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Received: 26.7.2015; Editorial decision: 3.3.2016

FULL REVIEW

Nephrol Dial Transplant (2017) 32: 439–449
doi: 10.1093/ndt/gfw075
Advance Access publication 4 May 2016

Obesity and the risk of cardiovascular and all-cause mortality in chronic kidney disease: a systematic review and meta-analysis

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ABSTRACT

Background: Obesity is a risk factor for cardiovascular disease and death in people without chronic kidney disease (CKD), but the effect of obesity in people with CKD is uncertain.

Methods: Medline and Embase (from inception to January 2015) were searched for cohort studies measuring obesity by body mass index (BMI), waist:hip ratio (WHR) and/or waist circumference (WC) and all-cause and cardiovascular mortality or events in patients with any stage of CKD. Data were summarized using random effects models. Meta-regression was conducted to assess sources of heterogeneity.

Results: Of 4065 potentially eligible citations, 165 studies ($n = 1$ 534 845 participants) were analyzed. In studies that found a

nonlinear relationship, underweight people with CKD (3–5) on hemodialysis experienced an increased risk of death compared with those with normal weight. In transplant recipients, excess risk was observed at levels of morbid obesity (>35 kg/m^2). Of studies that found the relationship to be linear, a 1 kg/m^2 increase in BMI was associated with a 3 and 4% reduction in all-cause and cardiovascular mortality in patients on hemodialysis, respectively {adjusted hazard ratio [HR] 0.97 [95% confidence interval (CI) 0.96–0.98] and adjusted HR 0.96 (95% CI 0.92–1.00)}. In CKD Stages 3–5, for every 1 kg/m^2 increase in BMI there was a 1% reduction in all-cause mortality [HR 0.99 (95% CI 0.0.97–1.00)]. There was no apparent association between obesity and mortality in transplanted patients or those on peritoneal dialysis. Sparse data for WHR and WC did not allow further analyses.

Conclusions: Being obese may be protective for all-cause mortality in the predialysis and hemodialysis populations, while being underweight suggests increased risk, but not in transplant recipients.

Keywords: cardiovascular mortality, chronic kidney disease, meta-analysis, mortality, obesity, systematic review

FULL REVIEW

INTRODUCTION

Obesity is highly prevalent and increasing worldwide, both in the general population and in people with chronic disease. Approximately 35% of the general population in high-income countries are overweight and 30% are obese [1]. Obesity often coexists with other risk factors and chronic diseases. The prevalence of type 2 diabetes, coronary heart disease, hypertension, high cholesterol and osteoarthritis varies from 1.2 to >18-fold higher in obese people compared with those with normal weight [2].

Obesity is also common in the chronic kidney disease (CKD) population. In the US, the prevalence of obesity among those on dialysis is >30% [3], a pattern consistent worldwide and similar to that observed in kidney transplant recipients. Generally, only potential transplant recipients with a body mass index (BMI) <35 kg/m^2 are accepted for transplantation, but after transplantation, recipients may be exposed to appetite-stimulating medications, including steroids, thus triggering weight gain.

In the CKD population, observational studies have reported contradictory findings about the association between obesity and mortality. Previous studies of people on hemodialysis have suggested an 'obesity paradox', where being obese is protective against all-cause and cardiovascular mortality [4, 5]. Other studies have reported a U- or J-shaped association between obesity measured by BMI and mortality, with a higher risk of death in underweight and morbidly obese categories compared with normal weight [6, 7].

The aims of our study were to determine the associations among obesity and the risk of all-cause mortality, cardiovascular mortality and cardiovascular events in individuals with CKD and to compare the relative prognostic strength of different measures of obesity.

MATERIALS AND METHODS

We performed a systematic review and meta-analysis of cohort studies evaluating the association between measures of obesity, including BMI, waist:hip ratio (WHR) and waist circumference (WC) and all-cause mortality, cardiovascular mortality and cardiovascular events. This study was conducted and reported using Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [8].

Study selection

Studies were included if they assessed the association between any measure of obesity including BMI, WHR and WC and the incidence of all-cause or cardiovascular mortality or cardiovascular events in adult patients with CKD Stages 3–5, CKD Stage 5D (on dialysis) or CKD Stage 5T (transplanted).

The investigators undertook a comprehensive literature search of Medline and Embase (from inception to January 2015) without language restriction (see Supplementary data, Appendix Table S1). Hand searching of reference lists of primary studies and review articles was conducted and full texts of relevant articles inspected. All titles and abstracts were independently screened by at least two people (M.L., P.C. and A.R.) and the full text of potentially relevant studies was reviewed for eligibility.

Data extraction and quality assessment

We extracted data on the characteristics of study design, participants, exposures and other covariates as well as outcome measures. If BMI was presented as a categorical variable, we assigned the relevant categories into World Health Organization (WHO) categories of BMI (<18.5, 18.5–25, 25–30 and ≤30 kg/m^2) where possible, to assess nonlinear relationships. In other cases we extracted the number of individuals at risk and adjusted relative risk or hazard ratios (HRs) per unit increase in baseline BMI (in kg/m^2), WHR (units) and WC (cm). The standard error, P-value and 95% confidence interval (CI) were also extracted. When more than one publication of a study existed, information from all reports was used to inform extraction, but care was taken to avoid duplication in analyses. Further information was requested from authors of studies when necessary and included if responses were obtained.

