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Examining the robustness of the obesity paradox in maintenance hemodialysis patients: a marginal structural model analysis

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ORIGINAL ARTICLE

ABSTRACT

Background. The inverse association between body mass index (BMI) and mortality observed in patients treated with maintenance hemodialysis (MHD), also known as the obesity paradox, may be a result of residual confounding. Marginal structural model (MSM) analysis, a technique that accounts for time-varying confounders, may be more appropriate to investigate this association. We hypothesize that after applying MSM, the inverse association between BMI and mortality in MHD patients is attenuated.
Methods. We examined the associations between BMI and all-cause mortality among 123 624 adult MHD patients treated during 2001–6. We examined baseline and time-varying BMI using Cox proportional hazards models and MSM while considering baseline and time-varying covariates, including demographics, comorbidities and markers of malnutrition and inflammation.
Results. The patients included 45% women and 32% African Americans with a mean age of 61(SD 15) years. In all models, BMI showed a linear incremental inverse association with mortality. Compared with the reference (BMI 25 to <27.5 kg/m^2), a BMI of <18 kg/m^2 was associated with a 3.2-fold higher death risk [hazard ratio (HR) 3.17 (95% CI 3.05–3.29)], and mortality risks declined with increasing BMI with the greatest survival advantage of 31% lower risk [HR 0.69 (95% CI 0.64–0.75)] observed with a BMI of 40 to <45 kg/m^2.
Conclusions. The linear inverse relationship between BMI and mortality is robust across models including MSM analyses that more completely account for time-varying confounders and biases.

Keywords: cardiovascular, dialysis, epidemiology, nutrition, obesity

INTRODUCTION

The prevalence of obesity has risen in America with more than one-third of adults and ∼17% of children considered obese in 2009–10 [1]. As an important risk factor for cardiovascular disease [2] and chronic kidney disease (CKD) [3], obesity is associated with increased risk of mortality in the general population [4]. However, in a seemingly paradoxical manner, obesity has been found to be associated with better survival in patients with chronic diseases such as congestive heart failure, chronic obstructive pulmonary disease and rheumatoid arthritis [5–7]. In particular, many observational studies in nephrology have demonstrated the phenomenon known as the 'obesity paradox' or 'reverse epidemiology', where obesity and mortality have an inverse relationship [8–12]. This relationship is particularly strong and consistent among patients with CKD stage 5 requiring maintenance hemodialysis (MHD) [13].

However, MHD patients are at especially high risk for frequent hospitalizations, infection and inflammation, often leading to worsening nutritional status with significant weight fluctuation [14]. Weight fluctuations may occur due to changes in prescribed dietary intake, dialysis dose and other factors that can change according to direction from healthcare providers including nephrologists and dietitians. Weight fluctuations can also occur as a result of protein-energy wasting or malnutrition, which may both lead to as well as result from inflammation

[15–17]. The relationship between body mass index (BMI) and changes in nutrition and inflammatory markers is dynamic. Thus, prior studies that evaluate the relationship between a fixed baseline BMI and long-term outcomes would be particularly susceptible to confounders and time-varying biases. While different analytical techniques have been used to investigate this complex association, uncorrected biases remain a concern [18].

Marginal structural model (MSM) analysis is a statistical technique used to estimate the causal effects of a time-varying exposure in the presence of time-varying covariates, which may simultaneously function as confounders and intermediate variables [19].

In the analysis of BMI and mortality associations, baseline as well as time-varying covariates may affect BMI levels. Certain BMI levels along with other markers of nutrition and inflammation may be associated with a higher probability of kidney transplant censoring, or informed censoring. The MSM method attempts to account for these potential time-varying biases by creating weights for each subject at each time interval according to the inverse probability of them being at their exposure (BMI) level for that time interval as well as them not having been censored at a prior time interval. The weights are constructed according to baseline and time-varying covariates and attempts to address time-varying confounding leading to BMI fluctuations (changes in exposure level) or informative censoring (BMI level leading to a higher probability of kidney transplant). Holding particular assumptions true in the use of MSM, associations found from MSM are believed to have a causal interpretation. We hypothesize that the inverse association between BMI and mortality in MHD patients is robust after the use of MSM to adjust for the confounders and intermediate variables.

METHODS

Study population and data

We extracted and examined data from all patients with end-stage renal disease who underwent hemodialysis treatments between July 2001 and June 2006 in any one of the 580 US outpatient dialysis facilities of DaVita, Inc. The creation of the DaVita MHD patient cohort has been described previously [20]. Only patients with a total dialysis treatment duration >90 days were included in the cohort. We additionally restricted our analysis to patients who were >18 or <99 years old and who were treated with only hemodialysis over the entire duration of follow-up. We further excluded those patients with missing BMI data ($n = 13\,486$) and those with BMI data of <12 or >60 kg/m^2 The final study population consisted of 123 624 patients (Figure 1). The study was approved by the institutional review committees of the Los Angeles Biomedical Research Institute at Harbor-University of California Los Angeles Medical Center and the University of California Irvine. The requirement for written consent was exempted due to the large sample size, patient anonymity and nonintrusive nature of the research.

Clinical measures and laboratory parameters for each patient were obtained during the study period (1 July 2001–31 March 2006) and patients were followed for outcomes until 31 March 2006. To minimize measurement variability, all repeated measures for each patient during any calendar quarter (i.e. over a 13-week interval) were averaged by the dialysis provider and summary estimates were used in all models. Quarterly averaged values were obtained for up to 19 calendar quarters (Q1–Q19) for each laboratory and clinical measure for each patient during the 5-year cohort period. Dialysis vintage was defined as the duration of time between a patient's first hemodialysis treatment and the first day of the baseline calendar quarter in which the patient entered the cohort. The first (baseline) studied quarter for each patient was the calendar quarter in which a patient's vintage was >90 days.

