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Associations of Protein–Energy Wasting Syndrome Criteria With Body Composition and Mortality in the General and Moderate Chronic Kidney Disease Populations in the United States

Srinivasan Beddhu[1,2], Xiaorui Chen[2], Guo Wei[2], Dominic Raj[4], Kalani L. Raphael[1,2], Robert Boucher[2], Michel B. Chonchol[5], Maureen A. Murtaugh[2] and Tom Greene[2,3]

[1]Veterans Affairs Salt Lake City Healthcare System, Salt Lake City, Utah, USA; [2]Department of Medicine, University of Utah School of Medicine, Salt Lake City, Utah, USA; [3]Department of Population Health Sciences, University of Utah School of Medicine, Salt Lake City, Utah, USA; [4]Department of Medicine, George Washington School of Medicine, Washington, DC, USA; and [5]Department of Medicine, University of Colorado School of Medicine, Denver, Colorado, USA

Introduction: It is unknown whether the criteria used to define protein–energy wasting (PEW) syndrome in dialysis patients reflect protein or energy wasting in the general and moderate CKD populations.

Methods: In 11,834 participants in the 1999 to 2004 National Health and Nutrition Examination Survey, individual PEW syndrome criteria and the number of PEW syndrome categories were related to lean body and fat masses (measured by dual-energy absorptiometry) using linear regression in the entire cohort and CKD subpopulation.

Results: Serum chemistry, body mass, and muscle mass PEW criteria tended to be associated with lower lean body and fat masses, but the low dietary protein and energy intake criteria were associated with significantly higher protein and energy stores. When the number of PEW syndrome categories was defined by nondietary categories alone, there was a monotonic inverse relationship with lean body and fat masses and a strong positive relationship with mortality. In contrast, when dietary category alone was present, mean body mass index was in the obesity range; the additional presence of 2 nondietary categories was associated with lower body mass index and lower lean body and fat masses. Thus, the association of a dietary category plus 2 additional nondietary categories with lower protein or energy stores was driven by the presence of the 2 nondietary categories. Results were similar in CKD subgroup.

Discussion: Hence, a definition of PEW syndrome without dietary variables has face validity and reflects protein or energy wasting.

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Measures of protein and energy stores such as body size,[1–7] muscle mass,[8,9] fat mass,[8,9] serum albumin,[10–12] and cholesterol[13] levels are strong predictors of survival in dialysis patients. The International Society of Renal Nutrition and Metabolism (ISRNM) developed objective criteria for the definition of the Protein-Energy Wasting (PEW) syndrome in dialysis and chronic kidney disease (CKD) patients.[14] Since PEW syndrome imposes high morbidity and mortality in dialysis patients, these efforts to define specific criteria for this syndrome are laudable. The PEW syndrome might be considered a specific "cachectic" condition of relevance for kidney disease and related chronic conditions. Nonetheless, whether these criteria are reflective of protein or energy stores or whether they associate with mortality in the general and moderate CKD populations have not been examined. Therefore, we tested the hypothesis that the PEW syndrome criteria reflect protein and/or energy wasting and associate with increased mortality in the general and CKD populations using the 1999 to 2004 National Health and Nutrition Examination Survey (NHANES) data.

Correspondence: Srinivasan Beddhu, 85 North Medical Drive East, Room 201, Salt Lake City, Utah 84112, USA. E-mail: Srinivasan.beddhu@hsc.utah.edu

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MATERIALS AND METHODS

Study Population and Baseline Data

The National Center for Health Statistics (NCHS) is conducting NHANES to sample a representative population of the noninstitutionalized US population. NHANES data collection details have been published elsewhere.[15]

In brief, trained study personnel conducted a home interview followed by an examination at a mobile examination center. Demographic and comorbidity data over the past year were by self-report. Participants were asked about their current and past weight 1 year ago (in pounds, without clothes or shoes) and whether any weight loss was intentional. Height, weight, mid-arm circumference, and triceps skinfold thickness were measured following standardized protocols.[16] Body mass index (BMI) was calculated from measured height and weight. Mid-arm muscle circumference (MAMC) was calculated as mid-arm circumference (mm) − (3.14 × triceps skin fold [mm]). Whole-body dual-energy x-ray absorptiometry (DXA) scans were performed with a Hologic QDR-4500A fanbeam densitometer (Hologic, Inc., Bedford, MA).[17] Hologic software version 8.26:a3* was used to administer all scans. A computer-assisted dietary interview (CADI) system was administered by trained study personnel to obtain 24-hour dietary recalls.[18] The interview files were imported into the University of Texas Food Intake Analysis System (FIAS) for coding. FIAS version 3.99 with the USDA 1994–1998 Survey Nutrient Database was used to code and report the dietary data. Serum albumin was measured with a bromcresol purple method using a Hitachi 917 analyzer (Roche Diagnostics, Indianapolis, IN), serum C-reactive protein using a Dade Behring Nephelometer II Analyzer (Dade Behring Diagnostics Inc., Somerville, NJ), and serum total cholesterol using a Hitachi 704 analyzer in the NHANES central laboratories following standardized protocols. The most recent Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to estimate glomerular filtration rate (GFR).[19]

