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ORIGINAL RESEARCH

Cohort Study and Bias Analysis of the Obesity Paradox Across Stages of Chronic Kidney Disease

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Objective: In advanced chronic kidney disease (CKD), patients with obesity often have better outcomes than patients without obesity, often called the 'obesity paradox'. Yet, in CKD, the prevalence of inflammation increases as CKD progresses. Although a potential confounder, inflammation may be left unaccounted in obesity–mortality studies. We examined the associations of body mass index (BMI) with all-cause and cause-specific mortality across CKD stages, with consideration for uncontrolled confounding due to unmeasured inflammation.

Methods: We investigated 2,703,512 patients with BMI data between 2004 and 2006. We used Cox models to examine the associations of BMI with all-cause, cardiovascular, and cancer mortality, (ref: BMI 25-<30 kg/m^2), adjusted for clinical characteristics and stratified by CKD stages. To address uncontrolled confounding, we performed bias analysis using a weighted probabilistic model of inflammation given the observed data applied to weighted Cox models.

Results: The cohort included 5% females and 14% African Americans. In adjusted analyses, the associations of the BMI with all-cause and cardiovascular mortality showed a reverse J-shape, where a higher BMI (>40 kg/m^2) was associated with a higher risk. Conversely, a lower mortality risk was observed with a BMI 30-<35 kg/m^2 across all CKD stages and for BMI >40 kg/m^2 in CKD stage 4/5. Cancer mortality analyses showed an inverse relationship. Bias analysis for uncontrolled confounding suggested that independent of inflammation, the obesity paradox was present.

Conclusion: We observed the presence of the obesity paradox in this study. This association was consistent in advanced CKD and in our bias analysis, suggesting that inflammation may not fully explain the observed BMI-mortality associations including in patients with CKD.

Key words: obesity paradox; body mass index; mortality; chronic kidney disease; bias analysis; inflammation

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Introduction

PUBLIC HEALTH INITIATIVES have targeted elevated body mass index (BMI) and obesity given the wealth of studies demonstrating adverse risks for cardiovascular disease (CVD), site-specific cancers, and all-cause mortality in the general population.[1-4] Yet, evidence has suggested an 'obesity paradox', where a greater BMI is not associated with a higher risk of all-cause mortality, but may be protective in certain populations, including those with CVD or chronic kidney disease (CKD).[5-8] The obesity paradox has both captivated and divided clinical and epidemiological communities. Opponents have suggested that the findings are an artifact of selection bias (or collider stratification) due to selecting or conditioning on a common consequence of the exposure and the outcome (or an unmeasured risk factor for the outcome) such as disease state. If the disease state and mortality relationship were confounded by an uncontrolled shared risk factor, the selection of a population can inadvertently open a biasing path between obesity and mortality and lead to possibly paradoxical findings. This phenomenon has been dissected in the context of the obesity paradox, suggesting that the culprit could be CVD.[9-13] However, alternative causal structures illustrating the obesity-mortality relationship, as well as the suggested evidence of a biological mechanism, lend support for an obesity paradox.[5,14,15,16]

Although traditional risk factors of CVD or smoking may explain these spurious findings, it has been suggested that specifically among patients with CKD, nontraditional risk factors, including cachexia, uremic toxins, and inflammation, play a bigger role in mortality risk and adverse events because of their high prevalence, even before progression to kidney failure.[5,14] Studies have identified inflammation, particularly by C-reactive protein (CRP), as useful in risk prediction in chronic disease populations.[17-21] In patients with CKD, elevated CRP levels are more prevalent than in non-CKD patients, and CRP can impact appetite, protein-energy wasting, and body size.[5,15,19,22,23,24] The obesity paradox has been observed in some cohorts of nondialysis-dependent CKD (NDD-CKD), but not in others, and with incomplete control for markers of inflammation including CRP.[5,14,25] It is unclear at which CKD stage the obesity-mortality association changes into an inverse relationship, thereby representing an obesity paradox, and whether the rise in inflammation across progressive CKD stages could explain these changes.