The outcome measures included all-cause mortality, cardiovascular mortality and cardiovascular events. Cardiovascular death was defined as mortality caused by coronary heart disease, heart failure, peripheral vascular disease and cerebrovascular disease. Cardiovascular events were defined as variations of major adverse cardiovascular events (nonfatal myocardial infarction, acute coronary syndrome, sudden death and stroke) and are included in Supplementary data, Appendix Table S2.

The risk of bias in individual studies was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies [9]. Risk assessment was conducted by two authors (M.L. and M.I.) and discrepancies resolved through discussion and consensus. Risk of bias domains included representativeness of the exposed, appropriate selection and comparison of the study groups, adequate ascertainment of exposure and whether comparability of the cohorts was evaluated appropriately with detailed

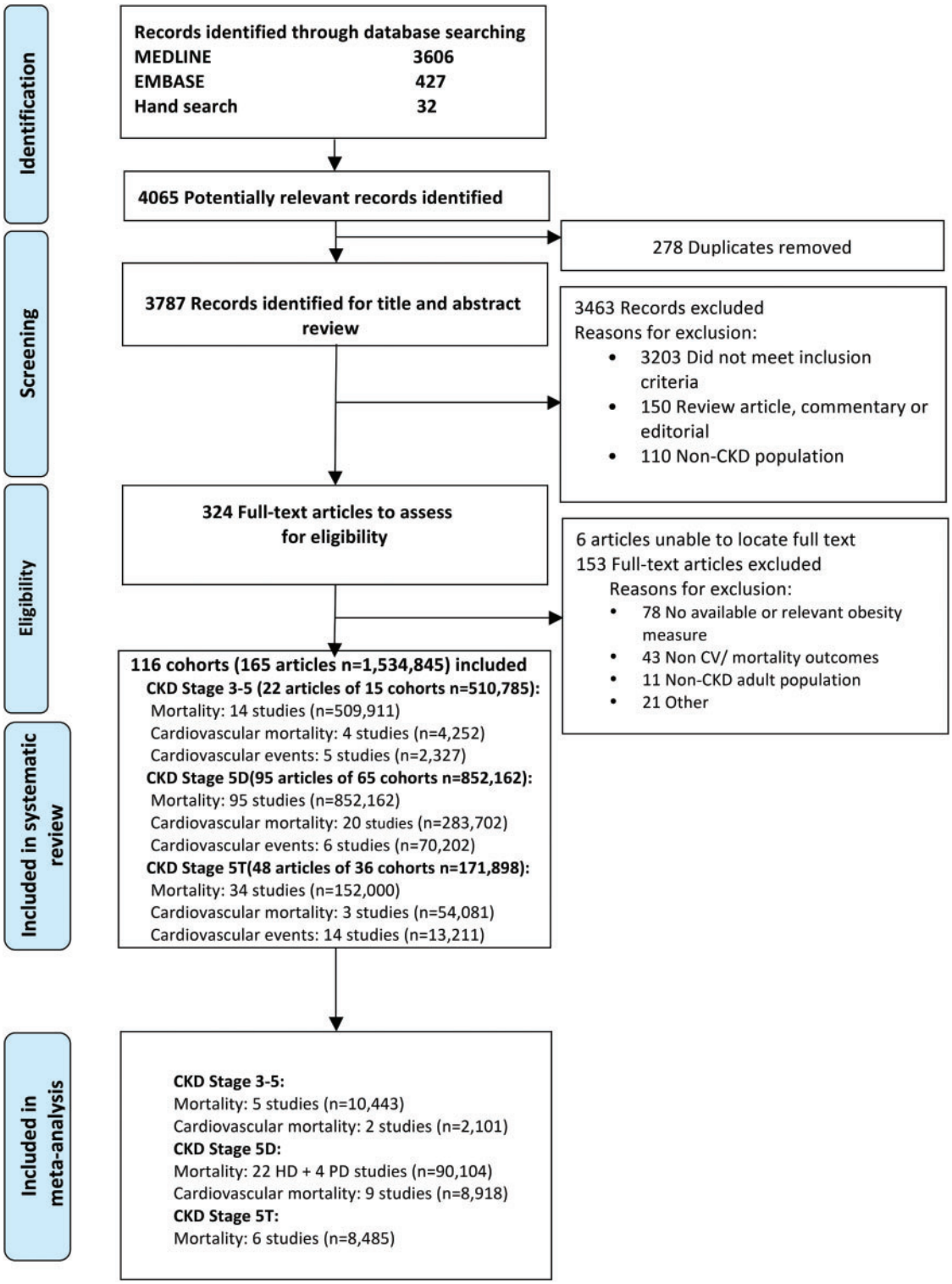

FIGURE 1: Search results.

assessment of outcomes within appropriate follow-up times. Confounding was assessed as partial or full adjustment. Partial adjustment suggested that only gender and age were included in modeling, while full adjustment implies inclusion of all relevant covariates such as race and other comorbidities.

