ORIGINAL ARTICLE

Fatty liver disease reverses the obesity paradox in chronic kidney disease stages 3–5: A follow-up study of NHANES III

Jiaofeng Huang[1,2] | Min Zhang[3] | Yinlian Wu[1,2] | Mingfang Wang[1,2] | Yueyong Zhu[1,2] | Su Lin[1,2]

[1]Department of Hepatology, Hepatology Research Institute, the First Affiliated Hospital, Fujian Medical University, Fuzhou, China

[2]Fujian Clinical Research Center for Liver and Intestinal Diseases, Fuzhou, China

[3]Department of Nephrology, Huashan Hospital, Fudan University, Shanghai, China

Correspondence
Su Lin, Department of Hepatology, Hepatology Research Institute, the First Affiliated Hospital, Fujian Medical University, No. 20, Chazhong Road, Taijiang District, Fuzhou, Fujian, 350005, China.
Email: sumer5129@fjmu.edu.cn

Abstract

High body mass index (BMI) has been associated with better survival in patients with end-stage kidney disease. Individuals with fatty liver disease (FLD) have a higher risk of chronic kidney disease. It remains unclear whether the survival benefit of high BMI in patients with chronic kidney disease is present when there is concomitant FLD. This study used the data set from the Third American National Health and Nutrition Examination Survey and the corresponding survival data. The Cox proportional hazards model was used to evaluate the effect of BMI on mortality. A total of 12,445 participants were included. The prevalence of FLD was 39.8%. The median follow-up time (with interquartile range) was 22.8 (20.8–24.8) years. During this period, 3749 (30.1%, 14.4 of 1000 person-year) deaths were observed. Among these, 1169 (31.2%) died within the first 10 years. The Cox regression analysis showed that the BMI level was not associated with 25-year mortality in patients with decreased glomerular filtration rate (GFR <60 ml/min/1.73 m^2), but 10-year mortality was significantly lower in patients with BMI ≥ 25 kg/m^2 than in those with BMI <25 kg/m^2 ($p = 0.049$). Multivariate analysis showed BMI ≥ 25 kg/m^2 was an independent protective factor for 10-year mortality (hazard ratio [HR] 0.691, 95% confidence interval [CI] 0.559–0.856; $p = 0.001$). This protective effect of higher BMI was lost in patients with FLD (HR 0.884, 95% CI 0.585–1.335; $p = 0.557$) but persisted in the non-FLD group (HR 0.625, 95% CI 0.479–0.816; $p = 0.001$). The survival benefit of overweight/obesity for patients with decreased GFR, which was attenuated by the presence of FLD, only existed in the first decade.

INTRODUCTION

Overweight/obesity, defined as a body mass index (BMI) over 25 kg/m^2, is a major global public health challenge in the 21st century. It is associated with a variety of complications including diabetes, hypertension, cardiovascular disease, and fatty liver disease (FLD).[1]

However, despite the markedly increased risk of adverse outcomes in the general population,[2] elevated BMI may also paradoxically be associated with survival benefits in specific patient populations. Higher BMI level has been reported many times as correlated with improved survival in patients with end-stage kidney disease (ESKD),[3] chronic heart failure,[4] chronic liver disease,[5] acute severe hepatitis,[6] and when admitted to intensive care units.[7] This phenomenon has been termed the "obesity paradox."

The obesity paradox is consistently observed in patients with ESKD on hemodialysis or peritoneal dialysis,[3] but the association of obesity and mortality in non-dialysis-dependent patients with chronic kidney disease (CKD) has not been fully elucidated. ESKD only accounts for a small group of CKD[8]; the heterogeneity of the CKD population also makes it difficult to determine the role that obesity plays as a protective factor in this group. It has also been proposed that the BMI–mortality association may vary according to the underlying severity of CKD.[9] Hence, survival bias may have heavily influenced the results of previous studies, and the conclusion cannot be generalized to the entire CKD population (and obviously not to the general population). Therefore, it is difficult to make ideal therapeutic weight management goals for patients with CKD based on current evidence.

