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# Association of Morbid Obesity and Weight Change Over Time With Cardiovascular Survival in Hemodialysis Population

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● **Background:** In maintenance hemodialysis (MHD) outpatients, a reverse epidemiology is described, ie, baseline obesity appears paradoxically associated with improved survival. However, the association between changes in weight over time and prospective mortality is not known. **Methods:** Using time-dependent Cox models and adjusting for changes in laboratory values over time, the relation of quarterly-varying 3-month averaged body mass index (BMI) to all-cause and cardiovascular mortality was examined in a 2-year cohort of 54,535 MHD patients from virtually all DaVita dialysis clinics in the United States. **Results:** Patients, aged  $61.7 \pm 15.5$  (SD) years, included 54% men and 45% with diabetes. Time-dependent unadjusted and multivariate-adjusted models, based on quarterly-averaged BMI controlled for case-mix and available time-varying laboratory surrogates of nutritional status, were calculated in 11 categories of BMI. Obesity, including morbid obesity, was associated with better survival and reduced cardiovascular death, even after accounting for changes in BMI and laboratory values over time. Survival advantages of obesity were maintained for dichotomized BMI cutoff values of 25, 30, and 35 kg/m<sup>2</sup> across almost all strata of age, race, sex, dialysis dose, protein intake, and serum albumin level. Examining the regression slope of change in weight over time, progressively worsening weight loss was associated with poor survival, whereas weight gain showed a tendency toward decreased cardiovascular death. **Conclusion:** Weight gain and both baseline and time-varying obesity may be associated with reduced cardiovascular mortality in MHD patients independent of laboratory surrogates of nutritional status and their changes over time. Morbidly obese patients have the lowest mortality. Clinical trials need to verify these observational findings. *Am J Kidney Dis* 46:489-500. © 2005 by the National Kidney Foundation, Inc.

**INDEX WORDS:** Hemodialysis (HD); obesity; weight loss; cardiovascular death; malnutrition; inflammation; time-varying model.

**O**F MORE THAN 300,000 maintenance hemodialysis (MHD) patients in the United States, at least 60,000 patients, or 20%, die every year, mostly because of cardiovascular disease (CVD).<sup>1,2</sup> Despite decades of ongoing efforts on treating such conventional cardiovascular risk factors in MHD patients as obesity, hypertension, hypercholesterolemia, and hyperhomocysteinemia, their survival has not improved substantially.<sup>2</sup> The recently completed Die Deutsche Diabetes Dialyse Studie (4D) of 1,255 dialysis

patients randomly assigned to either atorvastatin, 20 mg, or placebo did not show a significant advantage of using statins in improving survival in dialysis patients with diabetes.<sup>3</sup> In addition, several other recent multicenter clinical trials, including the Hemodialysis (HEMO) Study,<sup>4</sup> failed to show a survival advantage of increasing dialysis dose or using different dialysis membranes in MHD patients.

A number of epidemiological studies with large sample sizes indicated paradoxically in-

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*R.D.K. contributed to analysis of the data and reviewed and approved the final manuscript; C.J.M. contributed to the design of the study, provision of data, and final review and approval of the manuscript; C.S.S. contributed to analysis of the data and reviewed and approved the final manuscript; D.W.G. contributed to the design of the study and analysis of data and reviewed and approved the final manuscript; S.G. contributed to the design of the study, provided advice and consultation on the study design, analysis, and writing of the manuscript, and final review and approval.*

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verse associations between classic risk factors for CVD and death in MHD patients. For example, a high mortality rate has been observed in MHD patients who have low, rather than high, body mass index (BMI),<sup>5,6</sup> blood pressure,<sup>7</sup> and serum concentrations of cholesterol<sup>8</sup> and homocysteine.<sup>9</sup> High values of these risk factors paradoxically are protective and associated with improved survival.<sup>10,11</sup> The inverse relationship between such indices of body size as BMI and clinical outcome in MHD patients appears to be relatively consistent and has been studied extensively.<sup>6</sup> Moreover, other patient populations, including patients with heart failure, appear to have this so-called "obesity paradox."<sup>12</sup> However, most investigators studied the effect of baseline BMI at the start of the cohort on subsequent mortality. Virtually no study has examined the association between change in weight over time on cardiovascular mortality in the entire cohort or its subpopulations. No study has controlled for time-varying laboratory measures, including the available surrogates of nutritional status, when exploring the obesity paradox. Moreover, it is not clear whether morbid obesity has the same survival advantages as moderate obesity in MHD patients. We examined whether survival advantages of obesity, including morbid obesity, maintain even with changes in weight over time and whether these associations are independent of other nutritional measures and are observed uniformly across all subgroups of MHD patients. We also examined whether a decrease in weight over time is associated with increased cardiovascular death, and whether weight gain confers improved survival, independent of other nutritional factors.

## METHODS

### *Database Creation*

Database creation has been described elsewhere.<sup>7</sup> In summary, the data warehouse of DaVita, Inc, the then second largest dialysis care provider in the United States, had information on approximately 40,000 patients at any given time and was accessed to obtain all relevant data between July 1, 2001, and June 30, 2003. All repeated measures of every relevant variable for each patient within a given quarter (13-week interval) were averaged to obtain 1 quarterly mean value for that variable. Hence, 8 independent sets of quarterly database were created to include the entire 2-year observation period. The study was approved by the Instructional Review Committees of Harbor-UCLA and DaVita, Inc.

### *Body Size Measures*

Eleven categories of BMI<sup>9</sup> (weight/height<sup>2</sup>) were used, less than 18 kg/m<sup>2</sup>, 45 kg/m<sup>2</sup> or greater, and 9 categories from 18 to 44.99 kg/m<sup>2</sup>. Selected category boundaries included the cutoff levels defined by the World Health Organization classifications,<sup>13</sup> including overweight (25 to 29.99 kg/m<sup>2</sup>), obese (30 to 39.99 kg/m<sup>2</sup>), and morbidly obese (>40 kg/m<sup>2</sup> without any obesity sequelae or >35 kg/m<sup>2</sup> and experiencing a severe negative health effect of obesity). In our study, underweight is defined as a BMI less than 20 kg/m<sup>2</sup>, and normal weight range, as a BMI between 20 and 24.99 kg/m<sup>2</sup>. Patients with missing weight or height values in all 8 quarters or with values less than 10 kg/m<sup>2</sup> or greater than 60 kg/m<sup>2</sup> (corresponding to ~0.25th and 99.75th percentile levels) were excluded.