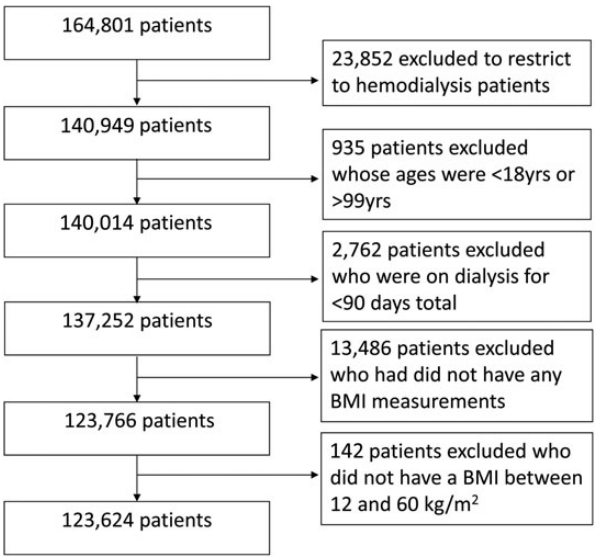

FIGURE 1: Cohort construction.

Demographic data were obtained from the DaVita database. A history of preexisting comorbid conditions and tobacco smoking were obtained by linking the DaVita database to the data from Medical Evidence Form 2728 from the U.S. Renal Data System (USRDS). Available preexisting comorbidities were grouped into seven categories: atherosclerotic heart disease, congestive heart failure, hypertension, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease and cancer.

Outcome measure

All-cause mortality was defined by date of death if it occurred during the follow-up period (1 July 2001–31 March 2006). Death information was obtained through the USRDS database. Patients who received a kidney transplant or who were lost to follow-up were censored. The proportion of patients censored for kidney transplantation and being lost to follow-up were 8.3 and 9.8%, respectively. Patient follow-up time was measured in days from the first day of the patient's baseline quarter until death or censoring due to transplant, loss to follow-up or end of study period (31 March 2006), whichever occurred first.

Main predictor of exposure

The primary exposure of interest is BMI. Each patient's weight was measured and recorded at the beginning and the end of every dialysis treatment. BMI was calculated by dividing a patient's postdialysis weight in kilograms by his/her height in meters squared. BMI was divided into 11 preselected ordinal categories: <18, 18 to <20, 20 to <21.5, 21.5 to <23, 23 to <25, 25 to <27.5, 27.5 to <30, 30 to <35, 35 to <40, 40 to <45 and ≥45 kg/m^2. The BMI category of 25 to <27.5 kg/m^2 was designated as the reference group because the National Kidney Foundation-Kidney Disease Outcome Quality Initiative guidelines have recommended that a BMI of at least 23.6 and 24 kg/m^2 be maintained in male and female MHD patients, respectively [21].

Laboratory measures

Blood samples were drawn using standardized techniques in all DaVita dialysis clinics and were transported to the DaVita Laboratory in Deland, FL, USA, typically within 24 h. All laboratory values were measured using automated and standardized methods in the DaVita laboratory. Most laboratory parameters were measured monthly, including complete blood cell counts, and serum levels of urea nitrogen, creatinine, albumin, bicarbonate, lymphocytes, hemoglobin, calcium, phosphorus, single-pool Kt/V and total iron-binding capacity (TIBC). The normalized protein equivalent of total nitrogen appearance (nPNA), known as normalized protein catabolic rate (nPCR), was measured monthly as an indicator of daily protein intake. Serum ferritin levels were measured at least quarterly. All blood samples were collected prior to hemodialysis, except for postdialysis serum urea nitrogen, to calculate urea kinetics.

Statistical analyses

Cox proportional hazards regression models were used to study the associations of baseline and time-varying BMI with mortality separately. In baseline models, BMI and covariates were determined at baseline and their association with mortality was estimated. In time-varying models, BMI and covariates were calculated and updated at each quarter over the entire follow-up period to assess short-term associations between BMI and risk of death. Patients who had a change in BMI in a subsequent patient quarter could cross over to a different BMI exposure category for that quarter.

Both of the models adjusted for the following baseline (fixed-in-time) covariates: entry calendar quarter, age, sex, race/ethnicity (non-Hispanic Caucasian, African American, Hispanic, Asian and other), dialysis vintage categories (3 to <6 months, 6 to <24 months, 2 to <5 years and ≥5 years), primary insurance (Medicare, Medicaid, private and others), presence of diabetes, seven preexisting comorbidities and history of tobacco smoking. Additionally, the following covariates were also adjusted for in baseline and time-varying models (in baseline models—baseline values were used and in time-varying models—values were time-updated per quarter): single-pool Kt/V, serum albumin levels, TIBC, ferritin, creatinine, bicarbonate, hemoglobin, peripheral white blood cell count (WBC), nPCR, calcium, phosphorus and lymphocyte percentage.