Definitions of Individual Criteria and Categories for PEW Syndrome

Definitions of individual criteria and categories for PEW syndrome are summarized in Table 1. The phrase "PEW criteria" refers to each individual variable, whereas the phrase "PEW category" refers to the grouping of each individual variable as serum chemistry, body mass, muscle mass, and dietary intake categories. Per ISRNM, the presence of at least 1 criteria in 3 of the 4 categories constitutes PEW syndrome. The ISRNM serum albumin criterion was based on the bromcresol green method measurement. In NHANES, serum albumin was measured by the bromcresol purple method, which is ∼0.55 g/dl lower than that obtained with the bromcresol green method.[20] Hence, we used bromcresol purple serum albumin < 3.25 g/dl (which is approximate bromcresol green serum albumin < 3.8 g/dl) for the definition of PEW in this analysis. Self-reported weight (current and 1 year prior) and whether there was an intention to lose weight were used to estimate unintentional weight loss; >10% unintentional loss over the past year was used as a PEW criterion. The ISRNM panel considered BMI < 23 kg/m^2 as a PEW criterion in dialysis patients, whereas BMI < 18.5 kg/m^2 was considered undernutrition in the general population.[21] There were only 197 participants with BMI < 18.5 kg/m^2 in this population. The fifth percentile of BMI in this cohort was 19.93 kg/m^2. As a result, we chose to use a cut-off of BMI < 20 kg/m^2 for PEW definition in this study. In additional sensitivity analyses, we also examined a BMI definition of <18.5 kg/m^2 as a PEW criterion. Total body fat% as measured by DXA was used. The ISRNM panel used total body fat percentage (fat%) of <10% as a PEW criterion. Because none of the study population had total body fat% of <10%, we dropped this criterion in this analysis. Based on the reported protein and calorie intake from the 24-hour dietary recall data and measured body weight, dietary protein intake and dietary energy intake were defined as ratios of reported dietary intakes and body weight in accordance with the ISRNM criteria (Table 1).

Table 1. ISRNM PEW syndrome criteria and categories[a]

Categories	Criteria within categories
Low serum chemistry	Serum albumin < 3.8 g/dl[b] Serum cholesterol < 100 mg/dl Serum prealbumin < 30 mg/dl[c]
Low body mass	BMI < 23 kg/m^2[d] Unintentional weight loss over time: 10% over 6 mo[e] Body fat percentage < 10%[f]
Low muscle mass	Muscle wasting: reduced muscle mass 5% over 3 mo or 10% over 6 mo[c] Reduced mid-arm muscle circumference area (reduction >10% in relation to 50th percentile of reference population) Creatinine appearance[c]
Low dietary intake	Dietary protein intake < 0.60 g/kg/d Dietary energy intake < 25 kcal/kg/d

BMI, body mass index; CKD, chronic kidney disease; ISRNM, International Society of Renal Nutrition and Metabolism; NHANES, National Health and Nutrition Examination Survey; PEW, protein–energy wasting.

[a]The term "criteria" refers to each individual variable, whereas "category" refers to grouping of criteria as serum chemistry, body mass, muscle mass, and dietary intake categories.

[b]ISRNM panel used bromcresol green method. In NHANES, serum albumin was measured by bromcresol purple method (see text for details).

[c]Data were not available in NHANES; hence, this criterion was not used in this analysis.

[d]ISRNM panel used BMI < 23 kg/m^2 in dialysis patients. The current study used BMI < 20 kg/m^2 (∼fifth percentile) in non-CKD and moderate CKD populations.

[e]ISRNM panel used 10% weight loss over 6 months.

[f]There were no patients with body fat < 10%; hence, this criterion was not used in this analysis.

Protein and Energy Stores

The ISRNM panel defined PEW syndrome as "the state of decreased body stores of protein and energy fuels (that is, body protein and fat masses)."[14] Therefore, the face validity of the criteria used to define PEW syndrome requires that these criteria reflect either protein wasting or energy wasting. Muscle is the largest protein store, and fat is the largest energy store in the body. Hence, we examined the associations of each of the criteria with protein stores (as estimated by lean body mass measured by DXA scan) and energy stores (as estimated by fat mass measured by DXA scan) in the entire cohort and the CKD subpopulation.

Mortality Data

A Linked Mortality File through 31 December 2011 was created by NCHS using a probabilistic match between NHANES and National Death Index death certificate records.[22]

Statistical Analyses

NHANES is based on a complex probability sample design. We used the svy suite of commands in Stata 13 (Stata Corporation, College Station, TX) and followed the NHANES analytical guidelines.[23] Hence, all reported results (including descriptive statistics, linear, and Cox regression models) take survey weights into account.

Descriptive statistics for baseline clinical characteristics and each PEW criterion are reported as means, SDs, or medians, 25th and 75th percentiles for numeric variables and as proportions for categorical variables.

Associations of Variables Contributing to the Definition of PEW Syndrome With Lean Body Mass and Fat Mass

Linear regression analyses were used to relate lean body mass and fat mass separately to each individual variable contributing to the definition of PEW syndrome with adjustment for the covariates age, gender, race, education, smoking, and alcohol use in the entire cohort and CKD subpopulation.