The confidence that may be placed in the summary estimates was assessed using Grading of Recommendations Assessment Development and Evaluation (GRADE) [10].

Data synthesis and analysis

Extracted data for individual studies were tabulated and available summary statistics for categorical and continuous data were collated and analyzed separately. We assessed the association between obesity measures and outcomes by visually inspecting the data, as categories of BMI differed between studies. We were unable to develop summary estimates within

Table 1. Characteristics of studies

	CKD Stages 3–5 (n = 22)		CKD Stage 5D (n = 95)		Transplant (n = 48)	
	n	%	n	%	n	%
Calendar year of publication						
1980–89	0	0	1	1	0	0
1990–99	0	0	8	8	7	15
2000–09	11	50	53	56	27	56
2010–15	11	50	33	35	14	29
Region of origin						
Asia-Pacific	3	14	23	24	3	6
Americas	15	68	40	42	20	42
Europe	4	18	28	29	19	40
Middle East	0	0	1	1	3	6
Multicentre	0	0	3	3	3	6
Number of patients						
<100	0	0	3	3	2	4
100–1000	9	41	53	56	30	63
1000–10 000	10	45	17	18	12	25
>10 000	3	14	22	23	4	8
Predictors assessed						
BMI index	22	100	94	99	48	100
WHR	1	5	1	1	0	0
WC	3	14	3	3	1	2
Duration of follow-up, months, mean (range)[a]	50 (22–174)		19 (12–96)		44 (12–104)	
Age, years, mean (range)[a]	73 (51–75)		62 (43–80)		48 (34–63)	
BMI, kg/m^2, mean (range)[a]	29.0 (26.1–29.2)		24.9 (20.0–27.7)		26.2 (22.0–34.3)	
Male patients, %, mean (range)[a]	91.4 (27.8–99.0)		52.5 (41.0–72.9)		57.4 (36.0–80.9)	
Diabetic patients, %, mean (range)[a]	39.9 (1.8–52.9)		43.1 (0–59.5)		24.4 (1.7–63.1)	

[a]From those papers with available information reported. For more details, please see Supplementary data, Appendix Table 3 : Characteristics of studies included.

different categories of BMI, as the definitions of these categories varied among studies. BMI was reassessed into four categories where possible and included underweight (<18.5 kg/m^2), normal weight (18.5–<25 kg/m^2), overweight (25–<30 kg/m^2) and obese (≥30 kg/m^2) and these categories were graphed against the reference point of BMI=21.8 kg/m^2.

With studies that included continuous analyses, we fitted random effects models to examine the association between continuous measures of obesity (as per unit increase in BMI, WHR and WC) and outcomes using the summary meta-analyses procedure from Review Manager version 5.3. Stratum weights were calculated as the inverse of the variance for the summary statistic supplied. Heterogeneity was quantified using the Cochran's Q and I^2 statistics.

Subgroup analyses and meta-regression

Subgroup analysis and meta-regression were used to assess heterogeneity between studies. Preplanned subgroup analyses by type of renal replacement therapy were used and a random effects regression model was used to evaluate sources of variability in the pooled estimates of mortality in hemodialysis patients. All covariates associated with mortality with a significance value of $P < 0.20$ in univariate analyses were included in the final meta-regression model. For these analyses, a significance level of 5% was established. All analyses were performed using STATA 11.2 (StataCorp, College Station, TX, USA).

RESULTS

Study characteristics of included studies

Using the search strategy outlined in Supplementary data Appendix Table S1, we identified 165 eligible studies (see Figure 1 and Supplementary data, Appendix Table S3). Studies ranged from 43 to 456 099 participants and were published from 1980 to 2015 (see Table 1). The duration of follow-up varied from 3 months to 14.5 years. The majority of studies were conducted in dialysis patients [95 studies (58%), n = 852 162]. Twenty-two studies (n = 510 785) included people with CKD Stages 3–5 and 48 studies (n = 171 898) included kidney transplant recipients. BMI was considered as a continuous variable in 61 studies, categorical in 61 and binary in 34. Nine studies used more than one method in the analyses for all-cause mortality. The lack of sufficient information and varying categories of BMI precluded the meta-analysis of all available studies. Twenty-nine studies did not provide data with sufficient detail (point estimate and variance estimate) to be included in the summaries presented.