A MSM fitted with stabilized weights (SWs) was used to determine the effects of BMI on mortality while controlling for the effects of time-varying confounders affected by previous BMI levels. The SW used in MSM analysis was calculated with the product of stabilized inverse probability of treatment weight (IPTW) and inverse probability of censoring weight (IPCW). Stabilized IPTW and IPCW were calculated from the ratio of (i) the estimated probabilities of BMI levels (or censorship) using previous delivered BMI and fixed baseline covariate values (numerator) to (ii) the estimated probabilities of BMI (or censorship) using previous BMI, fixed baseline covariates and time-varying covariates (denominator) as described in previous studies [22–25]. Multinomial logistic regression was used to estimate the numerators and denominators of the IPTW and IPCW. Weights were stabilized with numerator probabilities to reduce the variability in weight accounted for by patients with very low or very high probabilities of presence in their respective BMI exposure group. Stabilized weights also provide narrower confidence intervals for model estimates [19, 26]. Fixed baseline covariates included age, sex, race/ethnicity, dialysis vintage categories, primary insurance, presence of diabetes, the seven preexisting comorbidities, history of tobacco smoking and baseline measurements of the following nine laboratory values: serum levels of albumin, TIBC, ferritin, creatinine, bicarbonate, hemoglobin, peripheral WBC and lymphocyte percentage. Time-varying covariates included time-updated values for these nine laboratory measurements. For analysis with MSM, Cox proportional hazards models fitted using SWs were used to calculate hazard ratios for the risk of dying associated with BMI category. The distribution of SWs over cumulative quarters in MSM is shown in Supplementary data, Figure S1. Missing values of time-varying covariates (<1% for most laboratory variables) were imputed using the values in the previous quarter, whereas missing data on fixed baseline covariates (<3% for most demographic variables) were imputed by the means or medians of the existing values as appropriate. The same study population was used for the analyses with the Cox proportional hazards model and MSM. MSM analysis was also performed in predetermined subgroups of patients based on baseline age, sex, race/ethnicity, presence or absence of diabetes mellitus and vintage category. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Patient characteristics

The baseline demographics and clinical and laboratory characteristics of the patients stratified by categories of BMI are summarized in Tables 1 and 2. Based on baseline BMI during the follow-up period, 4795(4%), 9297 (8%), 11 099 (9%), 13 521 (11%), 18 422(15%), 20 060(16%), 15 098(12%), 17 767(14%), 8072(7%), 3346(3%) and 2156(2%) were grouped in the respective categories 1–11 for analysis.

The mean age of 123 624 MHD patients was 61 (SD 15) years, 45% of the patients were women, 32 and 14% were African American and Hispanic, respectively, and 57% were diabetic. The mean baseline BMI was 26.8 (SD 6.8) kg/m^2.

Table 1. Baseline characteristics of 123 624 MHD patients stratified by baseline BMI categories

	Total	Baseline BMI (kg/m^2)										
		<18	18 to 20	20 to <21.5	21.5 to <23	23 to <25	25 to <27.5	27.5 to <30	30 to <35	35 to <40	40 to <45	≥45
n (%)	123 624	4795 (4)	9297 (8)	11 099 (9)	13 512 (11)	18 422 (15)	20 060 (16)	15 098 (12)	17 767 (14)	8072 (7)	3346 (3)	2156 (2)
Death (*n*, %)	48 078 (39)	2875 (60)	4715 (51)	5114 (46)	5812 (43)	7396 (40)	7350 (37)	5238 (35)	5656 (32)	2413 (30)	919 (27)	590 (27)
Death rate per 1000 person-years [95% CI]	235 [233–237]	465 [448–482]	341 [331–351]	293 [285–301]	263 [256–269]	242 [237–248]	215 [211–220]	201 [195–206]	183 [179–188]	170 [163–177]	159 [149–140]	159 [147–172]
CV death (*n*, %)	20 384 (16)	1095 (23)	1870 (20)	2136 (19)	2420 (18)	3228 (18)	3174 (16)	2266 (15)	2489 (14)	1064 (13)	397 (12)	245 (11)
CV death rate per 1000 person-years [95% CI]	99 [98–101]	177 [167–188]	135 [129–141]	122 [117–128]	109 [105–114]	106 [102–109]	93 [90–96]	87 [83–91]	81 [77–84]	75 [71–80]	69 [62–76]	66 [58–75]
Age (year) (mean ± SD)	61 ± 15	63 ± 18	62 ± 18	62 ± 17	63 ± 17	63 ± 16	63 ± 15	62 ± 14	60 ± 14	58 ± 13	56 ± 13	53 ± 12
Female (%)	45	59	49	43	40	38	40	43	50	57	60	62
Diabetes	57	36	40	45	49	54	58	64	69	72	74	72
Race (%)												
Caucasian	43	42	42	42	44	44	43	43	43	43	44	42
African-American	32	34	32	31	30	30	30	32	35	39	40	45
Hispanic	14	11	12	14	15	16	17	16	14	11	11	8
Asian	3	6	6	5	5	4	3	2	1	1	1	0
Other	7	7	8	7	7	7	7	7	6	6	5	5
Dialysis vintage (%)												
<6 months	53	54	53	53	53	53	53	52	52	52	53	54
6–12 months	19	16	17	17	18	18	19	20	20	20	21	21
2–5 years	18	16	16	17	17	18	18	18	20	19	19	18
>5 years	11	14	14	13	13	11	11	10	9	9	7	7
Insurance (%)												
Medicare	69	71	71	69	69	69	69	69	68	67	65	67
Medicaid	6	7	7	7	7	6	5	5	5	5	5	7
Private	11	10	10	11	11	11	11	11	11	10	10	9
Other	15	12	12	13	13	14	15	15	17	19	20	18
Marital status (%)												
Married	49	38	42	45	48	51	51	51	50	49	49	43
Divorced	8	8	8	8	8	8	8	8	9	9	10	10
Single	28	32	31	31	29	28	25	26	27	29	30	39
Widowed	16	22	20	17	16	16	15	15	14	13	11	8

Table 2. Comorbidities and lab values of 123 624 MHD patients stratified by baseline BMI categories