Relationships of the Number of PEW Syndrome Categories With Body Size and Body Composition

As per ISRNM, a category is considered to be present if any 1 of the individual criteria within that category is present (Table 1). It has been suggested that inadequate dietary intake rarely contributes to protein or energy wasting in uremia.[14] Hence the distributions of body size and body composition parameters by the number of PEW categories defined by nondietary categories alone were first examined. These were also re-examined by including the dietary category in the number of PEW categories.

In multivariate linear regression models, the number of PEW categories defined by nondietary categories alone were related to lean body mass and fat mass (measured by DXA scans). These analyses were repeated by including dietary category in the number of PEW categories. These models were adjusted for age, gender, race, education, smoking, and alcohol use. All analyses were performed in the entire cohort and the CKD subpopulation.

Relationships of the Number of PEW Syndrome Categories With Mortality

The associations of the number of nondietary categories with mortality in the entire and CKD subpopulations were examined. These analyses were repeated by including dietary category. These models were adjusted for age, gender, race, education, smoking, alcohol use, myocardial infarction (MI), congestive heart failure (CHF), stroke, diabetes, hypertension, lung disease, cancer, serum C-reactive protein, and serum bicarbonate. Proportional hazards assumptions for the Cox regression analyses were evaluated by comparing Cox regression coefficients for the first 18 months to Cox regressions after 18 months in time-dependent analyses.

RESULTS

Of the 15,332 participants in 1999 to 2004 NHANES with age >20 years, 11,834 individuals with nonmissing data for estimated glomerular filtration rate, serum albumin and total cholesterol, MAMC, and mortality status were included.

All of the reported results (means, medians, proportions, regression coefficients, hazard ratios, SDs, and confidence intervals) are survey weight adjusted.

The mean age was 46.0 ± 13.4 years. Of the participants, 50.3% were men, and 9.5% were African American. The prevalence of CKD (estimated glomerular filtration rate < 60 ml/min/1.73 m^2) was 6.7%. Of those with CKD, 91.6% were in stage 3.

Baseline clinical characteristics of the study population by the number of PEW syndrome categories are summarized in Table 2. In general, those with ≥3 PEW categories were older and had a higher prevalence of comorbid conditions. However, those with 1 PEW category had the highest prevalence of diabetes, higher serum C-reactive protein levels, and higher BMI as well as body fat%.

The prevalence of the individual PEW criteria in the entire cohort and CKD subpopulation are summarized in Tables 3 and 4, respectively. Low dietary energy intake and protein intake were among the most common conditions, whereas no participant had body fat < 10%. Low serum albumin, low serum cholesterol,

Table 2. Baseline clinical characteristics[a] by number of PEW syndrome categories in entire cohort (N = 11,834)

Number of PEW syndrome categories	0 (43.15%)	1 (46.85%)	2 (9.41%)	≥3 (0.69%)
Demographics				
Age (yr)	43.2 ± 11.8	48.4 ± 14.3	46.8 ± 14.5	50.8 ± 16.6
Male (%)	60.8%	43.9%	35.7%	32.3%
African American race (%)	8.4%	10.8%	8.1%	13.6%
≥High school education (%)	82.2%	78.2%	78.2%	60.0%
Clinical parameters				
Myocardial infarction (%)	2.6%	4.2%	4.6%	6.6%
Congestive heart failure (%)	1.1%	3.0%	2.1%	4.6%
Stroke (%)	1.3%	3.1%	2.6%	2.5%
Diabetes (%)	5.0%	9.7%	7.4%	6.9%
Smoking (%)	50.8%	50.6%	47.6%	61.7%
Alcohol use (%)	74.6%	65.9%	64.7%	63.1%
Hypertension (%)	23.4%	35.4%	25.9%	35.2%
Lung disease (%)	5.6%	7.9%	10.5%	16.9%
Cancer (%)	6.4%	9.2%	9.2%	8.1%
C-reactive protein (mg/l)	1.6 (0.7–3.5)	2.3 (0.9–5.0)	1.3 (0.5–3.2)	1.5 (0.4–6.1)
Serum bicarbonate (mmol/l)	24.1 ± 1.7	24.1 ± 1.9	24.2 ± 1.9	24.6 ± 2.1
eGFR (ml/min/1.73 m^2)	95.6 ± 15.0	92.0 ± 18.4	94.6 ± 19.3	89.7 ± 23.7
PEW variables				
Serum albumin (g/dl)	4.4 ± 0.2	4.3 ± 0.3	4.3 ± 0.3	4.2 ± 0.5
Total cholesterol (mg/dl)	202.6 ± 32.9	204.1 ± 35.2	196.2 ± 32.6	194.2 ± 51.7
Body mass index (kg/m^2)	27.0 ± 3.2	28.5 ± 4.8	22.7 ± 3.7	19.4 ± 1.7
Weight change compared to last yr (%)	1.1 ± 5.8	0.9 ± 7.8	−1.8 ± 7.5	−2.2 ± 6.7
Body fat (%)	30.3 ± 6.0	35.2 ± 8.1	28.7 ± 7.3	26.0 ± 6.5
Mid-arm muscle circumference (cm)	27.3 ± 2.9	26.3 ± 3.4	22.0 ± 2.4	21.1 ± 1.8
Dietary protein intake (g/kg/d)	1.2 (1.0–1.6)	0.8 (0.6–1.1)	0.9 (0.7–1.4)	0.7 (0.5–0.9)
Dietary energy intake (kcal/kg/d)	33.5 (28.8–40.8)	20.7 (16.3–24.7)	23.8 (19.3–38.3)	19.9 (18.0–22.3)

