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Body Mass Index and Mortality in Kidney Transplant Recipients: A Systematic Review and Meta-Analysis

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Abstract
Background: A higher body mass index (BMI) seems to be linked to survival advantage in maintenance hemodialysis patients. However, it is uncertain if this 'obesity survival paradox' is also observed in kidney transplant recipients. Hence, we systematically reviewed the literature on the impact of pre-transplantation BMI on all-cause mortality in this population. **Methods:** We searched MEDLINE, EMBASE, Web of Science, CINAHL, and Cochrane CENTRAL for relevant studies up to July 2013. Two investigators independently selected the studies using predefined criteria, abstracted the data from the included studies, and independently assessed each study's quality using the Newcastle-Ottawa Quality Assessment Scale. In addition to the qualitative synthesis, we quantitatively pooled the results of the studies with clinical, methodological, and statistical homogeneity. **Results:** We screened 7,123 records, from which we included 11 studies (with a total of 305,392 participants) in this systematic review and 4 studies in the meta-analyses. In the only study that included children, obesity was linked to higher mortality in children of 6–12 years old. For adults, our meta-analyses indicated that compared to normal BMI, underweight [Hazard Ratio (HR): 1.09; 95% Confidence Interval (CI): 1.02–1.20], overweight (HR: 1.07; 95% CI: 1.04–1.12), and obese (HR: 1.20; 95% CI: 1.14–1.23) levels of BMI were associated with higher mortality. **Conclusion:** The presence of the obesity survival paradox is unlikely in kidney transplant recipients since both extremes of pre-transplantation BMI are linked to higher mortality in this population.   © 2014 S. Karger AG, Basel

Introduction

Obesity is a recognized cardiovascular risk factor [1] and is associated with increased risk of mortality in the general population [2]. In kidney transplant recipients

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(KTRs), *post*-transplantation obesity is associated with a higher risk of mortality and graft failure as well as higher risks of hypertension, dyslipidemia, and diabetes mellitus [3]. However, a higher body mass index (BMI), an indicator of obesity, is paradoxically associated with survival advantage in hemodialysis patients including those waitlisted for kidney transplantation [4–7]. The association of *pre*-transplantation BMI (PreT-BMI) with mortality post-transplant has remained uncertain in KTRs.

Because a substantial proportion of KTRs receive hemodialysis before transplantation, a better understanding of the true association between PreT-BMI and mortality is vital in KTRs. Hence, we systematically reviewed the literature on the possible association of PreT-BMI with all-cause mortality in KTRs.

Methods

Search Strategies

We performed a wide search to identify studies investigating the link between BMI and mortality in all chronic kidney disease patients including KTRs. We searched MEDLINE (PubMed), Web of Science, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Cochrane Central Register of Controlled Trials (CENTRAL) up to July 2013. To search PubMed, we used the following search query:

((Renal Insufficiency, Chronic) OR (chronic renal insufficient*) OR (Kidney Failure, Chronic) OR (chronic renal failure) OR (end-stage kidney disease*) OR (end-stage renal disease*) OR ESRD OR (chronic kidney disease*) OR (chronic renal disease*) OR (Renal Dialysis) OR ((renal OR kidney) AND dialys*) OR hemodialys* OR haemodialys* OR ((peritoneal OR extracorporeal) AND dialys*) OR Kidney Transplantation OR ((kidney OR renal) AND transplant*)) AND ((body mass index) OR BMI OR overweight OR obes*) AND (mortality OR (death rate*) OR (case fatality rate*) OR survival OR (reverse epidemiolog*) OR (obesity AND paradox*)).

A similar query was used to search Web of Science, CINAHL, and CENTRAL. To search EMBASE, the above search query was slightly tailored to match the searching keywords to EMTREE (the EMBASE's indexing thesaurus). Three field experts (*MZM, CPK, KKZ*) were consulted to recognize any unidentified relevant study.

Study Selection

Search results were imported into EndNote software and duplicate records were removed. Two investigators (*SFA, GZ*) independently screened the studies, blinded to the study authors and journals, and selected studies that met inclusion/exclusion criteria.

We included the studies with longitudinal comparisons, either observational studies or randomized controlled trials, which had studied the association of PreT-BMI with all-cause mortality in KTRs. Studies with 1,000 KTRs or more were included. Any discrepancies between the two reviewers on study eligibility were resolved by discussion and consensus.

Data Abstraction and Quality Assessment

Study characteristics and findings for eligible studies were extracted and tabulated (table 1). For the studies with insufficient data, we sent incomplete data tables to the corresponding authors and asked them to return the completed tables. To assess the study quality, the same two investigators independently applied the Newcastle-Ottawa Assessment Scale [8] assigning a quality score of 0–9 to each study. The quality score was calculated on the basis of three major components: selection of study participants (0–4 points), quality of the adjustment for confounding (0 to 2 points), and ascertainment of the exposure or outcome of interest in the case-control or cohorts, respectively (0–3 points). The maximum score was 9 points, representing the highest methodological quality. Disagreements in the scores were resolved by discussion and consensus.