FLD is a prevalent chronic liver disease characterized by the presence of hepatic steatosis and is often concomitant with considerable metabolic disruption.[10] Overweight/obesity is common in FLD and has been proposed as one of the diagnostic dysfunctional components of metabolic associated fatty liver disease.[11] There are more cases at risk of adverse outcomes and increased mortality in patients with FLD than those without.[12,13] Moreover, the presence of FLD increases the risk of CKD.[14–17] Given the complex interactions among BMI, FLD and CKD, it remains unclear whether the survival benefit of high BMI level in patients with CKD persists when there is concomitant FLD.

To clarify the unanswered questions, we used a nationally representative survey database to analyze the impact of FLD on the association between BMI and mortality in general populations and in patients with decreased glomerular filtration rate (GFR).

METHODS

Participants and ethics

A publicly accessible database, the Third American National Health and Nutrition Examination Survey (NHANES III) was used for this study. NHANES III is a nationally representative survey study conducted by the National Center for Health Statistics of the United States from 1984 to 1994. The data of survival status and lifespan of all survey participants were collected until December 2015. The entire data set is free to access online at https://www.cdc.gov/nchs/nhanes/about_nhanes.htm.

This study was performed in accordance with the Declaration of Helsinki regarding ethical standards for research involving human subjects. As this study used only public anonymous data, no further ethics approval was required.

The inclusion criteria of this study were all cases with available liver ultrasonography results. The exclusion criteria were cases with missing key data, such as survival or renal function data, see Figure 1 for detail.

Definition

FLD was defined according to ultrasound examinations. Categorized assessment of hepatic steatosis by ultrasound in the NHANES III was represented with categories of no, mild, moderate, and severe steatosis. Only mild to severe hepatic steatosis was regarded as evidence of FLD.

Estimated GFR (eGFR) was calculated according to the 2009 CKD-EPI eGFR formula[18]: $eGFR = 141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times (1.018 \text{ if female}) \times (1.159 \text{ if Black})$; $\kappa = 0.7$ (females) or 0.9 (males); $\alpha = -0.329$ (females) or -0.411 (males), where SCr is serum creatinine concentration (in mg/dl) and age refers to age in years.

Decreased GFR was defined as eGFR < 60 ml/min/1.73 m^2. CKD was defined as decreased eGFR (<60 ml/min/1.73 m^2) and/or abnormal albuminuria and/or overt proteinuria, in accordance with the Kidney Disease: Improving Global Outcome 2012 Practice Guideline for CKD.[19] CKD stages 3–5 were defined as eGFR < 60 ml/min/1.73 m^2, regardless of the presence of proteinuria.

Hypertension was defined as systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 80 mm Hg, a remarkable history of hypertension, and/or undertreatment of hypertension.[20]

Diabetes was defined as having a history of diabetes, current use of insulin or oral hypoglycemic agents, fasting blood glucose ≥ 7.0 mmol/L, or glycated hemoglobin ≥ 6.5% or 2-h postprandial glucose ≥ 11.0 mmol/L.

BMI was defined as body weight in kilograms divided by the square of the height in meters.

Statistical analysis

Continuous variables were represented as mean ± SD or median (interquartile range) and compared using the Student's t test. Categorical variables were expressed as counts (percentages) and compared using the chi-squared test. The Cox proportional hazards model was
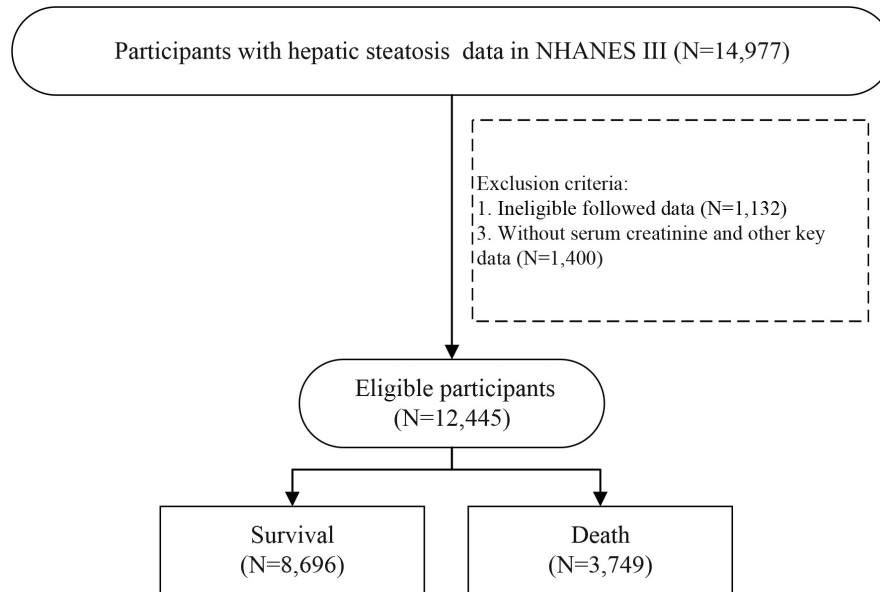
FIGURE 1 Flowchart for case selection. NHANES III, Third National Health and Nutrition Examination Survey.