Data are mean ± SD, median (interquartile range), or proportion as appropriate, adjusted by survey weight. All P values <0.001, except smoking ($P = 0.14$) and serum bicarbonate ($P = 0.04$). eGFR, estimated glomerular filtration rate; PEW, protein–energy wasting.
[a]Survey weight–adjusted means, medians, or proportions.

low BMI, unintentional weight loss, and low MAMC criteria tended to be associated with lower protein stores and lower energy stores, although statistical significance was not achieved in all cases. In contrast, low dietary protein and energy intakes were associated with significantly higher protein and energy stores.

When only nondietary categories were considered, 22.2% of the population had 1 or more nondietary categories (Table 5). BMI and fat and lean body masses measured by DXA and MAMC were progressively lower with the presence of additional nondietary categories.

In contrast, when only dietary category was present, the mean BMI was 30.2 ± 4.4 kg/m^2, which is in the obesity range (Table 6). Fat mass measured by DXA was also higher with only dietary category present, compared to when none of the categories were present (Table 6). The further presence of nondietary categories in addition to the dietary category was associated with lower BMI, fat and lean body masses, and MAMC (Table 6).

These relationships are more evident in the multivariate regression models relating the number of PEW syndrome categories with lean body and fat masses (Figure 1) in the entire cohort. When the numbers of PEW syndrome categories were defined by nondietary categories alone, there was a monotonic inverse relationship with lean body mass (Figure 1a) and fat mass

Table 3. Prevalence and associations[a] of individual PEW criteria with lean body mass and fat mass in entire cohort (N = 11,834)

	Prevalence	Lean body mass (kg) regression coefficient[b] (95% CI)	Fat mass (kg) regression coefficient[b] (95% CI)
Low serum albumin (<3.25 g/dl)	0.6%	−3.5 (−7.5 to 0.4)	−3.7 (−7.0 to −0.3)
Low serum cholesterol (<100 mg/dl)	0.2%	−2.5 (−6.8 to 1.8)	−4.6 (−9.7 to 0.5)
Low body mass index (<20 kg/m^2)	5.9%[c]	−9.7 (−10.3 to −9.1)	−14.2 (−14.5 to −13.8)
Unintentional weight loss (>10% over 1 yr)	2.4%	−2.2 (−3.3 to −1.0)	−3.4 (−4.8 to −1.9)
Low body fat % (<10%)	0	NA	NA
Low mid-arm muscle circumference area	17.1%	−8.6 (−9.0 to −8.3)	−8.3 (−8.8 to −7.9)
Low dietary protein intake (<0.60 g/kg/d)	15.2%	3.6 (3.0 to 4.2)	6.4 (5.8 to 7.1)
Low dietary energy intake (<25 kcal/kg/d)	42.7%	4.3 (3.9 to 4.7)	7.3 (6.9 to 7.7)

CI, confidence interval; NA, not applicable as none had body fat % <10%; NHANES, National Health and Nutrition Examination Survey; PEW, protein–energy wasting.
[a]NHANES survey weight adjusted.
[b]Each cell represents a separate model adjusted for age, gender, race, education, smoking, and alcohol use.
[c]Fifth percentile of BMI was 19.93 kg/m^2.

Table 4. Prevalence and associations[a] of individual PEW criteria with lean body mass and fat mass in CKD subpopulation (n = 1156)

	Prevalence	Lean body mass (kg) regression coefficient[b] (95% CI)	Fat mass (kg) regression coefficient[b] (95% CI)
Low serum albumin (<3.25 g/dl)	1.3%	−1.1 (−10.2 to 7.9)	0.3 (−6.8 to 7.3)
Low serum cholesterol (<100 mg/dl)	0.03%	−6.9 (−8.6 to −5.2)	−8.6 (−10.4 to −6.8)
Low body mass index (<20 kg/m²)[c]	4.9%	−9.3 (−10.5 to −8.1)	−15.4 (−16.9 to −13.8)
Unintentional weight loss (>10% over 1 yr)	5.4%	−1.8 (−4.6 to 1.1)	−4.9 (−8.7 to −1.1)
Low body fat % (<10%)	0	NA	NA
Low mid-arm muscle circumference area	15.8%	−7.7 (−9.0 to −6.4)	−8.8 (−10.1 to −7.5)
Low dietary protein intake (<0.60 g/kg/d)	25.8%	3.4 (2.3 to 4.5)	6.0 (4.5 to 7.4)
Low dietary energy intake (<25 kcal/kg/d)	65.4%	4.7 (3.6 to 5.8)	7.5 (6.1 to 9.0)

CI, confidence interval; CKD, chronic kidney disease; NA, not applicable as none had body fat % <10%; NHANES, National Health and Nutrition Examination Survey; PEW, protein–energy wasting.
[a]NHANES survey weight adjusted.
[b]Each cell represents a separate model adjusted for age, gender, race, education, smoking, and alcohol use.
[c]Fifth percentile of body mass index in entire cohort was 19.93 kg/m².