### *Cohort Time, Vintage, and Mortality*

Cohort time includes the number of days the patient participated in the cohort and was a number between 1 and 731 days. Left-censorship events include death, renal transplantation, or moving to a non-DaVita dialysis facility, among others. Change to peritoneal dialysis therapy is not considered a left-censorship event based on the intent-to-treat principle. Dialysis vintage is defined as time between the first day of dialysis treatment and the first day the patient entered the cohort. Four categories of vintage were formed: (1) first 6 months, (2) between 6 and 24 months, (3) between 2 and 5 years, and (4) greater than 5 years. The entry quarter is defined as the first quarter in which a patient's dialysis vintage was greater than 3 months for at least half the duration of the quarter. By implementing this criterion, any patient who was not maintained in the cohort beyond the first 3 months of MHD therapy was excluded. The computerized causes of death, reflecting, but not restricted to, the reported information in the Cause of Death form (Form 2746), were obtained and summarized into 6 main categories: cardiovascular, infectious, gastrointestinal, cancer related, others, and unspecified/unknown.

### *Laboratory Data and Indicators of Malnutrition-Inflammation Complex Syndrome*

Most blood samples were predialysis, with the exception of postdialysis serum urea nitrogen to calculate urea kinetics. Blood samples were drawn by using uniform techniques in all dialysis clinics across the nation and transported to the Central DaVita Laboratory in Deland, FL, within 24 hours. All laboratory values were measured by using automated and standardized methods in DaVita Laboratory. Most laboratory values, including complete blood cell counts; serum levels of urea nitrogen, albumin, creatinine, and ferritin; and total iron-binding capacity (TIBC), were measured monthly. Serum ferritin was measured quarterly. Hemoglobin was measured weekly to biweekly in most patients. Kt/V to reflect dialysis dose and normalized protein equivalent of total nitrogen appearance (nPNA), also known as protein catabolic rate, an estimation of daily protein intake, were measured monthly.

Eight quarterly-varying 13-week averaged laboratory measures with known associations with prospective mortality

were selected, some of which are considered potential surrogates of nutritional status, with some having a possible association with inflammation<sup>14</sup>: (1) serum albumin<sup>15</sup>; (2) nPNA as a marker of daily protein intake<sup>16</sup>; (3) serum TIBC, known to have a strong association with subjective global assessment of nutrition<sup>17</sup>; (4) serum ferritin, a possible inflammatory marker<sup>18</sup>; (5) serum creatinine, a marker of muscle mass<sup>19</sup>; (6) peripheral white blood cell count (WBC), known to correlate with serum C-reactive protein level<sup>20</sup>; (7) lymphocyte percentage, a known nutritional marker<sup>21,22</sup>; and (8) blood hemoglobin level.<sup>23</sup>

### *Epidemiological and Statistical Methods*

Because the dialysis population is a dynamic cohort with a high turnover rate, a nonconcurrent cohort was formed to include all existing MHD patients of the first quarter (q1) and all new MHD patients of the subsequent quarters (q2 through q8). Hence, 8 quarterly data sets were merged by using unique patient identifiers. For patients not linked to the database initially, additional merging methods using the initial letters of the patient's last and first names combined with his or her date of birth were performed. In addition to 8 quarterly values for every variable, a baseline value also was created for each measure by left-truncating the first available value of the entry quarter for each patient.

Because of the very large numbers involved, all associations we discuss have very low values for *P*. In addition to standard descriptive statistics, both regular and time-dependent Cox proportional hazard regression analyses for truncated and censored data<sup>24</sup> were performed to determine whether 2-year survival was associated with baseline and time-varying categories of BMI. The reference BMI category for all analyses was 23 to 24.99 kg/m<sup>2</sup>. This category was chosen as the reference because it is within the normal range of BMI set forth by the World Health Organization,<sup>13</sup> was adjacent to the modal category and had almost the same sample size, and had the highest number of death cases and allowed for the most precise comparison with higher BMI categories. Five race/ethnic groups were generated: (1) Caucasians (including non-Hispanic whites and Middle Easterners), (2) blacks (including African Americans and other Africans), (3) Asians (including Pacific Islanders), (4) American Indians, (5) Hispanics, and (6) others.

For each analysis, 3 models were examined based on the level of multivariate adjustment: (1) the unadjusted model included only BMI categories and mortality data; (2) case-mix-adjusted models included age, sex, race and ethnicity, diabetes mellitus, vintage categories, entry quarter, primary insurance (Medicare, Medicaid, private, and others), marriage status (married, single, divorced, widowed, and others), standardized mortality ratio of the dialysis clinic during the entry quarter, Kt/V (single pool), and residual renal function during the entry quarter; and (3) case-mix and laboratory-adjusted models included all mentioned covariates, as well as 8 surrogates of nutritional status, including nPNA, serum albumin level, TIBC, ferritin level, creatinine level, WBC count, lymphocyte percentage, and hemoglobin level.

In time-dependent models, in addition to time-varying quarterly BMI categories, 8 laboratory measures and Kt/V also were entered as quarterly time-varying variables. Missing covariate data (<5%) were input by the mean or median

of existing values. The rate of weight change over time for each patient was calculated as the slope ( $\beta$ ) of the regression model that included up to 8 quarterly BMI values. For this model, patients with fewer than 2 BMI values were excluded. All descriptive and multivariate statistics were carried out using SAS, version 8.02 (SAS Institute Inc, Cary, NC); most models were repeated using Stata, version 7.0 (Stata Corp, College Station, TX) for consistency verification.

## RESULTS

The original 2-year national database for all MHD patients included 69,819 subjects. After implementing the mentioned selection criteria, including deleting patients who were not maintained beyond 3 months of MHD therapy or who had inadequate or overtly missing data, the resulting cohort included 58,058 MHD patients, of whom 37,049 patients (64%) originated from the q1 data set, and the rest, from the subsequent quarters (q2 through q8). **Table 1** lists baseline demographic, clinical, and laboratory characteristics of the cohort. Almost 45% of patients had diabetes mellitus, and 40% had been on dialysis therapy for less than 6 months on entry to the cohort. Cardiovascular death comprised more than half of all known causes of death.

BMI was missing or an acceptable BMI value was not available in 3,523 patients (6.1%). **Table 2** lists the 11 BMI categories for the remaining 54,535 MHD patients. Only 13.1% of patients were underweight at baseline, whereas more than a third (37.1%) were within normal range. Overweight, obese, and morbidly obese MHD patients were 28.9%, 18.5%, and 7.7%, respectively; morbid obesity is defined as a BMI greater than 40 kg/m<sup>2</sup>. Both all-cause and cardiovascular mortality showed almost strictly decreasing rates across increasing BMI categories, ie, morbidly obese MHD patients had the greatest survival rates.