Thus, across strata of CKD stages, we sought to examine all-cause mortality and cause-specific deaths of CVD and cancer given their prominence in the general population. We evaluated the impact of a nontraditional risk factor in the form of uncontrolled inflammation using bias analysis. We hypothesize that the obesity paradox exists in this patient population across stages of CKD, independent of potential confounding due to inflammation.

Methods

Study Population and Data Source

The source population was derived from the LIPRO-VET (Lipid profiles and management in veterans with CKD) study, which included patients with at least one serum lipid measurement between October 1, 2004 and September 30, 2006 at any US Veterans Affairs (VA) medical centers.[26] For this study, we excluded patients for missing a BMI measurement, with kidney failure, and on renal replacement therapy or if they did not have at least two estimated glomerular filtration rates (eGFRs) measured at least 90 days apart and before the BMI measurement, and for missing information on censoring. Our cohort comprised 2,703,512 patients (Figure S1). This study was approved by the Tibor Rubin VA Medical Center (Long Beach, CA) institutional review board, and the written consent requirement was waived.

Clinical Measurements

Outcomes

The outcomes were all-cause, CVD, and cancer mortality. Cause-specific mortality was identified from the National Death Index. Reasons for CVD and cancer mortality are presented in Table S1. Censoring events and exclusion criteria data were extracted from composite VA, Centers for Medicare and Medicaid Services (CMS), United States Renal Data System, and National Death Index databases. Lost to follow-up was characterized as the last date of active use of any VA or CMS service. Patients were followed from the date of BMI measurement to death, lost to follow-up, or December 31, 2014, whichever occurred first.

Exposure

The BMI measurement was obtained from the VA database only and was categorized into the following groups as guided by the World Health Organization classification and prior studies[27]: <20, 20-<25, 25-<30 (reference), 30-<35, 35-<40, and ≥ 40 kg/m^2.

Covariates

Clinical characteristics were primarily derived from combined VA/CMS databases. Construction of the demographics and pre-existing comorbidities of the source population has been previously described elsewhere.[26] Prescription medications at the time of the BMI measurement were extracted with drug class codes and names from combined VA/CMS databases. Ever smoking and alcoholism statuses were obtained from the VA database only.[28]

All laboratory measurements were obtained from the VA database.[26] The laboratory values within a maximum of 90 days before the BMI measurement were used in analyses, although most measurements were drawn on the same day or within 2 weeks before the BMI measurement. Serum creatinine, and thus eGFR, was categorized into baseline

CKD stages (non-CKD, 3A, 3B, and 4/5, represented by eGFR ≥60, 45-<60, 30-<45, and <30 mL/min/1.73 m^2, respectively).[29] CKD staging was classified by the presence of at least two eGFR measurements of the same stage and measured at least 90 days apart.

Statistical Analysis

Baseline characteristics were presented as mean (±standard deviation), median (interquartile range), or proportion, as appropriate.

Cox proportional hazard models were used to examine the association of the BMI groups with each mortality outcome and stratified by the baseline CKD stage. Three adjustment models were used based on prior studies and theoretical considerations: (1) unadjusted; (2) case-mix adjusted, which included age, gender, race, ethnicity, ever smoking status, ever alcoholism status, Charlson comorbidity index, chronic obstructive pulmonary disease, cancer, diabetes, ischemic heart disease (including myocardial infarction), congestive heart failure, peripheral vascular disease, cerebrovascular disease, atrial fibrillation, and prescription for renin-angiotensin-aldosterone system inhibitors, statins, beta blockers, and alpha blockers; and (3) case-mix + laboratory adjusted (fully), which additionally included systolic and diastolic blood pressures. We defined the case-mix + laboratory–adjusted model as our primary model of interest. We additionally adjusted for serum albumin among 1,524,767 (56% of the cohort) patients, with available albumin data before the BMI measurement.