(Figure 1c). However, when dietary category was included, the presence of any 1 of the categories was associated with higher lean body mass (Figure 1b) and higher fat mass (Figure 1d). The further presence of additional categories was associated with lower lean body mass (Figure 1b) and fat mass (Figure 1c). Results were similar in the CKD subpopulation (Figure 2a–d).

Compared to those individuals with none of the nondietary categories, the presence of even 1 nondietary category was associated with increased mortality in the entire cohort (Figure 3a) and the CKD subpopulation (Figure 3c). On the other hand, the presence of any 1 of the dietary or nondietary categories was not associated with increased mortality in the entire population (Figure 3b) or the CKD subpopulation (Figure 3d). The presence of additional categories conferred higher mortality risk, but these relationships appear to be stronger when nondietary categories alone were used (Figure 3a–d).

Table 5. Body size and body composition characteristics by number of PEW categories defined by nondietary categories alone (N = 11,834)

	0 Nondietary (78.83%)[a]	1 Nondietary (16.57%)[a]	2 Nondietary (4.57%)[a]	3 Nondietary (0.03%)[a]
Body mass index	28.5 ± 4.0	23.8 ± 2.9	19.0 ± 1.4	17.2 ± 0.8
Mid-arm muscle circumference (cm²)	27.3 ± 3.1	22.8 ± 2.5	21.0 ± 1.9	20.3 ± 0.8
Lean body mass (kg)	52.3 ± 9.4	43.2 ± 7.0	37.6 ± 5.5	37.8 ± 2.9
Fat mass (kg)	28.3 ± 7.8	21.8 ± 5.4	13.6 ± 2.7	9.2 ± 3.1

PEW, protein–energy wasting.
[a]Survey weight–adjusted proportions.

Table 6. Body size and body composition of patients with dietary category alone compared to those with none of the categories or those with dietary category with additional nondietary categories (n = 10,137)[a]

	0 Dietary or nondietary (50.65%)[b]	Dietary alone (42.10%)[b]	Dietary + 1 nondietary (6.47%)[b]	Dietary + 2 or more nondietary (0.78%)[b]
Body mass index (kg/m²)	27.0 ± 3.1	30.2 ± 4.4	25.4 ± 3.4	19.5 ± 1.6
Mid-arm muscle circumference (cm²)	27.3 ± 2.9	27.3 ± 3.2	22.8 ± 2.6	21.1 ± 1.8
Lean body mass (kg)	52.6 ± 8.5	51.9 ± 10.2	43.0 ± 7.1	37.0 ± 5.4
Fat mass (kg)	25.0 ± 6.0	32.3 ± 8.4	25.1 ± 6.0	14.7 ± 2.8

[a]Patients with only nondietary categories without dietary category being present were not included in this table.
[b]Survey weight–adjusted proportions.

In sensitivity analyses, when defining BMI criteria as <18.5 kg/m², the relationships of the number of PEW syndrome nondietary categories with lean body mass (Supplementary Figure 1a), fat mass (Supplementary Figure 1b), and mortality (Supplementary Figure 1c) were similar.

DISCUSSION

The ISRNM panel defined PEW syndrome as "the state of decreased body stores of protein and energy fuels (that is, body protein and fat masses)."[14] The results of this study indicate that nondietary definitions are reflective of protein and/or energy wasting in the general and moderate CKD populations. However, dietary criteria as defined by the ISRNM panel do not appear to be reflective of either protein wasting or energy wasting in the general or moderate CKD population.

The strong associations of low dietary protein and energy intakes estimated from 24-hour dietary recalls with higher lean body mass and fat mass are likely because of mathematical coupling; as the dietary intakes were normalized to body weight, lower dietary protein and energy intakes reflect higher body weight and hence, higher lean body mass and fat mass. It is possible that other dietary cut-offs normalized to body weight or height might be related to protein or energy wasting, and those need to be examined in future studies in the general and moderate CKD populations. Furthermore, whether the ISRNM dietary definitions are indicative of protein or energy wasting in the dialysis population also needs to be tested in future studies.

In contrast, low serum albumin, low serum cholesterol, low BMI, unintentional weight loss, and low MAMC were associated with lower lean body mass and/or fat mass, suggesting the face validity of these variables as indicators of PEW syndrome.

The ISRNM panel definition of PEW syndrome requires the presence of all 3 nondietary categories or