Risk of bias assessment

The risk of bias assessment is shown in Supplementary data, Appendix Figure 1. Overall, the risk of bias for the total 165 studies was assessed as high. Of the 165 studies, 137 (83%) reported eligibility criteria and methods of selection adequately. Reporting of outcome measurement and statistical methods were adequate in 65 studies (39%). Full adjustment for confounders was conducted and reported in 88 studies (53%), with partial adjustment

Table 2. GRADE evidence profile

Outcomes	No. of studies	Quality of assessment (decrease in quality score)				Summary of findings	
		Risk of bias[b]	Consistency	Directness	Precision	Publication bias	Estimated hazard ratio (95% CI)	Quality of the evidence (GRADE)
CKD Stages 3–5								
All-cause mortality	4	Moderate (+1)	Moderate inconsistency (0)[c]	Direct (0)	Some imprecision (−1)	Insufficient studies	0.99 (0.97–1.00)	Moderate
Cardiovascular mortality	2	Moderate (+1)	Insufficient studies	Direct (0)	Some imprecision (−1)	Insufficient studies	1.00 (0.98–1.02)	Low
CKD Stage 5D—hemodialysis								
All-cause mortality	22	Moderate (+1)	Moderate inconsistency (0)[c]	Direct (0)	No serious imprecision (0)	No important publication bias	0.97 (0.96–0.98)	Moderate
Cardiovascular mortality	9	Moderate (+1)	Moderate inconsistency (−1)	Direct (0)	No serious imprecision (0)	Suspected publication bias (−1)	0.96 (0.92–1.00)	Low
CKD Stage 5D—peritoneal dialysis[a]								
All-cause mortality	4	Moderate (+1)	Substantial inconsistency (−1)	Direct (0)	Some imprecision (−1)	Insufficient studies	1.05 (0.95–1.17)	Very low
Transplant[a]								
All-cause mortality	6	Moderate (+1)	Substantial inconsistency (−1)	Direct (0)	Some imprecision (−1)	No important publication bias	1.00 (0.96–1.04)	Very low

[a]CKD Stage 5D—peritoneal dialysis and transplant had no studies to include for meta-analysis of cardiovascular mortality and hence have not been included in this table.
[b]In the context of prognostic evaluation: observational studies are the only available evidence and further studies of the same would not likely change the direction of evidence, hence studies were upgraded from zero.
[c]Despite statistical heterogeneity and inconsistency in magnitude; most studies are consistent in direction and hence points not deducted.

in 41 studies (25%). Table 2 summarizes the quality of evidence in the 47 studies included in the meta-analyses. Of the studies that provided data for the meta-analyses, the overall risk of bias was moderate. There was moderate to substantial inconsistency among included studies and suspected publication bias for cardiovascular mortality in those on hemodialysis. The overall quality of evidence varied from very low in transplant and peritoneal dialysis populations to low to moderate for all-cause mortality in CKD Stages 3–5 and those on hemodialysis. Estimates of effect are therefore reported with low confidence in transplant and peritoneal dialysis patients and moderate confidence in CKD Stages 3–5 and those on hemodialysis.

BMI and all-cause mortality

In CKD Stages 3–5, for every 1 kg/m^2 increase in BMI, the risk of death decreased by 1% [HR 0.99 (95% CI 0.97–1.00)] in the meta-analysis summary estimates (five studies, $n = 10\,104$; Figure 2) [11–15]. Figure 3a shows a plot of four studies ($n = 4807$) reporting BMI in categories [16–19]. Two studies reported an increased risk of all-cause mortality in underweight patients with CKD, but no statistically significant association was observed among those with BMI >25 kg/m^2. The largest available study in CKD Stages 3–5 ($n = 453\,946$) was conducted in a predominantly male population of veterans and was analysed in eight categories with BMI 30–<35 as the reference group. It reported a U-shaped association between BMI and mortality, with the reference group as the lowest risk [20].

In CKD Stage 5D, for every 1kg/m^2 increase in BMI there was a reduction in the risk of all-cause mortality of 3% [HR 0.97 (95% CI 0.96–0.98)], as shown in Figure 2 (22 studies in hemodialysis patients, $n = 89\,322$) [4, 21–40]. A similar association between BMI and all-cause mortality was not observed in patients on peritoneal dialysis [HR 1.05 (95% CI 0.95–1.17)] (four studies, $n = 782$) [27, 41–43]. Ten studies ($n = 182\,759$) were plotted and showed no obvious relationship between obesity and all-cause mortality in Stage 5D (Figure 3b).

In CKD Stage 5T, a statistically significant association between obesity and all-cause mortality was not observed when BMI was assessed as a continuous variable [HR 1.00 (95% CI 0.96–1.04)] (10 studies, $n = 17\,064$; Figure 2) or in categories (four studies, $n = 8810$; Figure 3c) [44–53]. Twenty-six studies used varying binary thresholds or categories that did not allow further analysis. In a single cohort of 51 927 transplant recipients, a reverse J-shaped association between BMI and all-cause mortality was observed [54].

BMI and cardiovascular mortality

In CKD Stages 3–5, we did not find a significant association between BMI and cardiovascular mortality (four studies, $n = 4252$) [11, 17, 55, 56].

In CKD Stage 5D, a linear and inverse relationship between BMI and cardiovascular mortality was observed. For every 1 kg/m^2 increase in BMI, there was a 4% reduction in cardiovascular mortality [HR 0.96 (95% CI 0.92–1.00)] (nine studies, $n = 8918$; Figure 4) [21, 22, 30, 39, 57–61]. Four studies assessed BMI and cardiovascular mortality in people on hemodialysis with varying BMI categories; of these, three showed a protective effect of BMI >30 kg/m^2 [62–65].