**Figures 1 and 2** show hazard ratios for all-cause and cardiovascular death for different time-varying BMI categories, respectively. Obesity, including morbid obesity, was associated with improved survival and decreased cardiovascular mortality, even after exhaustive adjustment for time-varying laboratory markers. These associations were independent of changes in BMI over time. Non-time-dependent Cox regression models also were performed by using baseline BMI

**Table 1. Baseline Data for the Nonconcurrent (left-truncated) Cohort of 58,058 MHD Patients, Including 37,049 From q1 and 21,009 From q2 to q8**

Variable	
Age (y)	60.7 ± 15.5
Age > 65 y (%)	43.8
Sex (% women)	46.2
Diabetes mellitus (%)	44.7
Race and ethnicity:	
Caucasians (%)	36.8
Blacks (%)	32.0
Asians (%)	4.3
American Indians (%)	2.2
Hispanics (%)	15.2
Vintage (time on dialysis):	
3-6 mo (%)	40.1
6-24 mo (%)	21.9
2-5 y (%)	24.1
>5 y (%)	13.8
Primary insurance	
Medicare (%)	69.9
Medicaid (%)	6.4
Private provider (%)	23.7
Causes of death:	
Cardiovascular (%)	51.6
Infectious (%)	10.9
Cancer (%)	2.9
Gastrointestinal (%)	1.6
Others (%)	8.2
Unknown/unspecified (%)	24.8
Standardized mortality ratio	0.81 ± 0.31
Cohort time (mo)	14.8 ± 8.5
Posthemodialysis weight (kg)	73.8 ± 19.8
BMI (kg/m <sup>2</sup> )	26.1 ± 6.3
Kt/V (single pool)	1.54 ± 0.32
nPNA (g/kg/d)	0.99 ± 0.25
Serum albumin (g/dL)	3.74 ± 0.41
Serum creatinine (mg/dL)	9.0 ± 3.4
Serum ferritin (ng/mL)	609 ± 521
TIBC (mg/dL)	202 ± 32
Blood hemoglobin (g/dL)	11.98 ± 1.28
WBCs (per fl)	7,326 ± 2,429
Lymphocytes (% of total WBCs)	20.9 ± 7.9

NOTE. Values expressed as mean ± SD or percent. To convert serum creatinine in mg/dL to  $\mu\text{mol/L}$ , multiply by 88.4; albumin and hemoglobin in g/dL to g/L, multiply by 10; ferritin in ng/mL to  $\mu\text{g/L}$ , multiply by 1.

Abbreviation: nPNA, normalized protein catabolic rate.

categories at the start of the cohort. Results were similar (not shown).

To explore the impact of several relevant cut-off levels of increased body weight on survival in different subgroups of patients, continuous BMI data were dichotomized at BMI levels of 25, 30, and 35 kg/m<sup>2</sup>. Figure 3 shows unadjusted and fully adjusted hazard ratios for cardiovascular

death in all patients and in different strata of diabetes status, sex, age (>65 years versus younger), dialysis vintage, serum albumin levels (>3.8 g/dL [ $>38$  g/L] versus lower), and dietary protein intake (>1.0 g/kg/d versus lower). Except for the adjusted hazard ratio in Asian patients, high BMI was associated with decreased all-cause and cardiovascular mortality. Non-time-dependent Cox models using baseline BMI gave essentially the same results (not shown).

In 47,629 MHD patients who had at least 2 quarterly BMI values, the rate of weight change per annual quarter was estimated as a proportion of baseline weight and based on the slope of the linear regression equation for each patient. Table 3 lists the selected weight gain categories for this analysis. Almost half of all patients ( $n = 22,784$ ) had stable weight, ie, a weight gain or loss less than 1% per quarter (reference group). Five weight-gain and 5 weight-loss categories were created based on increments of 1% weight change rate per quarter. The stable (reference) group had one of the lowest unadjusted mortality rates and the highest mean serum albumin concentration. Mean baseline BMI was the lowest in MHD patients with the greatest rate of weight gain; they also had a greater mortality rate than the stable group, although still substantially less than that in the group with the greatest rate of weight loss.

To examine whether the differences in baseline BMI and serum albumin levels could account for greater mortality rates across the weight-gain groups, Cox regression models with different multivariate adjustments were studied. Table 4 and Figs 4 and 5 show increases in the adjusted hazard ratio of death across decrements of weight-loss groups, whereas a tendency toward better survival and reduced cardiovascular death is observed across increments of weight-gain groups. Among relevant interactions examined, the statistical interaction between baseline BMI and weight change did not have significant effect on mortality ( $P = 0.67$ ).

## DISCUSSION

In a national database cohort that included all eligible MHD patients of a major dialysis care provider with uniform patient management practices and standardized laboratory values, all measured in 1 laboratory, we found



**Table 2. BMI Groups and 2-Year Mortality Census Among Them**

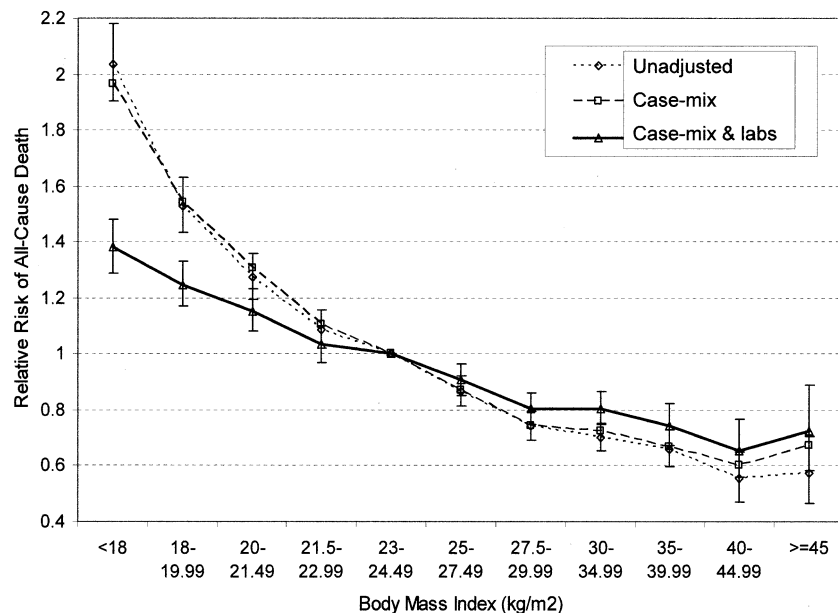
World Health Organization Category	BMI Range (kg/m <sup>2</sup> )	Sample Size	All-Cause Death	Cardiovascular Death
Underweight	<18	2,605 (4.8)	1,023 (39.3)	384 (15.9)
	18-19.99	4,515 (8.3)	1,498 (32.2)	601 (14.1)
Normal range	20-21.49	5,402 (9.9)	1,627 (30.1)	685 (13.4)
	21.5-22.99	6,452 (11.8)	1,753 (27.2)	728 (11.8)
	23-24.99 (reference)	8,383 (15.4)	2,095 (25.0)	926 (11.5)
Overweight	25-27.49	8,860 (16.2)	2,045 (23.1)	911 (10.7)
	27.5-29.99	6,385 (11.7)	1,326 (20.8)	580 (9.4)
Obese	30-34.99	7,028 (12.9)	1,399 (19.9)	657 (9.7)
	35-39.99	3,047 (5.6)	545 (17.9)	269 (9.1)
Morbidly obese	40-44.99	1,171 (2.1)	186 (15.9)	85 (7.5)
	>45	687 (1.3)	112 (16.3)	47 (7.0)
	All patients	54,535 (100)	13,609 (25.0)	5,873 (11.2)

NOTE. Values expressed as number (percent) unless indicated otherwise. The denominator for all-cause mortality is the total sample of MHD patients with at least 1 baseline BMI value ( $n = 54,535$ ), whereas the denominator for cardiovascular death is 52,300 because in 2,235 MHD patients, the cause of death was not registered in the database.