TABLE 1 Baseline characteristics of the overall population

Variables	Total	Survival	Death	p
Number of cases	12,445	8696	3749	<0.001
Race, n (%)				<0.001
Non-Hispanic White	4632 (37.2)	3017 (34.7)	1615 (43.1)	
Non-Hispanic Black	3528 (28.3)	2507 (28.8)	1021 (27.2)	
Mexican American	3764 (30.2)	2753 (31.7)	1011 (27.0)	
Other	521 (4.2)	419 (4.8)	102 (2.7)	
Male (%)	5839 (46.9)	3788 (43.6)	2051 (54.7)	<0.001
Age (years)	43.5±16.0	37.6±12.7	57.3±14.1	<0.001
Diabetes, n (%)	1835 (14.7)	680 (7.8)	1155 (30.8)	<0.001
Hypertension, n (%)	5127 (41.2)	2976 (34.2)	2151 (57.4)	<0.001
BMI (kg/m^2)	27.3±5.8	27.0±5.7	28.0±6.0	<0.001
BMI≥25 kg/m^2, n (%)	7621 (61.2)	5096 (58.6)	2525 (67.4)	<0.001
GFR<60 ml/min/1.73 m^2	1611 (12.9)	488 (5.6)	1123 (30.0)	<0.001
FLD, n (%)	4949 (39.8)	3240 (37.3)	1709 (45.6)	<0.001

used to evaluate the effect of BMI on mortality. All tests were two-tailed, and a *p* value <0.05 was considered statistically significant. All analyses were conducted using R 3.6.2 (https://www.r-project.org/).

RESULTS

In the general population, higher BMI was associated with higher mortality. A total of 12,445 participants were included in this study, with 46.9% males and a mean age of 43.5±16.0 years. The basic characteristics of the population are found in Table 1. The prevalence of diabetes was 14.7%, hypertension was 41.2%, and FLD was 39.8%. The mean BMI level was 27.3±5.8 kg/m^2. A total of 7621 cases (61.2%) were overweight.