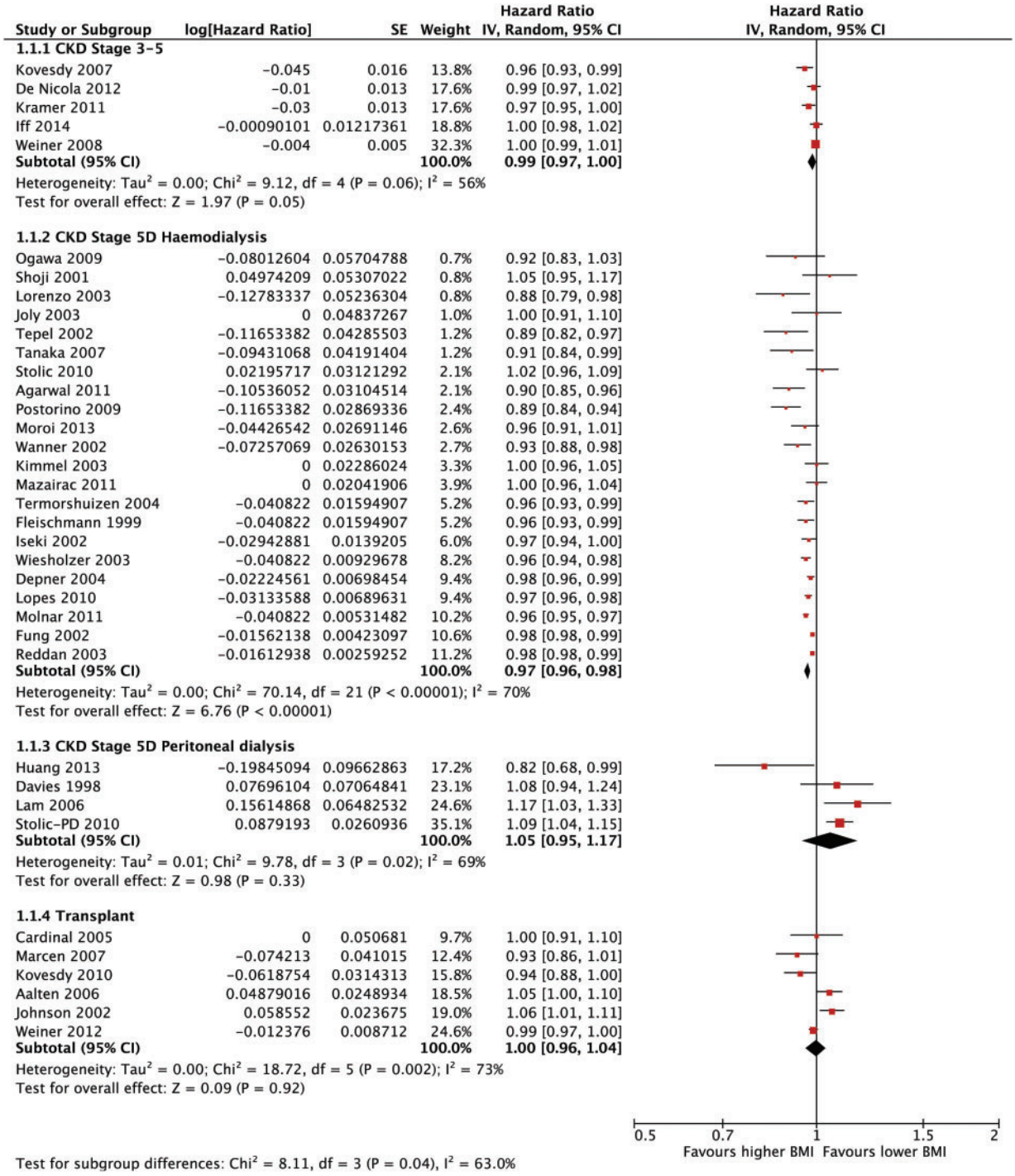

FIGURE 2: Association of BMI and all-cause mortality in CKD patients.

In CKD Stage 5T, studies assessing the relationship between BMI and cardiovascular mortality in transplanted patients reported inconsistent findings (three studies, $n = 54\,081$) [54, 66, 67]. Two studies reported no significant association between BMI and cardiovascular mortality when BMI was analyzed continuously. The other study demonstrated a U-shaped relationship between cardiovascular mortality and BMI. Compared with the reference category of 24–26 kg/m^2, risk was increased in those with a BMI <22 kg/m^2 as well as those >34 kg/m^2 [54].

BMI and cardiovascular events

Five studies (three cohorts) evaluated the association between BMI and cardiovascular events in CKD Stages 3–5. Of these, four showed no significant relationship between BMI and cardiovascular events [15, 68–70], while the other study (a mixed population of nondialysis and dialysis-dependent CKD) reported that every 1 kg/m^2 increase in BMI was associated with an increased risk of cardiovascular events [$n = 167$; adjusted HR 1.15 (95% CI 1.05–1.26)] [71].