Data were missing for <0.7%, 4.1%, 17.5%, and 0.5% of the cohort for demographics, smoking, alcoholism, and blood pressures, respectively. Missing data were handled with a missing category or imputation by mean, as applicable. Although CRP measurements were available, only 2.5% of the cohort had a value proximal to the BMI measurement. All analyses were performed with SAS Enterprise Guide (7.1) (Cary, NC).

Bias Analysis for Uncontrolled Confounding

Because of the high missingness for major laboratory measurements including CRP, we were unable to account for this confounding directly with covariate adjustment. Thus, we used bias analysis to examine the potential impact of uncontrolled confounding due to inflammation represented by CRP. This quantitative bias analysis allowed for the internal adjustment of uncontrolled confounding on an individual record data level. We used the limited data on CRP available within this cohort, expert opinion, and information from prior studies to inform the bias parameters for our sensitivity analysis using probability of confounder weighting.[30,31] We included a range of bias parameter values reflecting weak, moderate, and strong levels of confounding for the odds of inflammation (O_U) and the association between inflammation and BMI group (OR_{UX}) or mortality (OR_{UY}) to calculate the probability of inflammation (P_{1XY}) given the observed BMI group and mortality status and the implied associations with measured confounders. Although we did not specify parameters relating the measured confounders to the unmeasured confounder, we specified OR_{UX} and OR_{UY} to reflect their assumed expected values when conditioned on measured confounders. To simulate the presence of inflammation as a binary variable under a Bernoulli distribution, we used the bias parameters in expit (or inverse logit) functions in our calculations as follows:

$$P_{1XY} = \frac{1}{1+1/\left[(O_U)(OR_{UX})^{X=x}(OR_{UY})^{Y=y}\right]}$$

X represents the dummy-coded BMI groups with BMI 25-<30 kg/m^2 as the reference, and Y represents each mortality outcome. These calculated probabilities were used as the probabilities of uncontrolled confounding by unmeasured inflammation.[32-34] Finally, case-mix + laboratory–adjusted Cox proportional hazards models were weighted by the probability of inflammation given the BMI groups and mortality (P_{1XY}), which reweighted the observed data to the assumed joint distribution of the observed data and the unmeasured inflammation in our cohort. As a result, we obtained fully adjusted hazard ratios that were bias adjusted for uncontrolled confounding by unmeasured inflammation. The bias analysis was repeated for each mortality outcome and varied strength of confounding. Moreover, as the degree of uncontrolled confounding by unmeasured inflammation may differ across CKD stages, we repeated the bias analysis and weighted Cox models where the magnitudes of bias parameters were varied as per the CKD stage. Bias parameters are presented in Table S2.

Results

The cohort members had a mean (standard deviation) age of 64 ± 13 years, with 5% being female and 14% African Americans (Table 1). Patients with NDD-CKD comprised 23% of the cohort. Across BMI groups, patients with a greater BMI tended to be younger, had higher systolic and diastolic blood pressures, and had a higher prevalence of diabetes, yet a lower prevalence of peripheral vascular disease, cerebrovascular disease, cancer, and anemia. There were also nonlinear trends across BMI groups, where both lower- and higher-BMI groups had larger proportions of women, patients with congestive heart failure, and those without CKD than middle range BMI groups.

Associations of BMI with All-cause, CVD, and Cancer Mortality

Over a median follow-up of 8.7 years, there were 906,668 all-cause deaths, with a crude rate of 44.6 [44.5, 44.7] events per 1,000 person-years. A low BMI <20 kg/