The median follow-up time was 22.8 (20.8–24.8) years with 259,857 person-years of follow-up. During this period, 3749 (30.1%, 14.4 of 1000 person-years) death events were observed. Among the 3749 deaths, 1169 (31.2%) died within the first 10 years. As indicated in Table 1, the death group had a higher mean BMI than the survival group (28.0±6.0 vs. 27.0±5.7; *p*<0.001). A Kaplan–Meier curve illustrated the difference in 25-year and 10-year mortality between the BMI<25 kg/m^2 group and the BMI≥25 kg/m^2 group (Figure 2A,B). The higher BMI group (≥25 kg/m^2) showed significantly higher mortality than the lower BMI group (*p*<0.001).
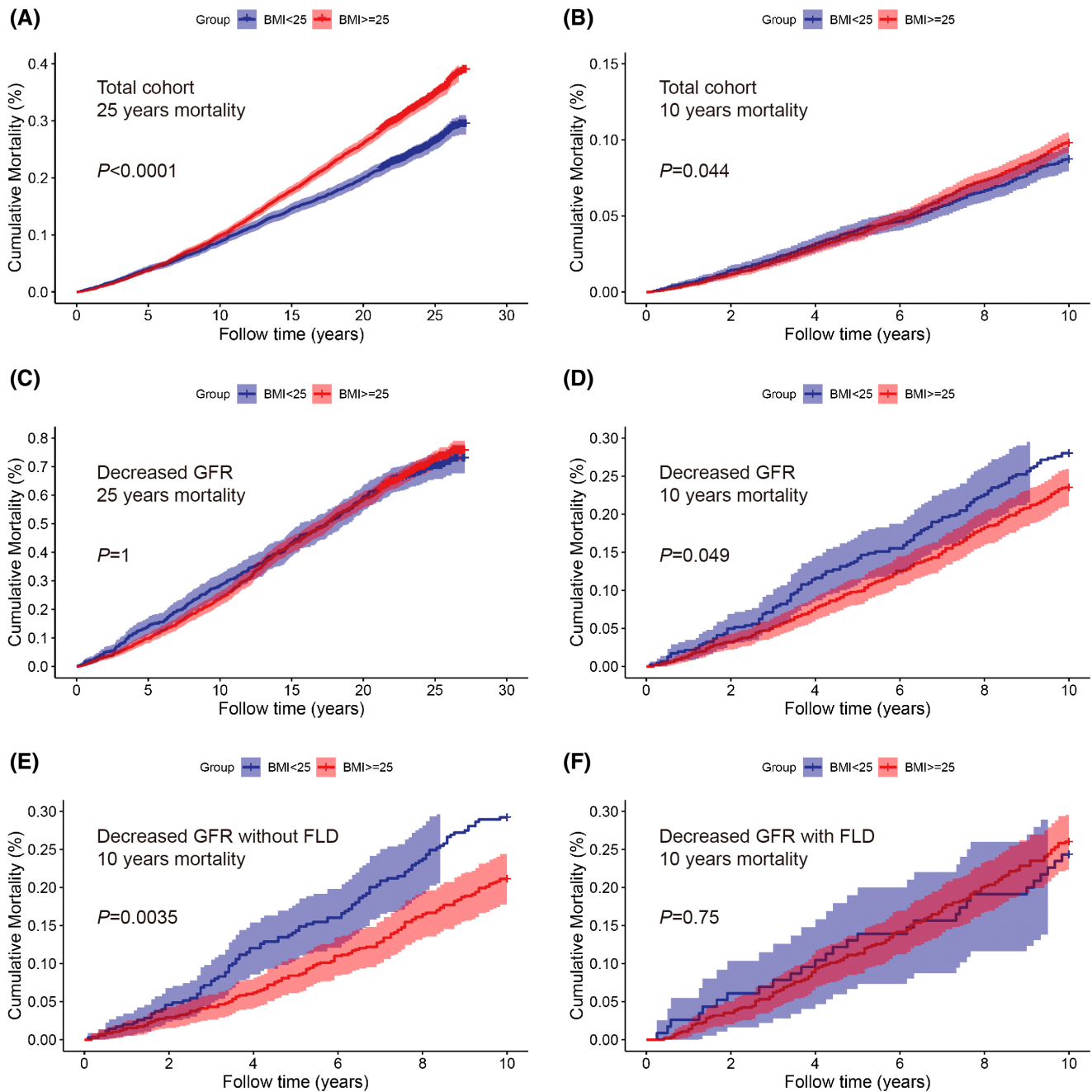
FIGURE 2 The Kaplan–Meier curve for cumulative mortality. (A) The 25-year cumulative mortality in the overall population. (B) The 10-year cumulative mortality in the overall population. (C) The 25-year cumulative mortality in patients with glomerular filtration rate (GFR)<60 ml/min/1.73 m². (D) The 10-year cumulative mortality in patients with GFR<60 ml/min/1.73 m². (E) The 10-year cumulative mortality in patients with GFR<60 ml/min/1.73 m² and without fatty liver disease. (F) The 10-year cumulative mortality in patients with GFR<60 ml/min/1.73 m² and fatty liver disease (FLD). BMI, body mass index.