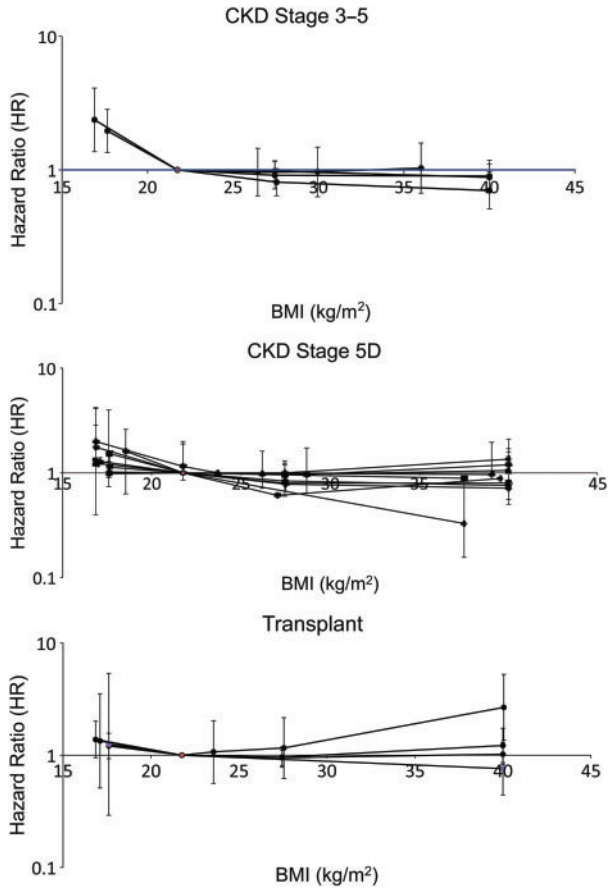

FIGURE 3: Association between BMI and all-cause mortality in CKD patients.

A total of five studies assessed the association between BMI and cardiovascular events in CKD Stage 5D. A single Japanese study reported that for every increase of 1 kg/m^2 BMI there was an average 20% decrease in the risk of a major cardiac event after dialysis initiation [HR 0.80 (95% CI 0.72–0.98)] [26]. The other studies ($n = 4$) did not show a statistically significant relationship between obesity and cardiovascular events [59, 72–74].

Fourteen studies assessed BMI as a predictor of cardiovascular events in 11 distinct cohorts among transplant recipients. Eight studies reported an increased risk of cardiovascular events with higher BMI [47, 66, 75–80]. One study showed a reduced risk of cardiovascular-related events among those with higher BMIs [48], while five studies, two with overlapping cohorts, showed no association between BMI and cardiovascular events [67, 81–84].

WHR and all-cause and cardiovascular mortality

WHR was utilized as a measure of obesity in one study ($n = 1669$) in CKD Stages 3–5 and one study ($n = 537$) in CKD Stages 5D [29, 68]. Patients with the greatest WHR (>0.96 in women and >1.02 in men) experienced an increased risk of cardiovascular events by 1.36 times [adjusted HR 1.36 (95% CI 1.01–1.83)] compared with those with the lowest WHR (<0.87 in women and <0.95 in men). Among those on dialysis, a 0.1-unit increase in WHR was associated with a 1.24-fold increased risk of all-cause mortality [adjusted HR 1.24 (95% CI 1.06–1.46), $P < 0.001$] but not cardiovascular mortality [adjusted HR 1.21 (95% CI 0.98–1.50)].

WC and all-cause and cardiovascular mortality

WC was assessed as a predictor of all-cause mortality and cardiovascular mortality in two studies ($n = 7432$) within the CKD Stages 3–5 population and another study with CKD Stages 1–4 ($n = 2153$). In CKD Stages 3–5, one study ($n = 5805$) reported an increased risk of all-cause mortality of 57% among those with the highest category of WC compared with those with the lowest [adjusted HR 1.57 (95% CI 1.12–2.21)]. For every 10 cm increase in WC there was a 23% increase in risk of all-cause mortality [adjusted HR 1.23 (95% CI 1.02–1.47)] [14]. Another observational analysis of 1627 patients with CKD Stages 3–5 found no statistically significant association between WC and cardiovascular events [adjusted HR 1.03 (95% CI 0.94–1.13)] [68]. The study in CKD Stages 1–4 showed no statistical association between WC and all-cause mortality analyzed as either a linear or categorical variable [85].

Two studies ($n = 944$) assessed WC as a predictor of mortality in CKD Stage 5D [27, 29]. One study found the overall risk of all-cause mortality and cardiovascular mortality was increased by 23% [adjusted HR 1.23 (95% CI 1.02–1.47), $P = 0.03$] and 37% [adjusted HR 1.37 (95% CI 1.09–1.73), $P = 0.006$], respectively, as WC increased by 10 cm. The other study reported WC was a significant predictor ($P = 0.03$) of mortality in peritoneal dialysis patients but not hemodialysis patients ($P = 0.26$). Central obesity (≥90 cm in men and ≥80 cm in women) was predictive of increased risk of cardiovascular events [HR 4.91 (95% CI 1.3–18.9), $P = 0.02$] in an Asian cohort [86].

Transplanted patients were found to have a 64% increased risk of all-cause mortality [HR 1.64 (95% CI 1.08–2.47)], as WC increased by 15 cm in the one available study [45].