	Total	Baseline BMI (kg/m^2)										
		<18	18 to <20	20 to <21.5	21.5 to <23	23 to <25	25 to <27.5	27.5 to <30	30 to <35	35 to <40	40 to <45	≥45
Number of patients (*n*)	123 624	4795 (4)	9297 (8)	11 099 (9)	13 512 (11)	18 422 (15)	20 060 (16)	15 098 (12)	17 767 (14)	8072 (7)	3346 (3)	2156 (2)
Comorbidities (%)												
History of hypertension	79	75	76	77	78	79	79	81	82	82	83	82
Atherosclerotic heart disease	21	19	20	21	21	23	23	23	22	20	18	15
Congestive heart failure	27	26	25	26	25	27	27	28	29	30	32	34
Peripheral vascular disease	11	12	12	11	11	12	12	11	11	11	10	10
Cerebrovascular disease	7	9	9	8	8	8	7	7	7	6	5	5
COPD	6	9	7	6	5	5	5	5	5	6	7	9
Cancer	5	6	6	5	5	5	5	4	4	3	2	2
Current smoker	5	8	7	6	5	5	4	4	4	4	4	3
BMI (kg/m^2)	26.78 ± 6.59	16.68 ± 1.14	19.14 ± 0.57	20.79 ± 0.44	22.27 ± 0.44	24.00 ± 0.59	26.21 ± 0.73	28.68 ± 0.72	32.19 ± 1.45	37.16 ± 1.43	42.19 ± 1.43	49.78 ± 3.92
Kt/V (dialysis dose)	1.53 ± 0.36	1.68 ± 0.36	1.63 ± 0.36	1.6 ± 0.36	1.57 ± 0.36	1.54 ± 0.35	1.52 ± 0.35	1.49 ± 0.35	1.47 ± 0.34	1.42 ± 0.35	1.39 ± 0.36	1.32 ± 0.34
KRU (residual renal function) (mL/min)	0.45 ± 1.52	0.21 ± 0.90	0.31 ± 1.14	0.34 ± 1.25	0.41 ± 1.45	0.42 ± 1.36	0.47 ± 1.51	0.51 ± 1.61	0.55 ± 1.76	0.58 ± 1.89	0.67 ± 2.08	0.64 ± 1.91
Laboratory parameters												
Hemoglobin (g/dL)	12.00 ± 1.37	11.82 ± 1.50	11.96 ± 1.40	12.00 ± 1.40	12.02 ± 1.39	12.05 ± 1.39	12.05 ± 1.36	12.05 ± 1.33	12.00 ± 1.32	11.92 ± 1.30	11.88 ± 1.31	11.72 ± 1.28
Creatinine (mg/dL)	8.08 ± 3.3	6.77 ± 2.83	7.52 ± 3.1	7.88 ± 3.26	8.05 ± 3.33	8.13 ± 3.33	8.24 ± 3.34	8.27 ± 3.34	8.35 ± 3.37	8.29 ± 3.40	8.30 ± 3.44	8.52 ± 3.65
Albumin (g/dL)	3.68 ± 0.46	3.47 ± 0.54	3.59 ± 0.51	3.64 ± 0.49	3.67 ± 0.48	3.69 ± 0.46	3.72 ± 0.45	3.72 ± 0.44	3.75 ± 0.40	3.70 ± 0.41	3.68 ± 0.40	3.65 ± 0.38
TIBC (mg/dL)	207.87 ± 45.77	185.34 ± 48.20	195.52 ± 45.99	199.99 ± 45.26	204.05 ± 44.55	206.93 ± 44.36	210.00 ± 44.8	212.78 ± 44.58	215.74 ± 45.16	216.70 ± 45.32	220.27 ± 44.47	222.48 ± 46.36
WBC (×10^3/mm^3)	7.44 ± 2.50	7.68 ± 3.0	7.48 ± 2.91	7.35 ± 2.75	7.27 ± 2.41	7.31 ± 2.51	7.37 ± 2.45	7.39 ± 2.30	7.53 ± 2.33	7.77 ± 2.31	7.93 ± 2.29	8.04 ± 2.25
Lymphocyte (%)	20.56 ± 7.89	18.90 ± 8.14	19.69 ± 8.07	20.19 ± 8.12	20.19 ± 7.96	20.41 ± 7.89	20.68 ± 7.77	21.10 ± 7.83	21.22 ± 7.73	21.09 ± 7.68	20.93 ± 7.57	20.96 ± 7.52
Ferritin (ng/mL)	388 (184–725)	490 (231–887)	441 (214–802)	420 (202–776)	406 (195–751)	392 (184–726)	384 (181–714)	369 (176–695)	364 (171–681)	350 (166–657)	334 (157–617)	306 (153–600)
Bicarbonate (mg/dL)	22.25 ± 3.00	22.55 ± 3.47	22.35 ± 3.16	22.30 ± 3.10	22.27 ± 3.01	22.29 ± 2.97	22.19 ± 2.95	22.20 ± 2.93	22.17 ± 2.93	22.16 ± 2.91	22.20 ± 2.87	22.10 ± 2.90
nPNA (g/kg/day)	0.95 ± 0.26	0.92 ± 0.28	0.94 ± 0.27	0.95 ± 0.27	0.96 ± 0.26	0.96 ± 0.26	0.96 ± 0.26	0.95 ± 0.25	0.95 ± 0.25	0.94 ± 0.25	0.94 ± 0.26	0.93 ± 0.25
Calcium (mg/dL)	9.19 ± 0.72	9.11 ± 0.79	9.16 ± 0.75	9.16 ± 0.74	9.18 ± 0.73	9.19 ± 0.72	9.21 ± 0.70	9.21 ± 0.70	9.24 ± 0.71	9.23 ± 0.7	9.20 ± 0.7	9.18 ± 0.69
Phosphorus (mg/dL)	5.59 ± 1.50	5.30 ± 1.65	5.43 ± 1.53	5.48 ± 1.54	5.53 ± 1.50	5.53 ± 1.49	5.59 ± 1.47	5.64 ± 1.47	5.72 ± 1.48	5.79 ± 1.48	5.87 ± 1.48	5.93 ± 1.49

Data are presented as percentages and means (±SD). Median (interquartile range) is used for serum ferritin level.
COPD, chronic obstructive pulmonary disease; TIBC, total iron-binding capacity; WBC, white blood cells; nPNA, normalized protein nitrogen appearance.