In patients with GFR <60 ml/min/1.73 m², higher BMI was associated with lower 10-year mortality, but not 25-year mortality. A total of 1611 patients with decreased eGFR were selected for further analysis (Table 2). The median follow-up time was 17.4 (10.0–22.8) years. There were 1123 death events within the 25-year follow-up period, with a mortality rate of 69.7%. Of the 1123 deaths, 400 (24.8%) died within the first 10 years. As it was in the general population, the proportions

of diabetes, hypertension, and FLD were significantly higher in the death group ($p < 0.05$).

Univariate Cox regression analysis showed that BMI level was not associated with 25-year mortality in this subgroup of patients (hazard ratio [HR] 1.002, 95% confidence interval [CI] 0.991–1.013; $p = 0.753$). Kaplan–Meier analysis demonstrated no difference in the 25-year mortality between the different BMI groups (Figure 2C); however, 10-year mortality was

TABLE 2 Baseline characteristics of patients with GFR<60 ml/min/1.73 m^2

Variables	Total	Survival	Death	p
Number of cases	1611	488	1123	
Race, n (%)				0.001
Non-Hispanic White	959 (59.5)	305 (62.5)	654 (58.2)	
Non-Hispanic Black	331 (20.5)	75 (15.4)	256 (22.8)	
Mexican American	266 (16.5)	83 (17.0)	183 (16.3)	
Other	55 (3.4)	25 (5.1)	30 (2.7)	
Male (%)	648 (40.2)	148 (30.3)	500 (44.5)	<0.001
Age (years)	63.6±9.2	57.4±10.7	66.3±7.0	<0.001
Diabetes, n (%)	505 (31.3)	79 (16.2)	426 (37.9)	<0.001
Hypertension, n (%)	964 (59.8)	242 (49.6)	722 (64.3)	<0.001
FLD, n (%)	680 (42.2)	186 (38.1)	494 (44.0)	0.032
BMI≥25 kg/m^2, n (%)	1147 (71.2)	345 (70.7)	802 (71.4)	0.816

TABLE 3 Cox regression for 10-year all-cause mortality in GFR<60 ml/min/1.73 m^2

	Univariate		Multivariate	
Variables	HR (95% CI)	p	HR (95% CI)	p
FLD	1.074 (0.882–1.309)	0.478		
Race				
Non-Hispanic White	1		1	
Non-Hispanic Black	1.306 (1.028–1.660)	0.029	1.230 (0.964–1.570)	0.096
Mexican American	1.252 (0.963–1.630)	0.094	1.149 (0.880–1.500)	0.307
Other	0.674 (0.346–1.313)	0.247	0.698 (0.358–1.360)	0.291
Male	1.694 (1.392–2.061)	<0.001	1.665 (1.367–2.028)	<0.001
Age (years)	1.063 (1.047–1.079)	<0.001	1.055 (1.039–1.071)	<0.001
Diabetes	2.286 (1.879–2.782)	<0.001	2.070 (1.688–2.538)	<0.001
Hypertension	1.335 (1.086–1.641)	0.006	1.114 (0.903–1.375)	0.315
BMI≥25 kg/m^2	0.807 (0.654–0.994)	0.044	0.691 (0.559–0.856)	0.001

Abbreviations: CI, confidence interval; HR, hazard ratio.

significantly lower in patients with BMI≥25 kg/m^2 than those with BMI<25 kg/m^2 (p = 0.049) (Figure 2D). The presence of FLD was not correlated with the 10-year mortality on the univariate analysis (HR 1.074, 95% CI 0.882–1.309; p = 0.478). Results of the multivariate Cox regression analysis are found in Table 3, suggesting that BMI≥25 kg/m^2 was an independent protective factor for the 10-year mortality in patients with GFR<60 ml/min/1.73 m^2 (HR 0.691, 95% CI 0.559–0.856; p = 0.001).

Survival benefit of BMI was lost in patients with FLD. Patients with decreased GFR were further divided into FLD and non-FLD groups, according to the presence of FLD (Table S1). As indicated in Table 4, the significant survival benefit seen in the general population was not present in the FLD group when adjusted for race, age, gender, diabetes, and hypertension. No significant impact from higher BMI levels (≥25 kg/m^2) was seen on the 10-year mortality rate (HR 0.884, 95%

CI 0.585–1.335; p = 0.557) in this group of patients. However, the protective effect of higher BMI persisted in the non-FLD group (HR 0.625, 95% CI 0.479–0.816; p = 0.001). This difference is shown on the Kaplan–Meier curves in Figure 2E,F.