Sources of heterogeneity

Meta-regression was only possible in studies that assessed the relationship of obesity and all-cause mortality in hemodialysis patients, given the small number of studies in other CKD stages. There was no evidence that the effects of obesity and mortality varied according to sample size, region, diabetic status, how studies chose participants or measured outcomes (Supplementary data, Appendix Table S4). Factors that explained some of the heterogeneity were the proportion of males included in the study ($P = 0.03$) and the methodological quality of the study ($P = 0.002$). Having an increased proportion of men as study participants and studies with adequate long-term follow-up increased the protective effect of obesity on survival in hemodialysis patients.

DISCUSSION

We have shown a differential effect of BMI and mortality according to CKD stage. In studies that assessed BMI as a linear variable, an inverse and linear association between increasing BMI and reduction in the overall risk of all-cause and cardiovascular mortality was observed in people on hemodialysis. For every 1 kg/m^2 increase in BMI, there was a 3 and 4% decrease in risk of all-cause death and cardiovascular-related mortality,

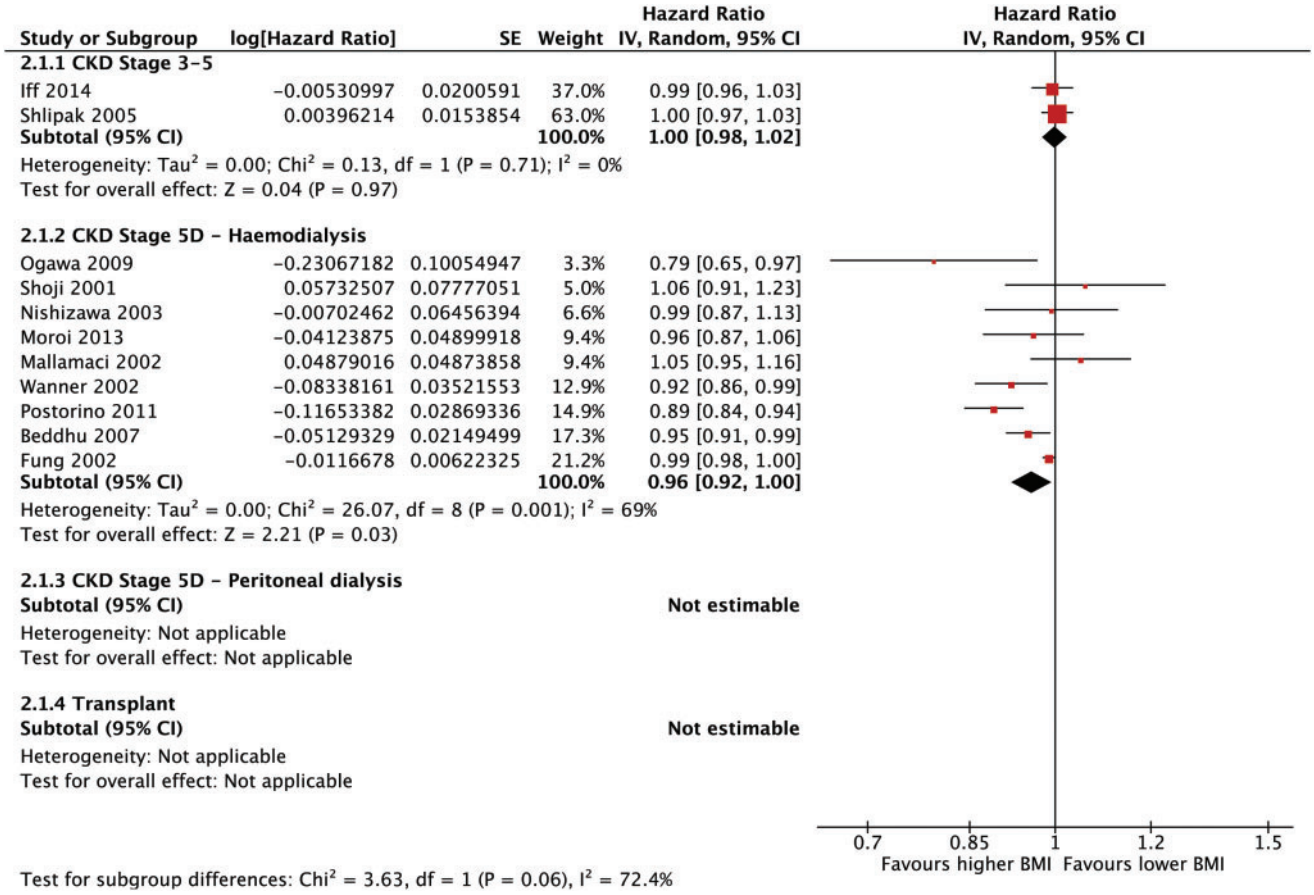

FIGURE 4: Association of BMI and cardiovascular mortality in CKD patients.

respectively. In CKD Stages 3–5, the reduction in risk for all-cause mortality per kg/m^2 was 1%. No association was apparent between BMI and mortality in transplant recipients or those on peritoneal dialysis. The group of patients most at risk appeared to be those who were underweight and with CKD Stages 3–5 or on hemodialysis. Aside from BMI, WHR and WC were the two most frequently reported measures of obesity; however, there were too few studies to be confident of any association between these alternate measures and the outcomes of interest in people with CKD.