At baseline, a total of 53% of patients were treated with dialysis for <6 months. The median duration of follow-up was 1.25 years (interquartile range 0.5–2.5). A total of 48 078 (39%) patients died during the follow-up and a total of 20 384 (16%) of patients died of cardiovascular causes. Notably, patients with a higher BMI tended to be younger, were more likely to be diabetic and had a lower achieved dialysis adequacy, but had higher residual renal function. Patients in the lowest BMI group tended to be older and had lower creatinine and albumin.

BMI and all-cause mortality

The observed association of BMI with mortality varied slightly according to the applied statistical models (Figure 2). An incrementally inverse relationship between BMI with all-cause mortality was observed using baseline and time-varying Cox proportional hazards regression models, and most significantly with the MSM analysis.

In the MSM analysis, when compared with the reference group of BMI of 25 to <27.5 kg/m^2, a BMI <18 kg/m^2 was associated with a 3.2-fold higher risk of mortality [HR 3.17 (95% CI 3.05–3.29)]. Mortality risks decreased significantly with increasing BMI, with the greatest survival advantage observed for patients with a BMI of 40 to <45 kg/m^2 in the MSM analysis (Figure 2).

BMI and cardiovascular mortality

The Cox proportional hazards models showed a similar inverse association between BMI and cardiovascular mortality (Figure 3). Again, the MSM analysis demonstrated a stronger association between BMI and cardiovascular mortality across the entire BMI spectrum, where the groups of BMI <18, 18 to <20, 20 to <21.5, 21.5 to <23 and 23 to <25 kg/m^2 had 175, 85, 52, 33 and 19% higher risk, respectively, of cardiovascular mortality as compared with the reference group in the total cohort. In contrast, a BMI of 27.5 to <30, 30 to <35, 35 to <40, 40 to <45 and ≥45 kg/m^2 had a 9, 14, 24, 28 and 27% lower mortality risk, respectively, in comparison with the reference group. Patients with a BMI of 40 to <45 kg/m^2 had the lowest cardiovascular mortality in the MSM analysis.

Subgroup analyses

All-cause mortality risks of different BMI groups were examined in patients stratified according to sex, age, race, diabetic status and vintage category. A similar inverse relationship between BMI and mortality was observed in all subgroups, although there appeared to be a markedly lower mortality risk among females, African Americans and non-diabetics with a BMI >27.5 kg/m^2 (Figure 4).

In terms of cardiovascular mortality, a similar trend was observed, as adjusted HRs were significantly higher for BMI categories <25 kg/m^2 and lower for those with a BMI >27.5 kg/m^2. This relationship is particularly strong among females and non-diabetic patients (Figure 5).

DISCUSSION

In a large contemporary cohort of 123 624 patients treated with thrice-weekly MHD in a single large US dialysis organization for up to 5 years, we found that a higher BMI up to 45 kg/m^2 was associated with lower all-cause and cardiovascular mortality, after adjustment for time-varying markers of nutritional and inflammatory status. Lower body weight was strongly associated with a higher risk of cardiovascular and all-cause death, whereas higher BMI clearly demonstrated improved survival and reduced cardiovascular mortality. These findings are in sharp contrast to the conventional epidemiology of obesity in the general population.

Our findings confirm previous observations of the obesity paradox among the MHD population. This phenomenon was first reported >30 years ago in the landmark Diaphane collaborative study, in which a low BMI of <20 kg/m^2 was associated with higher overall and cardiovascular mortality in

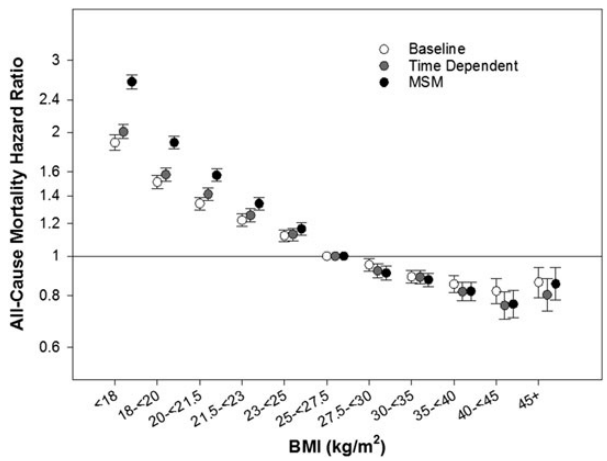

FIGURE 2: Hazard ratios (95% CI) for the associations between BMI categories (reference: 25 to <27.5 kg/m^2) and all-cause mortality obtained from baseline, time-varying and MSM models. Models adjusted for case-mix covariates and markers of malnutrition and inflammation (see text for covariate list).