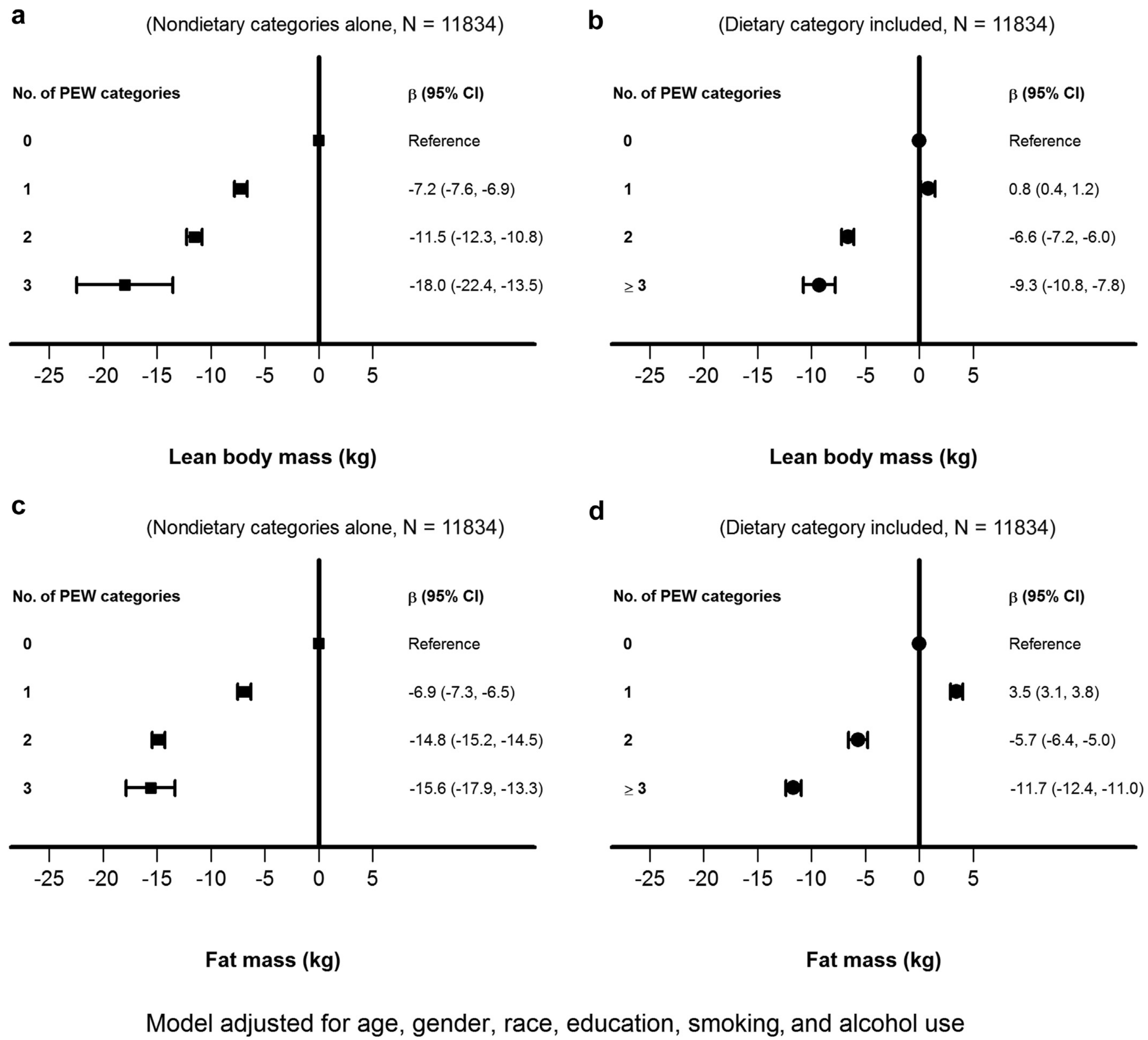

Figure 1. Associations of the number of protein–energy wasting (PEW) syndrome categories with lean body mass and fat mass measured by dual-energy x-ray absorptiometry scans in multivariate linear regression models in the entire cohort (N = 11,834). (a) Nondietary categories alone and lean body mass. (b) Dietary category included and lean body mass. (c) Nondietary categories alone and fat mass. (d) Dietary category included and fat mass.

dietary category plus 2 nondietary categories. As is evident from Table 5 and Figures 1 and 2, presence of all 3 nondietary categories was associated with significantly lower lean body mass and fat mass. It was also very strongly associated with increased mortality (Figure 3).

The presence of dietary category in addition to 2 nondietary categories was also associated with significantly lower lean body mass and fat mass and mortality (Table 6, Figures 1–3). However, as is evident from Table 6, inclusion of dietary category undermines the face validity of the PEW syndrome criteria as a measure of protein or energy wasting. When dietary category alone was present, the mean BMI was in the obesity range. The association of dietary category plus 2 additional nondietary categories with lower protein or energy stores was driven by the presence of the 2 nondietary categories (Table 6). Indeed, as shown in Figure 1, the lean body mass (−11.5 kg) and fat mass (−14.8 kg) were lower when 2 of the nondietary criteria were present than when 3 categories including dietary category were present (lean body mass −9.3 kg and fat mass −11.7 kg). Therefore, a modified definition PEW syndrome as the presence of 2 of 3 nondietary categories is likely a better indicator of protein or energy wasting than a definition of 3 of 4 categories that include dietary category.