Table 1. Baseline Clinical Characteristics Across Body Mass Index Groups

		Body Mass Index (kg/m^2)					
Characteristics	Total	<20	20-<25	25-<30	30-<35	35-<40	≥40
N (%)	2,703,512	71,717 (2.7)	520,892 (19.3)	1,052,889 (39.0)	672,338 (24.9)	258,236 (9.6)	127,440 (4.7)
CKD stage (%)							
Non-CKD	77	81	76	76	78	80	82
3A	15	11	15	16	14	13	12
3B	6	6	7	7	6	5	5
4/5	2	2	2	2	2	1	2
eGFR (mL/min/1.73 m^2)	76 [62, 91]	83 [65, 98]	76 [61, 91]	75 [61, 88]	76 [62, 90]	78 [64, 93]	81 [66, 95]
Age (year)	64 ± 13	67 ± 14	67 ± 14	66 ± 13	63 ± 12	61 ± 12	58 ± 10
Female (%)	5	7	5	4	5	6	9
Race (%)							
White	82	75	81	83	82	81	80
African American	14	21	15	13	14	15	16
Other	4	4	4	4	4	4	5
Hispanic ethnicity (%)	4	4	4	4	4	4	4
CCI	1 [0, 2]	2 [1, 3]	1 [0, 3]	1 [0, 2]	1 [0, 2]	1 [0, 2]	1 [0, 2]
Comorbid conditions (%)							
MI	7	8	8	7	7	6	6
CHF	11	13	11	10	10	12	16
PVD	10	17	13	11	9	8	7
Cerebrovascular disease	9	14	12	10	8	7	5
Atrial fibrillation	7	8	8	7	7	7	7
ISHD	29	25	29	30	29	28	26
COPD	20	43	25	18	18	20	23
Diabetes	31	14	20	27	37	47	56
Cancer	13	20	17	14	12	9	7
Anemia	13	27	17	12	10	10	10
Ever smoker	64	79	68	63	63	63	61
Ever alcoholism	24	30	28	26	22	19	14
SBP (mmHg)	134 ± 19	128 ± 22	131 ± 20	133 ± 18	135 ± 18	136 ± 18	137 ± 19
DBP (mmHg)	75 ± 12	72 ± 13	73 ± 12	74 ± 11	76 ± 11	77 ± 12	77 ± 12
Medications (%)							
Alpha blocker	11	8	10	11	12	12	11
Beta blocker	27	20	23	26	29	32	33
RAASi	35	21	27	33	39	44	49
Statin	39	20	32	39	42	43	43

CCI, Charlson comorbidity index; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ISHD, ischemic heart disease; MI, myocardial infarction; PVD, peripheral vascular disease; RAASi, renin-angiotensin-aldosterone system inhibitors; SBP, systolic blood pressure.

Data presented as mean ± standard deviation, median [interquartile range], or percentage as applicable.

Percentages may not add to 100% because of rounding.

m^2 had the highest crude rate of all-cause mortality: 123.5 [122.4, 124.7] events per 1,000 person-years. Similar patterns for crude rates were observed for CVD and cancer mortality, where a low BMI also had the highest rates. The all-cause and CVD mortality rates gradually declined across BMI groups, where the lowest rates were observed in patients with a BMI 35-<40 kg/m^2, whereas the lowest cancer mortality rate was observed with those with a BMI ≥40 kg/m^2.

In unadjusted analyses, compared with the referent group of a BMI 25-<30 kg/m^2, a BMI ≥30 kg/m^2 was associated with a lower risk of all-cause mortality across all stages, whereas a low BMI was associated with a higher risk. Likewise, the risk of CVD mortality demonstrated a slight reverse J-shaped relationship, where an elevated risk was observed for those with a BMI ≥40 kg/m^2 in non-CKD patients. Finally, the unadjusted relationship of the BMI groups with cancer mortality demonstrated an inverse linear relationship across all CKD stages.

For each outcome, additional adjustment for case-mix + laboratory covariates attenuated all relationships, and each exhibited a reverse J-shaped association (Figure 1A-C, Table S3). A low BMI (<20 kg/m^2) demonstrated close to a two-fold higher risk of all-cause, CVD, and cancer mortality across all stages than a BMI 25-<30 kg/m^2. A BMI 30-<40 kg/m^2 among patients with CKD stage 3B and 4/5 was associated with lower risks of outcomes. Notably, an elevated BMI ≥40 kg/m^2 was