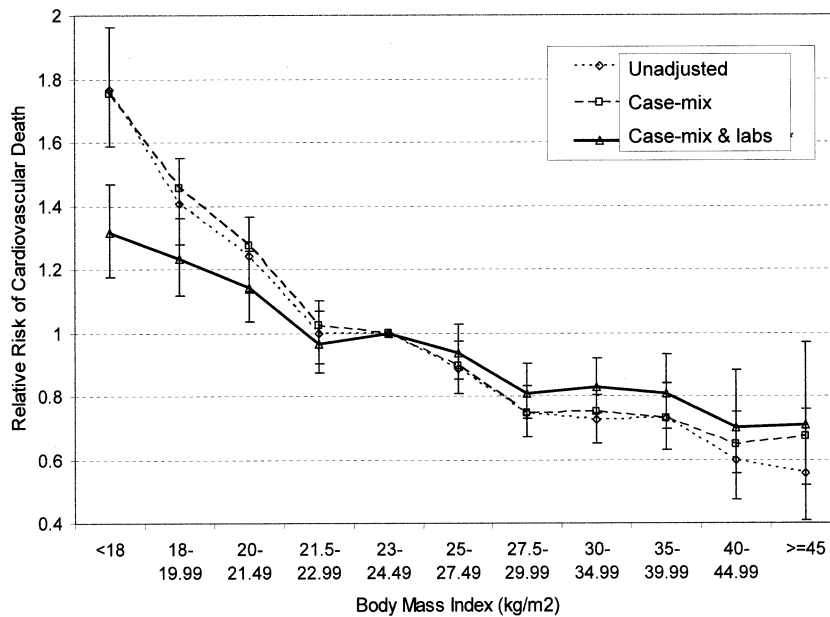
that obesity, including morbid obesity, is associated with improved survival and reduced cardiovascular death. These associations were independent of changes in BMI during the 2-year study period and held even after adjustment for time-varying laboratory surrogates of nutritional status. With the possible exception of Asian MHD patients, survival advantages of overweight, obesity, and morbid obesity held in different patient subgroups. Weight loss was associated with increased cardiovascular and all-cause death, whereas weight gain showed a

trend toward improved survival and reduced cardiovascular mortality. These findings are in sharp contrast to the conventional understanding of the epidemiology of obesity, especially morbid obesity, in the general population.<sup>25</sup>

In the United States, as well as in most industrialized nations, mean body weight is increasing.<sup>26</sup> Many epidemiological studies have shown a strong association between obesity and decreased survival, especially because of an increased risk for CVD,<sup>27,28</sup> although recent studies have found a more reduced relative risk for



**Fig 1. Time-dependent association between BMI and 2-year all-cause mortality in 54,535 MHD patients (95% confidence interval bars are not shown for the case-mix-adjusted group to enable better distinction of confidence intervals for other 2 groups).**



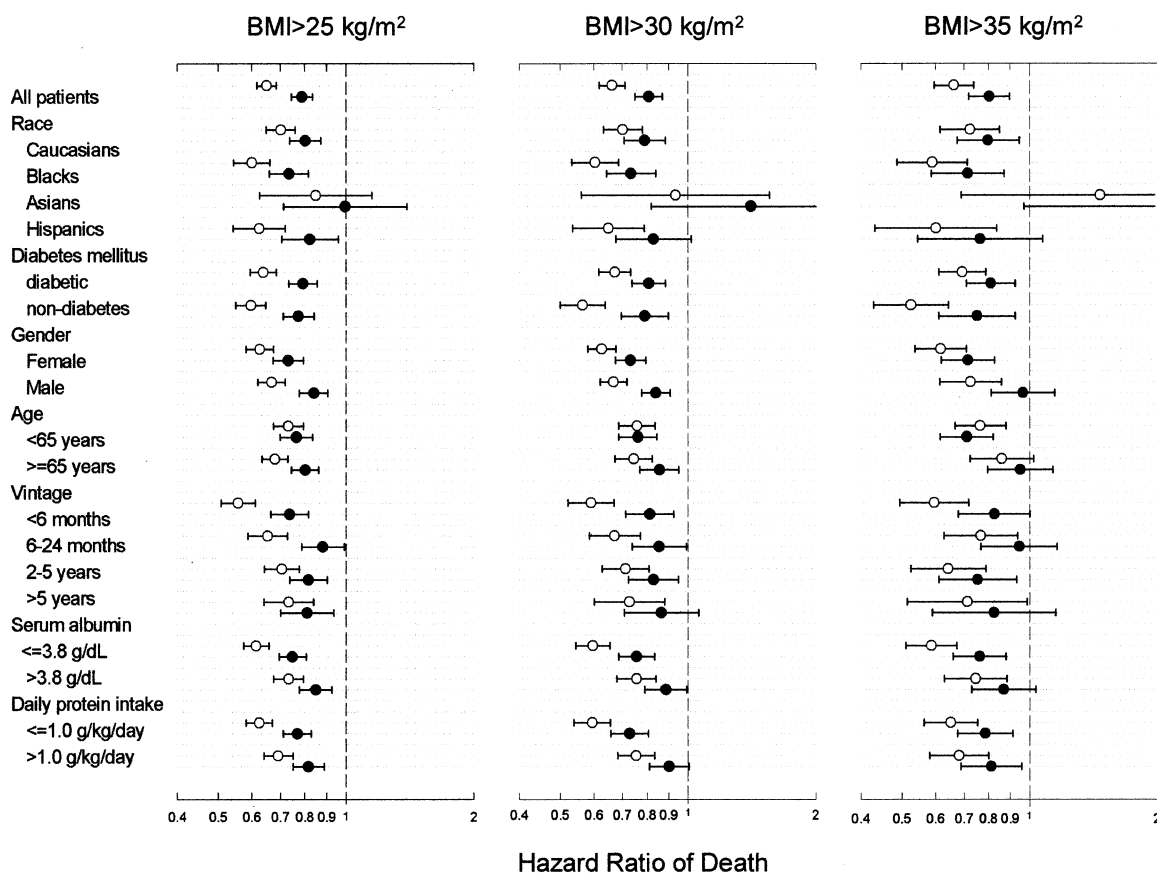
**Fig 2. Time-dependent association between BMI and 2-year cardiovascular mortality in 54,535 MHD patients (95% confidence interval bars are not shown for the case-mix-adjusted group to enable better distinction of the confidence intervals for other 2 groups).**

death associated with obesity than previously reported.<sup>29,30</sup> There is a direct relationship between BMI and body weight, as well as body fat. In some studies of healthy adults, a “J” curve effect was observed in which individuals with a low BMI also showed increased mortality, although not as high as obese individuals.<sup>28,31</sup> This “J” shape may disappear when data are adjusted for smoking status.<sup>28</sup>