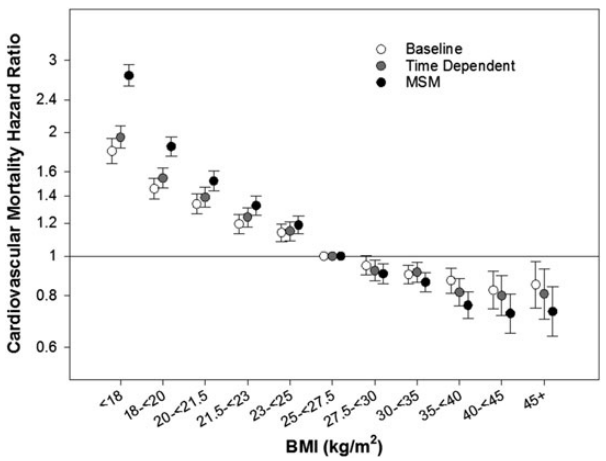

FIGURE 3: Hazard ratios (95% CI) for the associations between BMI categories (reference: 25 to <27.5 kg/m^2) and cardiovascular mortality obtained from baseline, time-varying and MSM models. Models adjusted for case-mix covariates and markers of malnutrition and inflammation (see text for covariate list).

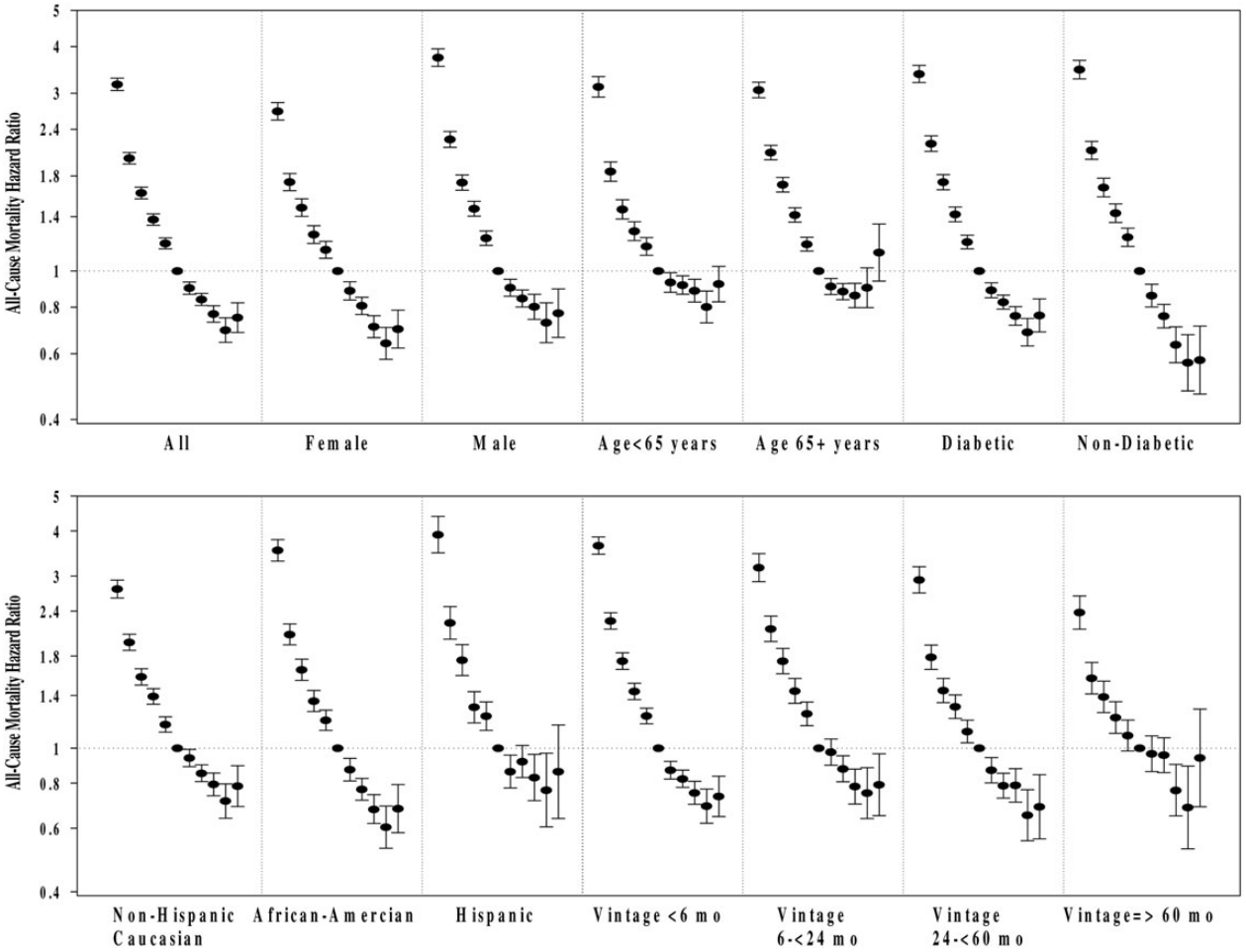

FIGURE 4: Subgroup analyses of the association between BMI categories (<18, 18 to <20, 20 to <21.5, 21.5 to <23, 23 to <25, 25 to <27.5 reference, 27.5 to <30, 30 to <35, 35 to <40, 40 to <45 and ≥45 kg/m^2) and all-cause mortality using a MSM. Models adjusted for case-mix covariates and markers of malnutrition and inflammation (see text for covariate list).