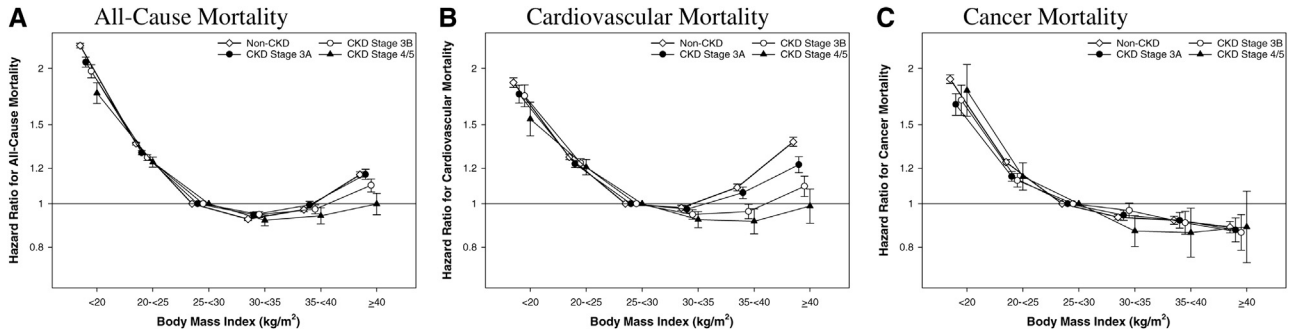

Figure 1. Association of the body mass index with (A) all-cause, (B) cardiovascular, and (C) cancer mortality across strata of CKD stages after case-mix + laboratory adjustment. Covariate adjustment included the following: age, gender, race, ethnicity, ever smoking status, ever alcoholism status, Charlson comorbidity index, chronic obstructive pulmonary disease, cancer, diabetes, ischemic heart disease (including myocardial infarction), congestive heart failure, peripheral vascular disease, cerebrovascular disease, atrial fibrillation, prescription for renin-angiotensin-aldosterone system inhibitors (RAASi), statins, beta blockers, and alpha blockers, and systolic and diastolic blood pressures. CKD, chronic kidney disease.

associated with a higher risk of all-cause and CVD mortality that cascaded across stages, except for CKD stage 4/5. This elevated risk with severe obesity was not observed in cancer mortality outcomes, where a lower risk was observed among all stages. Additional adjustment for serum albumin in a subcohort of patients reflected similar patterns to that of our main analyses.

Bias Analysis for Uncontrolled Confounding by Inflammation in the Associations Between BMI and All-Cause, CVD, and Cancer Mortality

Among the few patients with CRP data, we observed a U-shaped trend between CRP and BMI groups, where both lower- and higher-BMI groups had higher median CRP levels and a greater proportion of patients with inflammation (defined as CRP ≥2 mg/L) (Table S4). Under a range of bias parameters selected for the whole cohort, we observed similar shaped associations to our main analyses, particularly under weak and moderate plausible uncontrolled confounding (Figure S2). Our bias-adjusted estimates showed that a BMI 30-<40 kg/m^2 was associated with a lower risk of outcomes among patients with CKD stage 3B-5. A BMI ≥40 kg/m^2 was also associated with a lower or null risk of mortality outcomes after bias adjustment for weak and moderate uncontrolled confounding in most patients with CKD stage 4/5. For all-cause mortality, a BMI ≥30 kg/m^2 was associated with a lower risk than in the main analysis under stronger uncontrolled confounding. Moreover, under strong uncontrolled confounding, a BMI 20-<25 kg/m^2 and a BMI ≥30 kg/m^2 were associated with a lower risk of CVD and cancer mortality across several CKD stages. A similar pattern was observed when assigning bias parameters specific to each CKD stage and models adjusted for weak plausible uncontrolled inflammation (Figure S3). Moderate or strong uncontrolled confounding also demonstrated a lower observed risk, especially in patients with CKD stage 3B-5. The relationship of the BMI groups with CVD mortality resembled a U-shape in bias analysis for moderate and strong uncontrolled confounding, where a BMI ≥40 kg/m^2 had higher risks among patients without CKD.