The biological rationale for the apparent differences of BMI and adverse health outcomes by CKD stage is unclear. It is likely that obese patients with CKD have survived 'traditional' factors that are associated with obesity, such as hypertension, diabetes mellitus and cardiovascular disease, and may have a unique survival advantage when reaching end-stage disease. Further, previous *in vitro* studies have shown that the differences may be mediated by the availability of reserve fat stores in those with advanced stage kidney disease. Adipose tissue is active in cytokine, chemokine and hormonal production, in addition to its role in energy storage. Adiponectin is one protein in adipose tissue that has an anti-inflammatory and anti-atherogenic effect while increasing insulin sensitivity, which may decrease the likelihood of atherosclerosis and thus the risk of cardiovascular mortality as observed in the end-stage kidney disease (ESKD) population [87]. The lack of a statistically significant association between obesity, cardiovascular and all-cause mortality in kidney transplant recipients is unexpected and requires future studies to better understand the biological mechanisms of how adipose tissue may differentially impact on different stages of CKD.

BMI may not necessarily be a reliable and accurate marker of adiposity in people with CKD. Measurement error and misclassification may exist, causing an overrepresentation of those with lower cardiovascular disease risk in higher BMI categories, thus inflating the observed protective effects in obese individuals with advanced-stage CKD [88, 89]. WHR and WC may in time prove to reduce these errors; however, as yet there are insufficient data to accurately compare their prognostic performance.

Previous reviews have assessed the relationship of BMI and all-cause mortality in people on hemodialysis and found a significant inverse relationship regardless of whether BMI was assessed as a continuous or categorical variable [90, 91]. Patients on dialysis with a BMI >25 kg/m^2 experienced a 25% reduction in all-cause mortality compared with those with BMI <25 kg/m^2. The protective effects of obesity in transplant recipients are less certain. Observational studies, using data from registries, have failed to demonstrate any statistically significant association between obesity, graft and patient survival up to 20 years after transplantation [50]. In a recent systematic review that assessed the impact of BMI on outcomes in kidney transplant recipients, a lower pre-transplant BMI incurred a survival

advantage at 1, 2 and 3 years after transplantation compared with those with a higher BMI (>30 kg/m^2) [92]. This contrasts with another review of the same topic, which reported an increased risk of delayed graft function in obese transplant recipients but no statistically significant relationship between BMI and acute rejection or graft and patient survival [93].

Our study has several strengths and limitations. Our study has a broad inclusion criterion. A comprehensive literature search was conducted to include studies that assessed the impact of obesity on patient-relevant and important outcomes, including cardiovascular events and cardiovascular and all-cause mortality, across the full spectrum of CKD. Using a rigorous and systematic approach to critical appraisal and data analyses, we were able to produce meaningful and important prognostic information about the impact of obesity in CKD patients. The main weakness of this review is the relative paucity of high-quality observational studies, with sufficient follow-up data to assess the long-term impact of obesity and outcomes in people with CKD. There is also a scarcity of data in patients on peritoneal dialysis. In light of these limitations, we were unable to provide any confirmative evidence regarding the relationship between obesity and adverse patient outcomes in this group. Our confidence in the estimates was also limited by the heterogeneity of the studies, potential residual confounding and the statistical analysis chosen by individual studies. Ideally a more diverse range of obesity measures, such as dual-energy X-ray absorptiometry fat mass or other imaging, would have been included to further explore the associations between obesity and outcomes.

Implications for clinical practice and future research

There is now established epidemiological and trial-based evidence suggesting a direct link between intentional weight loss and improved health outcomes in the general population, thus supporting a potential causal relationship between weight and health [94–97]. In the CKD population and among those with chronic disease, this relationship is complex, often confounded by many factors, making any inferences between obesity and health outcomes difficult. We have shown consistencies across observational studies that the 'obesity paradox' exists in patients with ESKD on hemodialysis. Future studies should focus on understanding which components of obesity may lead to our current observations. These potentially modifiable factors should then be tested in well-designed intervention trials. Until then, any firm conclusions regarding the reverse relationship between obesity and adverse health outcomes, including cardiovascular and all-cause mortality, cannot be made with certainty.

CONCLUSIONS

In conclusion, our study findings suggest that being obese may be protective for all-cause death in the predialysis and hemodialysis populations, but not in transplant recipients. However, this relationship is unlikely to be linear, with the greatest risk of death occurring at the extreme categories of BMI.

SUPPLEMENTARY DATA

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

ACKNOWLEDGEMENTS

M.L. is the recipient of a National Health and Medical Research Council Postgraduate Scholarships Grant: Clinical Postgraduate Research Scholarship APP1074409. We thank A.R. for data collection.

CONFLICT OF INTEREST STATEMENT

None declared.

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Received: 21.1.2016; Editorial decision: 12.3.2016