DISCUSSION

We examined the association of BMI with mortality in this prospective cohort of patients with CKD stages 3–5 and detected an optimal 10-year survival rate in cases with BMI≥25 kg/m^2. However, the survival advantage did not extend to 25 years. The survival benefit of increased BMI was attenuated and no longer significant in CKD stages 3–5 with FLD, even at 10 years. This result may have substantial clinical implications in the management of obesity in patients with CKD. According to the clinical practice guideline Management of Obesity

TABLE 4 Effect of BMI on all-cause mortality in CKD with and without FLD

Variables	25-year mortality				10-year mortality			
	Non-FLD		FLD		Non-FLD		FLD	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Race, n (%)								
Non-Hispanic white	1		1		1		1	
Non-Hispanic black	1.417 (1.170–1.716)	<0.001	1.223 (0.967–1.547)	0.093	1.289 (0.940–1.769)	0.115	1.136 (0.767–1.683)	0.524
Mexican-American	0.932 (0.733–1.184)	0.564	0.977 (0.775–1.232)	0.845	1.262 (0.867–1.837)	0.224	1.043 (0.714–1.524)	0.826
Other	0.735 (0.476–1.135)	0.165	0.617 (0.304–1.250)	0.180	0.816 (0.379–1.753)	0.602	0.476 (0.117–1.941)	0.301
Male	1.497 (1.277–1.755)	<0.001	1.406 (1.176–1.682)	<0.001	1.830 (1.405–2.382)	<0.001	1.442 (1.068–1.946)	0.017
Age (years)	1.071 (1.058–1.084)	<0.001	1.079 (1.064–1.094)	<0.001	1.050 (1.029–1.071)	<0.001	1.062 (1.036–1.088)	<0.001
Diabetes	1.601 (1.345–1.904)	<0.001	1.693 (1.405–2.040)	<0.001	2.197 (1.671–2.889)	<0.001	1.845 (1.349–2.523)	<0.001
Hypertension	1.265 (1.074–1.490)	0.005	1.135 (0.938–1.374)	0.192	1.066 (0.808–1.406)	0.653	1.181 (0.851–1.639)	0.320
BMI≥25 kg/m^2	0.871 (0.740–1.026)	0.099	0.897 (0.705–1.141)	0.374	0.625 (0.479–0.816)	0.001	0.884 (0.585–1.335)	0.557

in Kidney Transplant Candidates and Recipients, ESKD with a BMI<35 kg/m^2 is acceptable for kidney transplantation.[21] Therefore, appropriate weight control (at least BMI<35 kg/m^2) should be emphasized, especially because the protective role of overweight/obesity no longer exists in patients with both CKD and FLD.

In the present study, higher BMI level was associated with higher 25-year and 10-year mortality rates in the general population. These findings were in line with the well-established idea that overweight/obesity links with poor prognosis overall.[1] Consistent with previous reports, the obesity paradox (i.e., the protective effect of higher BMI in patients with renal disease) was evident in individuals with GFR<60 ml/min/1.73 m^2 in this study. These results suggest that our present study population was representative.

One important result of this study was that the survival advantage was found in the first 10 years only and did not extend to 25 years. Leavey et al. reported changes to the obesity paradox in an ESKD population over time.[22] They found the greatest protective effect of BMI occurred early, within the first 5 years of follow-up. In fact, the follow-up duration of most previous studies evaluating the obesity paradox was less than 10 years,[3,9,23,24] which is substantially shorter than the present study. This probably explains why the loss of the obesity paradox over the long term has never been reported. To our knowledge, this study is the first to examine the effect of the obesity paradox on such a long-term mortality rate. Moreover, previous studies focused primarily on patients with ESKD, for whom the

expected lifespan is not very long. In this study, we included the general population and the CKD stages 3–5 subgroup. These patients have less severe disease, and a longer life expectancy. The inclusion of patients with moderate-stage CKD enabled us to explore the association of BMI and mortality for a much longer follow-up duration.