Discussion

We observed the presence of the obesity paradox for all-cause, CVD, and cancer mortality in a large cohort of veteran patients, where patients with a BMI 30-<35 kg/m^2 had lower adjusted risks of mortality across all CKD stages. Furthermore, patients with a BMI 35-<40 kg/m^2 also had a lower or null relationship with mortality, especially in patients with late-stage CKD (3B-5). Additional bias analysis for uncontrolled confounding due to unmeasured inflammation suggests that strong inflammation may not fully explain the observed associations.

Our study corroborates prior studies of the obesity paradox in patients with NDD-CKD. Lu et al. showed a U-shaped association between the BMI groups and all-cause mortality in a similar veteran CKD cohort.[14] Like Lu et al., we observed lower and null risks of all-cause and CVD mortality in our patients with CKD stage 4/5 with a BMI 30-<35 kg/m^2 and a BMI ≥40 kg/m^2, respectively. These similar relationships were independent after accounting for lifestyle factors of smoking and alcohol status which have been noted confounders, yet previously absent in Lu et al. Despite the higher smoking prevalence in our study than in the general population, our results independent of smoking suggest that other mechanisms may be involved.[35,36] Akin to Navaneethan et al., we also observed that a BMI 25-<35 kg/m^2 had lower risks for cause-specific mortality among patients with CKD stage 3A-3 B.[25] Conversely, we observed higher risks of all-cause and CVD mortality and a BMI ≥40 kg/m^2, even among patients with CKD stage 3A-3 B. Although we could not control for several markers of inflammation like Navaneethan et al., our sensitivity analyses that included adjustment for serum albumin in a subcohort of patients with data did not alter our conclusions. Moreover, similar to these

previous studies, we observed a lower risk under bias analysis for moderate and strong uncontrolled confounding by inflammation in our cohort.

In our sensitivity analyses for weak and moderate uncontrolled confounding by unmeasured inflammation, we observed little difference to our original results. However, when adjusting for parameters representing stronger unmeasured inflammation, we still observed this obesity paradox, independent of this inflammation. These patterns were also evident in sensitivity analyses with CKD-specific bias parameters aimed at examining the impact of uncontrolled inflammation through the progression of CKD. The associations between an elevated BMI and outcomes were lower to null, especially in patients with CKD stage 4/5. Although we chose strong bias parameters to understand the influence of strong uncontrolled confounding, the lower risk of mortality for a high BMI among patients with CKD stage 4/5 was similar to studies in patients with kidney failure including those on hemodialysis, where both the prevalence of inflammation and risk of death are elevated compared with the general population and patients with earlier CKD stage. Among the patient population on hemodialysis, studies have suggested that the presence of inflammation modifies the obesity paradox relationship, and others have also suggested that these associations were independent of inflammation, and mechanisms may be through pathways of protein-energy wasting.[6,37,38] Most patients with CKD die before transitioning to end-stage renal disease, and the patient population on hemodialysis may present with a worse inflammation profile than our NDD-CKD cohort, yet the concordance of our results in patients with CKD stage 4/5 to those of hemodialysis patients suggests that the associations may be independent of inflammation and akin to studies of a similar 'lipid paradox' among patient populations with NDD-CKD and on hemodialysis.[30,39,40] The transition between states of NDD-CKD to end-stage renal disease particularly in the context of obesity and changes in inflammation profiles requires further study.[41] In the context of CKD, we can only speculate that other factors are driving the observed lower risk of mortality associated with obesity in patients with CKD, and further studies are needed to investigate this complex relationship.[5,15,42]