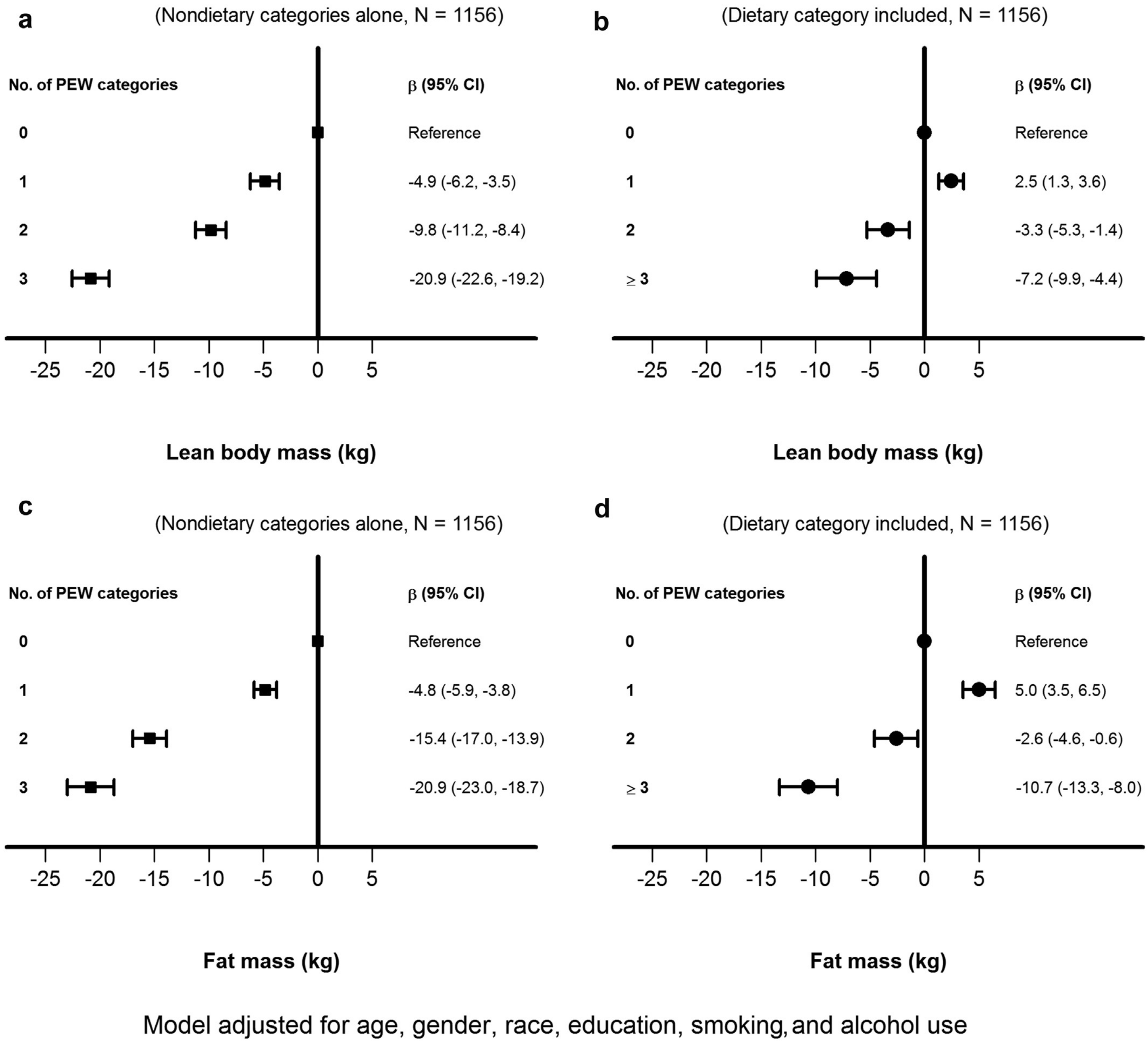

Figure 2. Associations of the number of protein–energy wasting (PEW) syndrome categories with lean body mass and fat mass measured by dual-energy x-ray absorptiometry scans in multivariate linear regression models in the chronic kidney disease (CKD) subpopulation (n = 1156). (a) Nondietary categories alone and lean body mass. (b) Dietary category included and lean body mass. (c) Nondietary categories alone and fat mass. (d) Dietary category included and fat mass.

Both muscle mass and serum albumin are commonly considered nutritional markers and are known to be associated with better survival in the general, CKD, and dialysis populations.[10,24–26] Even though much of the focus is on the associations of higher BMI with increased mortality BMI in the general population, it is also known to have a "U"-shaped association with mortality in that population.[27,28] Similarly, the U-shaped association of total cholesterol with mortality in the general population is also well known.[29] The results of the current study show that the presence of PEW syndrome defined by a combination of the above criteria was strongly associated with increased mortality in the entire cohort and the moderate CKD subpopulation.

Furthermore, the valid assessment of nutrient intake with dietary recalls or questionnaires even in research settings might be difficult. This might be even more difficult in routine clinical practice. Thus, using dietary variables as diagnostic criteria for PEW syndrome lacks face validity.

It is generally considered that the hypercatabolism of uremia (induced by uremic toxins, inflammation,[30] oxidative stress, insulin resistance,[31] metabolic acidosis,[32] and the dialysis procedure itself[33]) is the cause of PEW syndrome in the dialysis population.[34–36]