In contrast to trends seen in the general population, in MHD patients, lower BMI at baseline consistently is found to be a strong predictor of elevated mortality.<sup>6,32-38</sup> Furthermore, greater BMI generally has not been associated with an increase in mortality risk in MHD patients, except in Asian-American MHD patients.<sup>36,39</sup> The Diaphane Collaborative Study Group<sup>32</sup> was one of the first to report on the paradoxical observation of low mortality with high baseline BMI in 1,453 younger, mostly nondiabetic, French MHD patients followed up between 1972 and 1978.<sup>32</sup> Leavey et al,<sup>34</sup> Fleischmann et al,<sup>35</sup> Wolf et al,<sup>40</sup> and Port et al<sup>41</sup> reported similar findings in larger MHD cohorts. Kopple et al<sup>42</sup> found the same trend for weight-for-height percentiles. The Dialysis Outcomes and Practice Patterns Study<sup>33</sup> found similar associations among western European MHD patients. Glanton et al<sup>38</sup> found that the inverse relationship between BMI and mortality was stronger in African-American MHD pa-

tients. Finally, Johansen et al<sup>39</sup> recently showed that markers of body fat or muscle mass are associated with improved survival in obese MHD patients, although this was not found by Beddhu et al,<sup>43</sup> which may be caused by method flaws in the latter study, discussed elsewhere.<sup>6,11</sup> A few studies with much smaller sample sizes did not detect improved survival in obese MHD patients,<sup>44,45</sup> including a study by Kutner and Zhang<sup>45</sup> reporting that the association of race and BMI with mortality differed by sex. However, these studies did not examine changes in weight over time or the rate of change and its relation to survival and cardiovascular death.

The reverse epidemiology of obesity is not unique to dialysis populations. Patients with chronic heart failure,<sup>12,46</sup> geriatric populations,<sup>47</sup> hospitalized patients,<sup>48</sup> and patients with malignancy<sup>49</sup> or acquired immunodeficiency syndrome<sup>50</sup> also show a risk-factor reversal. Hence, a better understanding of the phenomenon of reverse epidemiology in dialysis patients, especially as it pertains to obesity and body size, may help improve the poor outcome in this and other similar, but distinct, populations and disease states, altogether more than 20 million Americans.<sup>11</sup> Moreover, the reverse epidemiology phenomenon is not restricted to obesity. Blood pressure and serum cholesterol, creatinine, and homocysteine levels also appear to have an in-



**Fig 3.** Impact of (left) overweight (BMI > 25 kg/m<sup>2</sup>), (middle) obesity (BMI > 30 kg/m<sup>2</sup>), and (right) morbid obesity (BMI > 35 kg/m<sup>2</sup>) on 2-year survival in 54,535 MHD patients and their subgroups according to race, diabetes, sex, age, dialysis vintage, serum albumin level, and dietary protein intake. Analyses are based on time-dependent Cox regression models. Open circles, unadjusted hazard ratios; filled circles, multivariate-adjusted hazard ratios. To convert albumin in g/dL to g/L, multiply by 10.

verse association with survival in these populations.<sup>7,9,51</sup>

The concept of reverse epidemiology may appear counterintuitive, especially because obesity, especially morbid obesity, is an established risk factor for CVD and poor outcome in the general population. Nonetheless, given the consistency of the observations, there must be conditions in these populations that render them more susceptible to a poor outcome when low BMI is present. Several explanations have been suggested,<sup>6,52</sup> including a more stable hemodynamic status in obese individuals,<sup>53</sup> greater concentration of tumor necrosis factor  $\alpha$  receptors in obesity,<sup>54</sup> neurohormonal alterations of obesity,<sup>55</sup> endotoxin-lipoprotein interaction,<sup>56</sup> reverse causation,<sup>57</sup> survival bias,<sup>10</sup> time discrepancies among competitive risk factors (overnutrition

versus undernutrition),<sup>10</sup> and the overwhelming effect of malnutrition inflammation complex on traditional cardiovascular risks.<sup>14</sup> Because most MHD patients die within 5 years of starting dialysis treatment,<sup>1</sup> long-term effects of conventional risk factors on future mortality must be overwhelmed by the short-term effects of these or other risk factors intrinsic to dialysis populations, such as undernutrition and inflammation. It may be that dialysis patients do not live long enough to die of the consequences of overnutrition.

Our study lacked data for history of cardiovascular comorbidity and smoking. However, diabetes data were available and adjusted for in all multivariate models. Moreover, many other covariates included in the models have strong associations with comorbid conditions. Hence, we



**Table 3. Categories of Weight Change Percentage Over Time in 47,629 MHD Patients With at Least 2 Quarterly BMI**

Weight Change Category (%)	Group Population	All-Cause Mortality (%)	Baseline BMI (kg/m <sup>2</sup> )	Baseline Serum Albumin (g/dL)
>+5 (weight gain)	1,038 (2.2)	29.2	22.3 ± 6.2	3.61 ± 0.44
+4 to +5	625 (1.3)	24.0	24.2 ± 5.5	3.68 ± 0.39
+3 to +4	1,319 (2.8)	21.6	24.5 ± 5.7	3.70 ± 0.39
+2 to +3	2,680 (5.6)	19.3	25.2 ± 6.0	3.73 ± 0.37
+1 to +2	5,510 (11.6)	17.4	25.7 ± 5.9	3.78 ± 0.36
-1 to +1 (no change)	22,784 (47.8)	17.5	26.5 ± 6.2	3.85 ± 0.34
-2 to -1	6,189 (13.0)	27.1	26.8 ± 6.3	3.78 ± 0.37
-3 to -2	3,102 (6.5)	33.7	26.9 ± 6.4	3.73 ± 0.38
-4 to -2	1,649 (3.5)	43.2	27.2 ± 6.4	3.66 ± 0.40
-5 to -4	909 (1.9)	48.1	26.8 ± 6.3	3.58 ± 0.41
<-5 (weight loss)	1,824 (3.8)	53.7	26.4 ± 6.7	3.49 ± 0.47

NOTE. Values expressed as number (percent) or mean ± SD unless noted otherwise. To convert albumin in g/dL to g/L, multiply by 10.