The results from our bias analysis are on par with the hypothesis that although obesity due to high fat mass is related to inflammation in patients with CKD, malnutrition may exert a stronger effect on mortality among lower-weight individuals, thus showing that patients with obesity have immediate survival.[15] Patients with a greater BMI may have better energy stores and improved appetites even in light of added comorbidities as CKD progresses to kidney failure.[38] This hypothesis may be applicable to cancer mortality as it has been suggested that the elevated postcancer diagnosis BMI is associated with lower mortality risks because patients with obesity may be more tolerable of treatment side-effects.[25,43] Among patients with advanced CKD, nontraditional risk factors are the leading hypotheses for the seemingly paradoxical relationships. Activation of inflammatory biomarkers can alter appetite and promote cachexia, thereby leading to higher risks of outcomes through vascular endothelial damage.[4] We undertook this bias analysis for unmeasured inflammation and CRP as they are important markers that should be routinely measured in high-risk patients with CVD and included in large electronic medical records.[17] Despite the literature suggesting CRP's clinical importance, it was rarely measured in our database compared with prospective cohorts and trials that feature closer patient monitoring.[31,37] In our database, underweight individuals may have had clinical indications that would prompt for a CRP measurement, which is reflected in the higher proportion of CRP measurements in patients with a BMI$<$20 kg/m^2. Although this proposed mechanism is supported by our results, we cannot fully evaluate inflammation or malnutrition by other means as nutritional markers were not drawn proximal to the baseline period in this predominantly non-CKD population. Therefore, additional studies are needed for more routine biomarker measurements as to better account for nutritional or dietary status among all stages of patients with NDD-CKD.

This study is not without limitations. The source cohort was derived from older male veterans such that the results may be less generalizable to the broader population. BMI has been the conventional measurement for obesity but is a poor surrogate for body fat distribution and composition especially in older adults and racial minorities. Other measurements to evaluate obesity were highly missing. We hypothesized that inflammation was an uncontrolled and unmeasured confounder in the BMI-mortality association, but we acknowledge that inflammation may also mediate the relationship and present in alternative causal structures. Obesity and inflammation are complex processes involving multiple interrelated mechanisms that each can be implicated in mortality. Disentangling these relationships in the context of the obesity paradox remains an arduous task. Although our bias analysis investigated unmeasured inflammation as a potential explanation, there are other factors that remain uncontrolled, including genetics, diet, and physical activity. Moreover, we evaluated uncontrolled confounding as a binary and baseline condition and did not account for the severity or duration of pre-existing inflammation. Finally, given the dynamic nature of BMI, inflammation, and CKD progression during a long period of follow-up, stronger methods are needed to evaluate the intricate time-dependent relationships and examine the impact of time-dependent uncontrolled confounding. Yet, despite these limitations, our study holds several strengths including the ability to evaluate patients with advanced CKD who had previously been understudied. We used multiple serum creatinine measurements to

categorize the CKD stage and avoid potential misclassification. Finally, we undertook bias analysis to address uncontrolled confounding by unmeasured inflammation over a series of strengths as to test the robustness of results.

In conclusion, we observed that the relationships between obesity and all-cause and cause-specific mortality were consistent across CKD stages. Additional bias analysis for uncontrolled confounding suggests that unmeasured inflammation cannot fully explain the observed associations. Future studies are needed to elucidate physiological mechanisms for the obesity paradox particularly for all-cause and CVD mortality and to examine further the role of inflammation in relation to CKD.

Practical Application

Lower risks of mortality were observed in patients with CKD and moderate obesity, and this was consistent across CKD stages. Thus, standard obesity and weight management therapies may not be appropriate for all patients as their NDD-CKD progresses.

CRediT authorship contribution statement

Melissa Soohoo: Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Visualization. **Elani Streja:** Methodology, Formal analysis, Investigation, Writing – review & editing, Supervision. **Jui-Ting Hsiung:** Validation, Investigation, Writing – review & editing. **Csaba P. Kovesdy:** Investigation, Writing – review & editing. **Kamyar Kalantar-Zadeh:** Software, Investigation, Resources, Writing – review & editing. **Onyebuchi A. Arah:** Conceptualization, Methodology, Software, Investigation, Writing – original draft, Writing – review & editing, Supervision.

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Data were presented as poster presentations at the 2017 American Society of Nephrology Kidney Week meeting in New Orleans, LA, and the 2019 Society for Epidemiologic Research Annual Meeting in Minneapolis, MN.

Supplementary Data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1053/j.jrn.2021.10.007.

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