The potential mechanisms underlying the loss of survival benefit after 10 years are not clear. Several hypotheses have been proposed for the obesity paradox in the literature. These include protein-energy wasting and inflammation, hemodynamic stability, alteration of circulatory cytokines, sequestration of uremic toxin in adipose tissue, and endotoxin-lipoprotein interaction.[3] The protective effect may attenuate with time, but the harms of obesity on multiple system diseases may increase and overwhelm the benefits of higher BMI for patients with CKD. This could partially explain the loss of survival advantage after 10 years. However, this hypothesis should be verified in further prospective studies.

Another finding of this study was that the survival benefit of obesity was less pronounced in participants with FLD. In fact, it was no longer significant after the adjustment for confounding factors. The underlying mechanism of this phenomenon remains unclear, but the systemic inflammation and additional metabolic derangement of FLD could accelerate the progress of CKD and worsen the prognosis.[25] Moreover, FLD may result in more cardiovascular comorbidities, and thus higher risk of CVD events.[26] The presence of FLD

may cumulatively attenuate the protective role of obesity paradox.

The diagnosis of CKD includes eGFR<60 ml/min/1.73 m^2 and/or the presence of proteinuria.[8] We included only a population whose eGFR was<60 ml/min/1.73 m^2, named decreased GFR. The eGFR was more easily obtained than albuminuria in the clinical setting. Moreover, eGFR<60 ml/min/1.73 m^2 (CKD 3–5) is considered the threshold for discriminating mild versus moderate to high risk of disease progression.[8]

When examining the obesity paradox, previous studies have usually set the threshold of BMI at 30 kg/m^2.[3] We found that 25 kg/m^2 was a more appropriate cutoff value, and this has been supported by other studies. Obermayr et al. reported that the effect of BMI was a U curve, with 25 kg/m^2 as the turning point.[27] In hemodialysis patients, a lower relative mortality risk has been observed for BMI≥25 kg/m^2 than BMI 23–24.9.[28] Furthermore, some pooled analyses have demonstrated a reverse J-shaped association with death, such that those who were underweight had higher mortality risk.[23,24,29] In this study, the population of BMI<20 kg/m^2 was small and did not allow us to examine the effect of underweight. The difference in population characteristics and the much longer follow-up duration in the general population of our present study may explain the discrepancy between ours and previous studies.

The advantage of this study was that it was based on a nationally representative database, with a large sample size and long-term follow-up duration. The results may be more reliable and generalizable than other studies.

However, some limitations should also be noted. First, the measurement of renal function was performed only once. The diagnosis of CKD generally requires two testing occasions and at least 3 months of abnormal results. It is difficult to perform multiple measurements in a large national survey. It is possible that some patients would have had substantially different test results on two occasions, and this could have led to the misclassification of patients. However, errors in measurement would be minimized given the standardized nature of the NHANES III examination. Second, the diagnosis of FLD was based on ultrasonography examination. Although liver biopsy is considered the gold standard for detecting liver steatosis, it would have been impossible to biopsy each asymptomatic participant in the survey study. Liver ultrasound examination has been recommended by several guidelines for the diagnosis of liver steatosis.[11,30]

In conclusion, the survival benefit of overweight/obesity for patients with CKD with decreased GFR only existed in the first decade, and the presence of FLD attenuated this effect. Our results emphasize the importance of weight control in patients with both FLD and CKD. The obesity paradox is less relevant in these patients.

CONFLICT OF INTEREST

Nothing to report.

DATA AVAILABILITY STATEMENT

Publicly available data sets were analyzed in this study. The raw data are available from National Health and Nutrition Examination Survey program (https://www.cdc.gov/nchs/nhanes/index.htm). The validation data set is available on request.

ETHICS STATEMENT

The NHANES data set contained publicly available anonymous data; therefore, further ethics approval was not required. All patient records and information were anonymized before the analysis.

ORCID

Yueyong Zhu https://orcid.org/0000-0002-0746-4911
Su Lin https://orcid.org/0000-0001-7517-9859

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.