hemodialysis patients [27]. This finding was later verified in multiple observational and retrospective studies across different time periods, in secular trends and in several racial groups [28–31]. Most recently, in a study of >450 000 US veterans with earlier stages of CKD not yet dependent on dialysis, low BMI was again found to be associated with high mortality and kidney disease progression [32]. Another notable finding in our study is the relationship between cardiovascular mortality and obesity. While obesity leads to the development of metabolic syndrome and risk factors that are often the ultimate cause of kidney disease and renal failure, based on our findings, obesity appears to be associated with fewer cardiac-attributed deaths in the MHD population. Several explanations for the obesity paradox have been postulated. First, obese patients may have a more stable hemodynamic status, allowing for better fluid removal during dialysis, better tolerance for antihypertensive agents and better management of heart failure and cardiac disease. Second, obesity may provide more lipoproteins, which can actively bind and remove endotoxins. While heightened sympathetic and renin-angiotensin activities are associated with a poor prognosis in cardiac patients with heart failure, obesity may be associated with an altered neurohormonal stress response, leading to a reduced maladaptive response and possibly resulting in better cardiac function [33]. Another possible explanation for the obesity paradox phenomenon may be due to the time discrepancy between competitive risk factors. While obesity is a major long-term cardiovascular risk factor, MHD patients have a very high short-term mortality risk within 5 years of commencing dialysis treatment [34]. Therefore, long-term effects of conventional risk factors on future mortality may be overwhelmed by the short-term effects of acute illnesses, inflammation, subsequent protein-energy wasting and malnutrition. Thus, in end-stage renal disease patients with short life expectancy, treatment of obesity may not necessarily result in long-term benefit.

A potential criticism of the obesity paradox is the use of BMI as a measure of nutritional status in the CKD population [35]. We acknowledge that BMI is not the best indicator of body composition, as it does not differentiate lean muscle mass or body water from adiposity [36–38]. Lean body mass can serve as an index of muscle and somatic protein storage, whereas fat mass more directly reflects energy storage. The impact of body composition on mortality remains complicated. Two recent studies found survival advantages with both higher mid-arm muscle circumference (MAMC), a surrogate of muscle mass, and greater triceps skin fold (TSF), a measure of fat [39, 40].

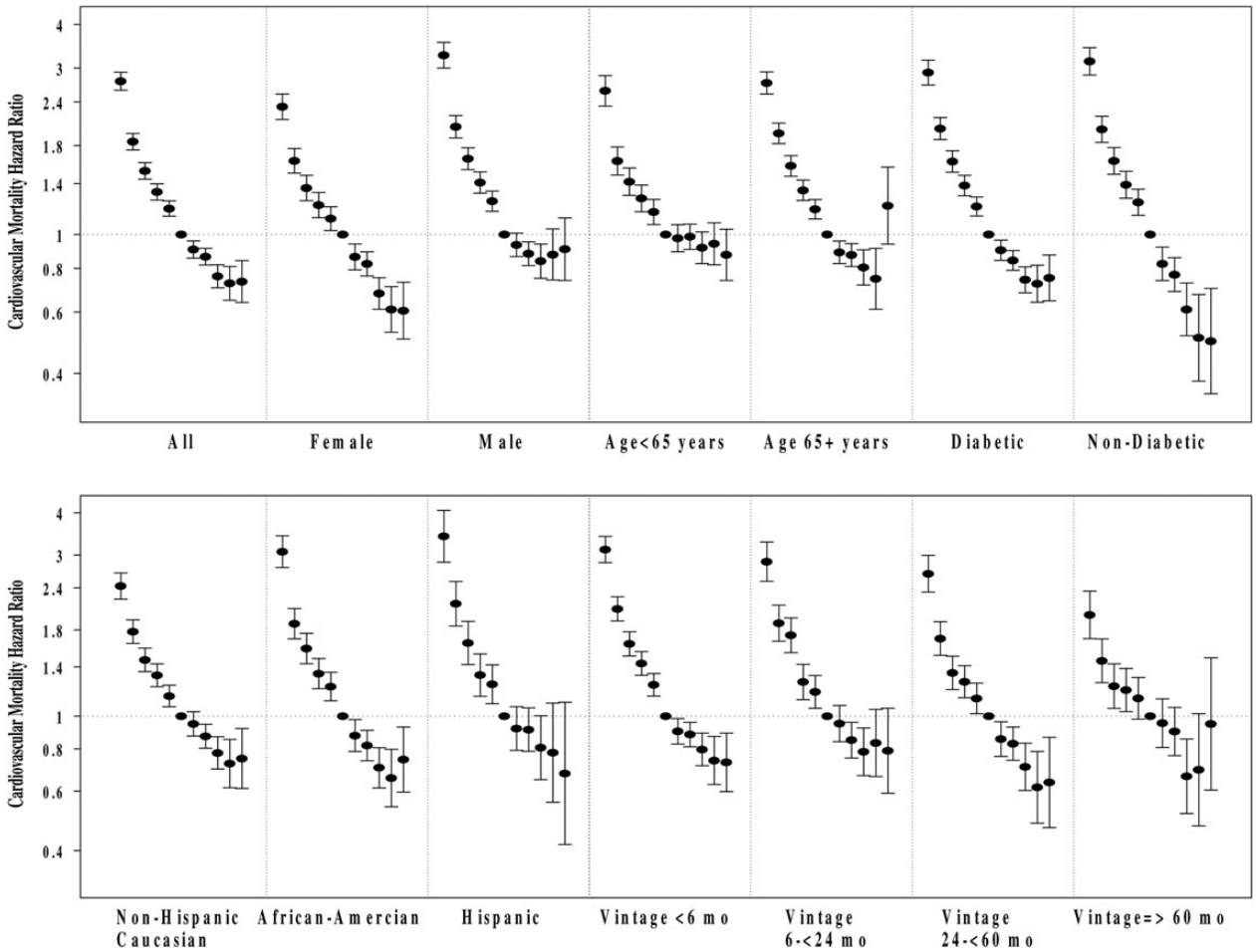

FIGURE 5: Subgroup analyses of the association between BMI categories (<18, 18 to <20, 20 to <21.5, 21.5 to <23, 23 to <25, 25 to <27.5 reference, 27.5 to <30, 30 to <35, 35 to <40, 40 to <45 and ≥45 kg/m^2) and cardiovascular mortality using a MSM. Models adjusted for case-mix covariates and markers of malnutrition and inflammation (see text for covariate list).

