heart disease.

In summary, as a result of mathematical coupling, high baseline DPI or DEI is associated with increased odds of the PEW syndrome at follow-up in patients on MHD. Inclusion of these variables in the definition of the PEW syndrome will result in erroneous conclusions about the presence of the PEW syndrome.

DISCLOSURES

All the authors declared no competing interests.

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