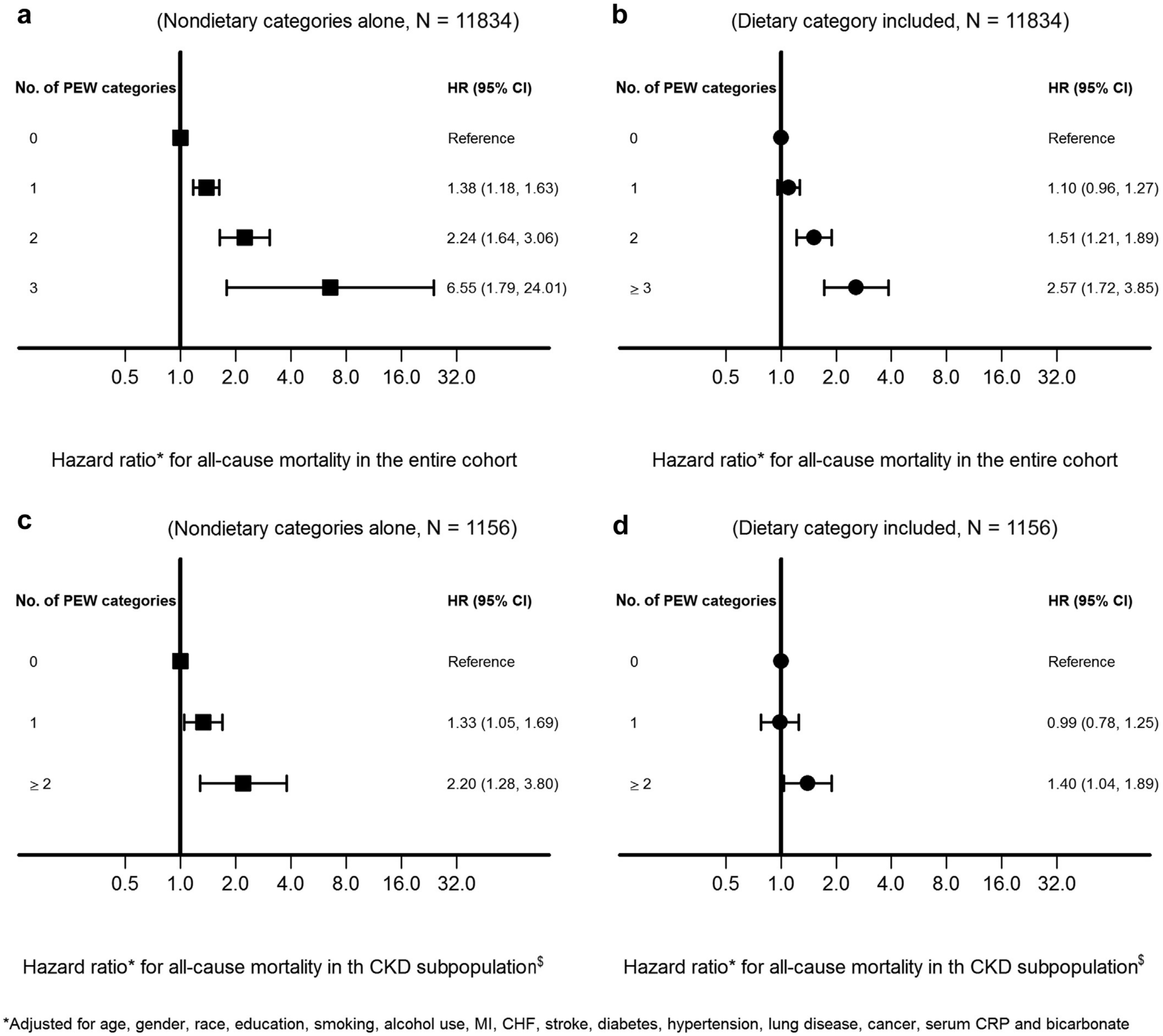

Figure 3. Mortality associations of the number of protein–energy wasting (PEW) syndrome categories with mortality in multivariate Cox regression models in the entire cohort (N = 11,834) and chronic kidney disease (CKD) subpopulation (n = 1156). (a) Nondietary categories alone and mortality in the entire cohort. (b) Dietary category included and mortality in the entire cohort. (c) Nondietary categories alone and mortality in the CKD subpopulation.* (d) Dietary category included and mortality in the CKD subpopulation.$ *There was only 1 observation with 3 nondietary categories present in the CKD subpopulation and hence this observation was included as ≥2 categories in this figure). $There were only 19 observations with ≥3 categories (1 dietary and 2 or 3 nondietary) present in the CKD subpopulation and hence these observations were included as ≥2 categories in this figure.

It is unclear to what extent these factors play a role in the causation of PEW syndrome in the general and moderate CKD populations. Further studies are warranted to determine the causes of PEW syndrome in these populations.

The strengths of the study include the use of NHANES, a national survey designed to obtain a representative sample of the noninstitutionalized US population. Furthermore, data collection in NHANES was rigorous. The limitations include the observational nature of the study.

In summary, the dietary variables used in the ISRNM PEW syndrome criteria do not appear to reflect either protein wasting or energy wasting in the general or moderate CKD populations. A definition of PEW syndrome without the dietary variables in these populations has better face validity and might be a better reflection of protein and energy wasting.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Figure S1. Associations of number of protein–energy wasting (PEW) syndrome categories (defined with body mass index < 18.5 kg/m^2 as a PEW criterion) with lean body mass, fat mass measured by dual-energy x-ray absorptiometry scans, and mortality in multivariate linear regression models and Cox regression models in the entire cohort (N = 11,834). (a) Nondietary categories alone and lean body mass; (b) nondietary categories alone and fat mass; (c) nondietary categories alone and mortality.

Supplementary material is linked to the online version of the paper at http://www.kireports.org.

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