Both Noori *et al.* [39] and Huang *et al.* [40] evaluated the relationship between body fat and muscle mass and mortality among MHD patients. Having high MAMC, high TSF or both was associated with better survival when compared with those with low MAMC and low TSF. On the other hand, Postrino *et al.* [41]. conducted a prospective cohort study of 537 European dialysis patients between 2003 and 2006. While higher BMI was again confirmed to be protective, abdominal obesity, represented by higher waist circumference and waist:hip ratio, was found to be directly associated with higher all-cause and cardiovascular mortality. In fact, patients with high BMI and low waist circumference had the lowest mortality risk and those with low BMI and high waist circumference had the highest mortality risk. This finding was also seen in a cohort of 933 kidney transplant recipients, where higher waist circumference was associated with higher mortality, yet high BMI with low waist circumference was associated with lower mortality risk [42]. Thus, the role of adiposity and its effect on MHD patients are still not clear.

In contrast, multiple studies have shown that increased lean muscle mass is associated with a survival advantage among MHD patients [39, 40, 43, 44]. Kalantar-Zadeh *et al.* [44] previously evaluated the relationship between mortality and dry weight gain with an increase in lean body mass in >50 000 MHD patients. Creatinine was validated as a surrogate marker for lean body mass in this study. The authors found that patients who had increased estimated dry weight, associated with higher lean muscle mass, had better survival. Applying a composite ranking score analysis in >120 000 MHD patients, the same authors examined the relative role of muscle mass to body weight [43]. Again, the study confirmed that a discordant change of weight and muscle conferred distinct mortality risk. Specifically, patients who lost weight but had an increase in serum creatinine had lower death rates than those who had gained weight but had lower serum creatinine. These results led to the conclusion that higher muscle mass likely contributed to the protective role of higher BMI. In addition, a review by Jahangir *et al.* [45] concluded that older adult patients should focus on weight maintenance and lean body mass preservation, rather than on losing weight, in order prevent a higher risk of morbidity and mortality [45].

Importantly, studies on the obesity paradox are often retrospective or observational in nature; hence, they are limited by the inability to answer the question, does lower BMI contribute

directly to patient death, or is it a reflection of poorer health status? Traditional methods of studying the causal effects are often limited to modeling the probability of outcome as a function of a baseline BMI and other fixed covariates. However, nutritional status, inflammatory markers and acute illnesses vary with time and are often sporadic. They can act simultaneously as confounders and mediators of weight change. Therefore, these time-varying confounders remain a conundrum to epidemiologists and nephrologists in interpreting observational data and developing a more clear understanding of the relationship between BMI and survival. Statistical methods such as the MSM are particularly useful to reduce bias. MSM, first described by Robins *et al.* [19], takes into account time-varying confounding by inverse probability weighting for time-varying exposures and covariates. While randomized controlled trials are not logistically and ethically possible to study this question, MSM may be an excellent epidemiological tool to evaluate the causal inference of the complex relationship between BMI and long-term survival. To our knowledge, this is the first time the MSM model was used to evaluate the relationship of survival and BMI among MHD patients. By taking into account nutritional and inflammatory markers, MSM has the advantage of estimating the causal effect of BMI and survival [46, 47]. Our robust findings of the significant inverse relationship between BMI and mortality using MSM analysis confirm the results found using Cox proportional hazard models and allow us to conclude with greater certainty that a higher BMI in an MHD patient may indeed be protective and affords survival advantage, warranting interventional studies to examine this hypothesis.

Our study is not without limitations. As mentioned earlier, while BMI is a measurement of weight, it does not differentiate lean muscle mass or body fat, as discussed earlier. Additionally, residual confounding may still be a limitation, as we did not have complete data on comorbidities and change in residual renal function over time. Additional confounding factors such as acute illnesses, hospitalization, infection or chronic comorbid conditions including congestive heart failure or cancer were not captured in this database. Therefore, we cannot assume that all measured covariates are sufficient to adjust for all biases. Additionally, previous studies have shown that combined cardiorespiratory fitness and weight status is a more important predictor of mortality than BMI alone [8, 48–51]; however, data of cardiorespiratory fitness were not available in our cohort. Our study may be subject to potential selection bias due to the cohort and study inclusion and exclusion criteria. While excluding patients whose vintage is <90 days may lead to survivor bias, this criterion allows for examination of a cohort with greater generalizability to the broader HD population [52]. In addition, our study examined associations in patients treated with hemodialysis for the entire duration of follow-up and did not examine potential effects of treatment with other dialysis modalities. Future studies that can both examine the effect of varying dialysis modalities as well as include patients with early mortality are needed. Lastly, there were no significant differences in clinical and laboratory values between patients included in our analysis and those excluded for missing BMI values (data not shown). The strengths of the study lie in the large population number, uniform laboratory measurements (with all laboratory data obtained from a single laboratory facility), large sample size and examination of an extended 5-year cohort.

CONCLUSIONS

In CKD patients treated with MHD, larger body size or greater muscle mass, represented by higher BMI, is associated with greater survival. Our study shows a significant incrementally inverse relationship between BMI and all-cause as well as cardiovascular mortality in MHD patients across all models and especially in the MSM analyses. These findings have important clinical implications in dialysis patient care management. The interesting results of this study warrant further investigation through interventional trials in CKD and MHD patients.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

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CONFLICT OF INTEREST STATEMENT

K.K.Z. has received honoraria from Genzyme/Sanofi and Shire and was the medical director of DaVita Harbor-UCLA/MFI in Long Beach, CA, USA, during 2007–12.

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