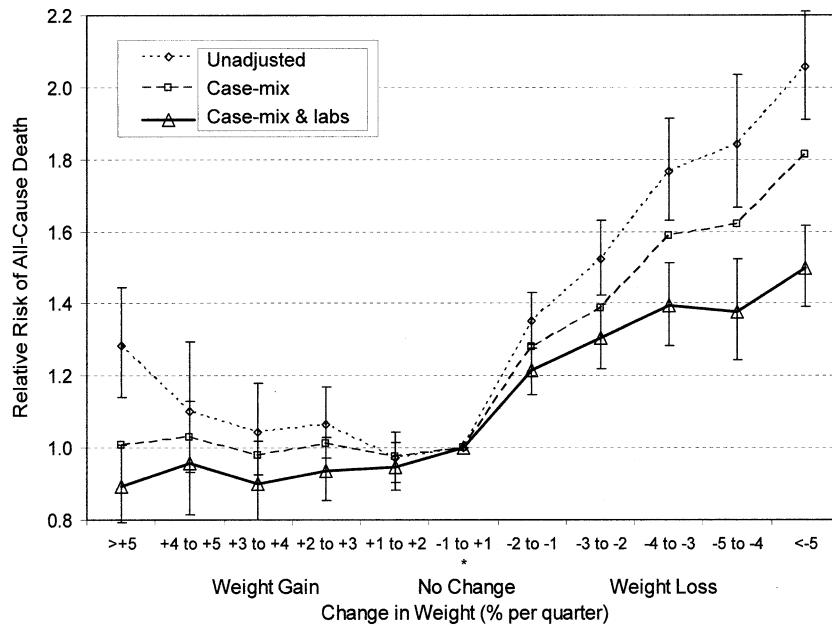
suspect that the associations would not have been very different if additional adjustments had been made for other comorbidity. Our adjustments are not too different from those of past studies because the limited comorbidity data used in those studies usually originated from the

dialysis initiation form (Form 2728), in which comorbid conditions are significantly underreported,<sup>58</sup> and that is outdated for prevalent patients with higher vintage periods. Another limitation of our study is the lack of explicit laboratory markers of inflammation, such as C-reactive pro-

**Table 4. Hazard Ratio of Death for Categories of Weight Change Percentage Over Time**

Weight Change Category (%)	Unadjusted		Case-Mix Adjusted		Case-Mix & MICS Adjusted	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
<b>All-cause mortality</b>						
>+5 (weight gain)	1.28 (1.14-1.44)	<0.001	1.01 (0.89-1.14)	0.897	0.89 (0.79-1.01)	0.068
+4 to +5	1.10 (0.93-1.30)	0.255	1.03 (0.87-1.21)	0.734	0.96 (0.81-1.13)	0.605
+3 to +4	1.04 (0.93-1.18)	0.478	0.98 (0.87-1.11)	0.750	0.90 (0.80-1.02)	0.094
+2 to +3	1.07 (0.97-1.17)	0.175	1.01 (0.92-1.11)	0.788	0.94 (0.85-1.03)	0.169
+1 to +2	0.97 (0.91-1.04)	0.421	0.98 (0.91-1.05)	0.521	0.95 (0.88-1.02)	0.124
-1 to +1 (no change)	1.00	NA	1.00	NA	1.00	NA
-2 to -1	1.35 (1.28-1.43)	<0.001	1.28 (1.21-1.36)	<0.001	1.21 (1.15-1.29)	<0.001
-3 to -2	1.52 (1.42-1.63)	<0.001	1.39 (1.30-1.49)	<0.001	1.30 (1.22-1.40)	<0.001
-4 to -2	1.77 (1.63-1.91)	<0.001	1.59 (1.46-1.72)	<0.001	1.39 (1.28-1.51)	<0.001
-5 to -4	1.84 (1.67-2.04)	<0.001	1.62 (1.47-1.79)	<0.001	1.38 (1.24-1.52)	<0.001
<-5 (weight loss)	2.06 (1.91-2.21)	<0.001	1.81 (1.68-1.95)	<0.001	1.50 (1.39-1.62)	<0.001
<b>Cardiovascular mortality</b>						
>+5 (weight gain)	1.20 (1.01-1.44)	0.043	0.96 (0.80-1.15)	0.645	0.86 (0.71-1.03)	0.101
+4 to +5	1.05 (0.81-1.34)	0.728	0.99 (0.77-1.28)	0.955	0.93 (0.72-1.19)	0.562
+3 to +4	0.95 (0.78-1.14)	0.558	0.90 (0.75-1.09)	0.289	0.84 (0.69-1.01)	0.064
+2 to +3	1.10 (0.97-1.26)	0.143	1.06 (0.93-1.21)	0.409	0.99 (0.87-1.13)	0.878
+1 to +2	0.97 (0.87-1.08)	0.556	0.98 (0.89-1.09)	0.766	0.95 (0.86-1.06)	0.361
-1 to +1 (no change)	1.00	NA	1.00	NA	1.00	NA
-2 to -1	1.29 (1.19-1.41)	<0.001	1.23 (1.13-1.34)	<0.001	1.18 (1.08-1.29)	<0.001
-3 to -2	1.41 (1.27-1.57)	<0.001	1.28 (1.15-1.42)	<0.001	1.22 (1.10-1.36)	<0.001
-4 to -2	1.51 (1.33-1.71)	<0.001	1.34 (1.17-1.52)	<0.001	1.21 (1.06-1.38)	0.004
-5 to -4	1.68 (1.44-1.96)	<0.001	1.49 (1.28-1.75)	<0.001	1.33 (1.14-1.56)	<0.001
<-5 (weight loss)	1.90 (1.70-2.13)	<0.001	1.64 (1.46-1.84)	<0.001	1.44 (1.28-1.62)	<0.001

Abbreviations: MICS, malnutrition-inflammation complex syndrome; HR, hazard ratio; CI, confidence interval; NA, not applicable.

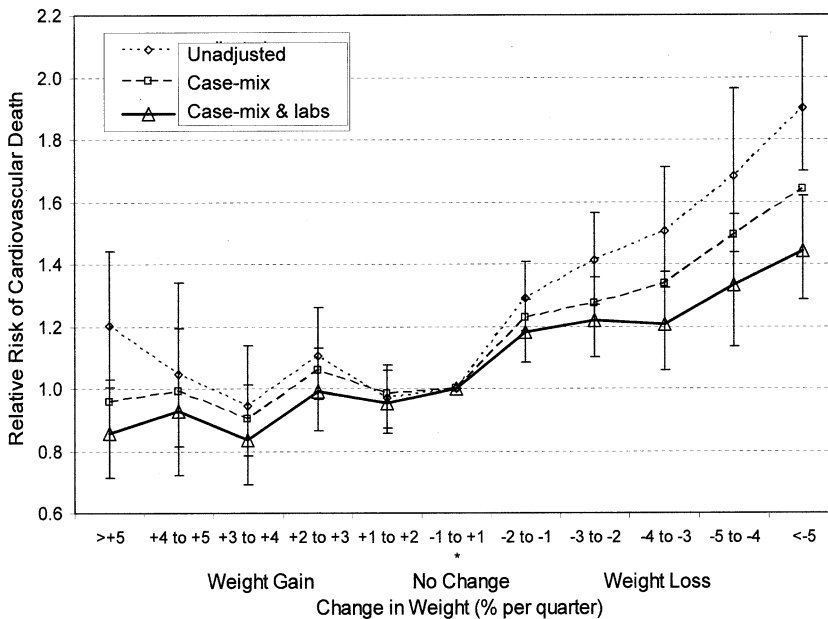


**Fig 4.** Association between the rate of weight change over time and subsequent all-cause mortality in 46,629 MHD patients (95% confidence interval bars are not shown for the case-mix-adjusted group to enable better distinction of confidence intervals for other 2 groups).

tein level. However, we used data for serum albumin and ferritin, TIBC, and WBCs, which may have associations with inflammation.

Among the strengths of our study is the use of time-dependent models to examine the association between quarterly-varying weight on cardiovascular mortality while controlling for the time-varying effect of laboratory surrogates of nutritional status. A limitation of our time-

dependent analysis is that it is based on 2-year cross-sections of the cohort, rather than longer longitudinal follow-up over many years, and thus may not apply to long-term survival of individuals. Nonetheless, the narrow time window of our study ensures that confounding by changes in practice or technology is minimal. Our time-dependent findings are supported by the observed relations of different rates of weight



**Fig 5.** Association between the rate of weight change over time and subsequent cardiovascular mortality in 46,629 MHD patients (95% confidence interval bars are not shown for the case-mix-adjusted group to enable better distinction of the confidence intervals for other 2 groups).

gain and weight loss over time with cardiovascular survival. Data originate from 1 dialysis care provider that has uniform patient management practices; all laboratory measurements are performed in 1 facility, and most data are means of several measures. Hence, measurement variability is minimized.

If causal, the inverse association of obesity with survival would have major clinical and public health implications. Hence, it may be time for clinical trials of weight-increasing interventions in populations that show reverse epidemiology. Currently, more than 60% of dialysis patients die within 5 years of starting dialysis treatment; thus, long-term consequences of such interventions may be of secondary concern. However, as more effective treatments for dialysis patients become available, these patients may live long enough for the long-term adverse effects of obesity to come back into play, as found in kidney transplant recipients<sup>59</sup>; hence, so-called “reversal of the reverse epidemiology” or “back to normal.” However, because the causality of our reported associations is not known, extreme caution needs to be practiced. Therefore, initial trials would probably best be limited to patients with low initial BMIs (eg, BMI < 23 kg/m<sup>2</sup>), and even if weight gain is found to be beneficial for short-term survival, periodic reevaluation of its net long-term effects will be needed.

## REFERENCES

1. Foley RN, Parfrey PS, Sarnak MJ: Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 32:S112-S119, 1998 (suppl 3)
2. US Renal Data System: Excerpts from the USRDS 2004 Annual Data Report. *Am J Kidney Dis* 45:S1-S280, 2005 (suppl 1)
3. Wanner C, Krane V, Marz W, et al: Randomized controlled trial on the efficacy and safety of atorvastatin in patients with type 2 diabetes on hemodialysis (4D study): Demographic and baseline characteristics. *Kidney Blood Press Res* 27:259-266, 2004
4. Eknoyan G, Beck GJ, Cheung AK, et al: Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med* 347:2010-2019, 2002
5. Salahudeen AK: Obesity and survival on dialysis. *Am J Kidney Dis* 41:925-932, 2003
6. Kalantar-Zadeh K, Abbott KC, Salahudeen AK, Kilpatrick RD, Horwich TB: Survival advantages of obesity in dialysis patients. *Am J Clin Nutr* 81:543-554, 2005
7. Kalantar-Zadeh K, Kilpatrick RD, McAllister CJ, Greenland S, Kopple JD: Reverse epidemiology of hypertension and cardiovascular death in the hemodialysis population: The 58th annual fall conference and scientific sessions. *Hypertension* 45:811-817, 2005
8. Nishizawa Y, Shoji T, Ishimura E, Inaba M, Morii H: Paradox of risk factors for cardiovascular mortality in uremia: Is a higher cholesterol level better for atherosclerosis in uremia? *Am J Kidney Dis* 38:S4-S7, 2001 (suppl 1)
9. Kalantar-Zadeh K, Block G, Humphreys MH, McAllister CJ, Kopple JD: A low, rather than a high, total plasma homocysteine is an indicator of poor outcome in hemodialysis patients. *J Am Soc Nephrol* 15:442-453, 2004
10. Kalantar-Zadeh K, Block G, Humphreys MH, Kopple JD: Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. *Kidney Int* 63:793-808, 2003
11. Kalantar-Zadeh K, Kilpatrick RD, Kuwae N, Wu DY: Reverse epidemiology: A spurious hypothesis or a hardcore reality? *Blood Purif* 23:57-63, 2005
12. Curtis JP, Selter JG, Wang Y, et al: The obesity paradox: Body mass index and outcomes in patients with heart failure. *Arch Intern Med* 165:55-61, 2005
13. Joint WHO/FAO Expert Consultation on Diet Nutrition and the Prevention of Chronic Diseases: Diet, Nutrition and the Prevention of Chronic Diseases: Report of a Joint WHO/FAO Expert Consultation. Geneva, Switzerland, World Health Organization, 2003
14. Kalantar-Zadeh K, Ikizler TA, Block G, Avram MM, Kopple JD: Malnutrition-inflammation complex syndrome in dialysis patients: Causes and consequences. *Am J Kidney Dis* 42:864-881, 2003
15. Owen WF Jr, Lew NL, Liu Y, Lowrie EG, Lazarus JM: The urea reduction ratio and serum albumin concentration as predictors of mortality in patients undergoing hemodialysis. *N Engl J Med* 329:1001-1006, 1993
16. Kalantar-Zadeh K, Supasyndh O, Lehn RS, McAllister CJ, Kopple JD: Normalized protein nitrogen appearance is correlated with hospitalization and mortality in hemodialysis patients with Kt/V greater than 1.20. *J Ren Nutr* 13:15-25, 2003
17. Kalantar-Zadeh K, Kleiner M, Dunne E, et al: Total iron-binding capacity—estimated transferrin correlates with the nutritional subjective global assessment in hemodialysis patients. *Am J Kidney Dis* 31:263-272, 1998
18. Kalantar-Zadeh K, Rodriguez RA, Humphreys MH: Association between serum ferritin and measures of inflammation, nutrition and iron in haemodialysis patients. *Nephrol Dial Transplant* 19:141-149, 2004
19. Beddhu S, Samore MH, Roberts MS, Stoddard GJ, Pappas LM, Cheung AK: Creatinine production, nutrition, and glomerular filtration rate estimation. *J Am Soc Nephrol* 14:1000-1005, 2003
20. Reddan DN, Klassen PS, Szczech LA, et al: White blood cells as a novel mortality predictor in haemodialysis patients. *Nephrol Dial Transplant* 18:1167-1173, 2003
21. Wolfson M, Strong CJ, Minturn D, Gray DK, Kopple JD: Nutritional status and lymphocyte function in maintenance hemodialysis patients. *Am J Clin Nutr* 39:547-555, 1984
22. Kuwae N, Kopple JD, Kalantar-Zadeh K: A low lymphocyte percentage is a predictor of mortality and hospitalization in hemodialysis patients. *Clin Nephrol* 63:22-34, 2005

23. Lowrie EG: Acute-phase inflammatory process contributes to malnutrition, anemia, and possibly other abnormalities in dialysis patients. *Am J Kidney Dis* 32:S105-S112, 1998 (suppl 1)
24. Kalbfleisch JD, Prentice RL: *The Statistical Analysis of Failure-Time Data* (ed 2). New York, NY, Wiley, 2002
25. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW Jr: Body-mass index and mortality in a prospective cohort of US adults. *N Engl J Med* 341:1097-1105, 1999
26. Kuczmarski RJ, Flegal KM, Campbell SM, Johnson CL: Increasing prevalence of overweight among US adults. The National Health and Nutrition Examination Surveys, 1960 to 1991. *JAMA* 272:205-211, 1994
27. Byers T: Body weight and mortality. *N Engl J Med* 333:723-724, 1995
28. Manson JE, Willett WC, Stampfer MJ, et al: Body weight and mortality among women. *N Engl J Med* 333:677-685, 1995
29. Mark DH: Deaths attributable to obesity. *JAMA* 293:1918-1919, 2005
30. Flegal KM, Graubard BI, Williamson DF, Gail MH: Excess deaths associated with underweight, overweight, and obesity. *JAMA* 293:1861-1867, 2005
31. Kushner RF: Body weight and mortality. *Nutr Rev* 51:127-136, 1993
32. Degoulet P, Legrain M, Reach I, et al: Mortality risk factors in patients treated by chronic hemodialysis. Report of the Diaphane Collaborative Study. *Nephron* 31:103-110, 1982
33. Leavey SF, McCullough K, Hecking E, Goodkin D, Port FK, Young EW: Body mass index and mortality in 'healthier' as compared with 'sicker' haemodialysis patients: Results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant* 16:2386-2394, 2001
34. Leavey SF, Strawderman RL, Jones CA, Port FK, Held PJ: Simple nutritional indicators as independent predictors of mortality in hemodialysis patients. *Am J Kidney Dis* 31:997-1006, 1998
35. Fleischmann E, Teal N, Dudley J, May W, Bower JD, Salahudeen AK: Influence of excess weight on mortality and hospital stay in 1346 hemodialysis patients. *Kidney Int* 55:1560-1567, 1999
36. Wong JS, Port FK, Hulbert-Shearon TE, et al: Survival advantage in Asian American end-stage renal disease patients. *Kidney Int* 55:2515-2523, 1999
37. Abbott KC, Glanton CW, Trespalacios FC, et al: Body mass index, dialysis modality, and survival: Analysis of the United States Renal Data System Dialysis Morbidity and Mortality Wave II Study. *Kidney Int* 65:597-605, 2004
38. Glanton CW, Hypolite IO, Hsieh PB, Agodoa LY, Yuan CM, Abbott KC: Factors associated with improved short term survival in obese end stage renal disease patients. *Ann Epidemiol* 13:136-143, 2003
39. Johansen KL, Young B, Kaysen GA, Chertow GM: Association of body size with outcomes among patients beginning dialysis. *Am J Clin Nutr* 80:324-332, 2004
40. Wolfe RA, Ashby VB, Daugirdas JT, Agodoa LY, Jones CA, Port FK: Body size, dose of hemodialysis, and mortality. *Am J Kidney Dis* 35:80-88, 2000
41. Port FK, Ashby VB, Dhingra RK, Roys EC, Wolfe RA: Dialysis dose and body mass index are strongly associated with survival in hemodialysis patients. *J Am Soc Nephrol* 13:1061-1066, 2002
42. Kopple JD, Zhu X, Lew NL, Lowrie EG: Body weight-for-height relationships predict mortality in maintenance hemodialysis patients. *Kidney Int* 56:1136-1148, 1999
43. Beddhu S, Pappas LM, Ramkumar N, Samore M: Effects of body size and body composition on survival in hemodialysis patients. *J Am Soc Nephrol* 14:2366-2372, 2003
44. Kaizu Y, Tsunega Y, Yoneyama T, et al: Overweight as another nutritional risk factor for the long-term survival of non-diabetic hemodialysis patients. *Clin Nephrol* 50:44-50, 1998
45. Kutner NG, Zhang R: Body mass index as a predictor of continued survival in older chronic dialysis patients. *Int Urol Nephrol* 32:441-448, 2001
46. Kalantar-Zadeh K, Block G, Horwich T, Fonarow GC: Reverse epidemiology of conventional cardiovascular risk factors in patients with chronic heart failure. *J Am Coll Cardiol* 43:1439-1444, 2004
47. Stevens J, Cai J, Pamuk ER, Williamson DF, Thun MJ, Wood JL: The effect of age on the association between body-mass index and mortality. *N Engl J Med* 338:1-7, 1998
48. Landi F, Onder G, Gambassi G, Pedone C, Carbone P, Bernabei R: Body mass index and mortality among hospitalized patients. *Arch Intern Med* 160:2641-2644, 2000
49. Yeh S, Wu SY, Levine DM, et al: Quality of life and stimulation of weight gain after treatment with megestrol acetate: Correlation between cytokine levels and nutritional status, appetite in geriatric patients with wasting syndrome. *J Nutr Health Aging* 4:246-251, 2000
50. Chlebowski RT, Grosvenor M, Lillington L, Sayre J, Beall G: Dietary intake and counseling, weight maintenance, and the course of HIV infection. *J Am Diet Assoc* 95:428-432; quiz, 433-435, 1995
51. Liu Y, Coresh J, Eustace JA, et al: Association between cholesterol level and mortality in dialysis patients: Role of inflammation and malnutrition. *JAMA* 291:451-459, 2004
52. Kalantar-Zadeh K: Causes and consequences of the reverse epidemiology of body mass index in dialysis patients. *J Ren Nutr* 15:142-147, 2005
53. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Woo MA, Tillisch JH: The relationship between obesity and mortality in patients with heart failure. *J Am Coll Cardiol* 38:789-795, 2001
54. Mohamed-Ali V, Goodrick S, Bulmer K, Holly JM, Yudkin JS, Coppel SW: Production of soluble tumor necrosis factor receptors by human subcutaneous adipose tissue in vivo. *Am J Physiol* 277:E971-E975, 1999
55. Weber MA, Neutel JM, Smith DH: Contrasting clinical properties and exercise responses in obese and

lean hypertensive patients. *J Am Coll Cardiol* 37:169-174, 2001

56. Rauchhaus M, Coats AJ, Anker SD: The endotoxin-lipoprotein hypothesis. *Lancet* 356:930-933, 2000

57. Macleod J, Davey Smith G: Psychosocial factors and public health: A suitable case for treatment? *J Epidemiol Community Health* 57:565-570, 2003

58. Longenecker JC, Coresh J, Klag MJ, et al: Validation of comorbid conditions on the end-stage renal disease medical evidence report: The CHOICE study. *Choices for Healthy Outcomes in Caring for ESRD*. *J Am Soc Nephrol* 11:520-529, 2000

59. Pischon T, Sharma AM: Obesity as a risk factor in renal transplant patients. *Nephrol Dial Transplant* 16:14-17, 2001