Data Analysis and Synthesis

We quantified the inter-rater agreement for the study selection and the quality assessment by comparing investigator-assigned, study-inclusion codes and quality scores, respectively.

For the main meta-analyses, results of the studies were pooled if the studies were clinically, methodologically, and statistically homogeneous. Clinical homogeneity was defined as having similar patients as well as BMI and mortality measurements. Methodological homogeneity was defined as having similar study designs and quality. Statistical homogeneity was defined as having an I-squared statistic <25% for the corresponding summary statistics. Although our pre-specified outcome was all-cause mortality, we also pooled the results for 'graft-failure' and 'combined mortality or graft failure' outcomes when possible. For the main meta-analyses, we used the fixed-effects model since the risk estimates were homogeneous. In addition, we performed a set of sensitivity analyses to test whether assigning equal weights to the studies would yield similar results. For this purpose, we used the fixed-effects model or the random-effects model to pool the risk estimates with I-squared statistics of <25 or ≥25%, respectively. We investigated the risk of reporting bias using Funnel Plots and Egger's Tests of asymmetry. A 95% confidence interval (CI) with no overlap with the null effect value (Hazard Ratio = 1) was considered significant in our study. For statistical procedures, we used Stata 12 (StataCorp, College Station, Tex., USA).

Results

Our initial search yielded 7,123 records, from which 11 studies were included in this systematic review [9–19] (fig. 1). Two of the included studies lacked necessary numerical results [18, 19] and no reply was received after request of further information from authors. All of the studies employed a retrospective cohort design utilizing pre-existing registry data, and reported hazard ratios (HRs) from Cox proportional hazard models. The overall quality of the studies was fair with a quality score range of 6–9. Agreement between the two investigators was 94% (Kappa: 0.77) for the study selection and 82% (Kappa: 0.69) for the quality assessment.

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Kovesdy/Gillen/Steiner/Kalantar-Zadeh

Table 1. Characteristics of included studies

Study ID	Data sources and settings	Participants	% Female	Age	BMI variable	Time of BMI measurement	Mortality index	Quality score	Take-home message
Studies of children									
Hanevold et al. (2005) [16]	'North American Pediatric Renal Trials and Collaborative Studies' data, 1987–2002, Canada, Mexico, and US.	6,658 children of 2–17 years old with kidney transplant.	39.7	Mean: 10.6	Binary: Non-obese (BMI[a] ≤95% for age), Obese (BMI >95% for age)	Right before transplantation	HRs[b] from multivariate Cox regression to predict all-cause mortality.	7	In children of 6–12 y/o[c], obesity yields higher mortality; but, in children of other ages, obesity yields no significantly different mortality.
Studies of adults included in meta-analyses									
Curran et al. (2013) [9]	'Comprehensive Renal Transplant Research Information System' of Toronto General Hospital data, 2000–2010, Canada.	1,151 adult kidney transplant recipients.	62.50	Mean: 49.4	Ordinal: <20, 20–24.9, 25–29.9, 30–34.9, ≥35	Right before transplantation	HRs from multivariate Cox regressions to predict death with functioning graft.	8	Compared to BMIs of 20–24.9, higher or lower BMIs yield no significantly different mortality.
Hatamizadeh et al. (2013) [11]	'Scientific Registry of Transplant Recipients' data, 2001–2007, US.	145,470 kidney transplant recipients. (a subset of 15,667 elderly patients was analyzed in the original report)	40	Mean: 47.3 SD[d]: 13.6	Binary: ≤30, >30	Right before transplantation	HRs from multivariate Cox regression to predict all-cause mortality in the elderly patients (≥60 y/o).	7	In patients of 60–75 y/o, BMIs >30 yield no significantly different mortality compared to BMIs ≤30; but in patients ≥75 y/o, BMIs >30 yield (slightly) higher mortality.
Hoogeveen et al. (2011) [12]	'Netherlands Organ Transplantation Registration' data, 1984–1997, the Netherlands.	1,810 adult kidney transplant recipients with no graft loss during the first 3 months.	39	Median: 46 IQR[e]: 35–56	Ordinal: ≤20, 20.1–25, 25.1–30, >30	Right before transplantation	HRs from multivariate Cox regression to predict all-cause mortality.	8	Compared to BMIs of 20.1–25, higher or lower BMIs yield no significantly different mortality.
Chang et al. (2007) [15]	'Australia and New Zealand Dialysis and Transplant Registry' data, 1991–2004, Australia and New Zealand.	5,684 kidney transplant recipients.	39	16–29 y/o: 18%; 30–49 y/o: 43%; ≥50 y/o: 39%	Ordinal: <18.5, 18.5–24.9, 25–29.9, ≥30	Right before transplantation	HRs from multivariate Cox regression to predict all-cause mortality.	7	Compared to BMIs of 18.5–24.9, higher or lower BMIs yield no significantly different mortality.
Studies of adults excluded from meta-analyses									
Cannon et al. (2013) [10]	'United Network for Organ Sharing' data, 2004–2010, US.	74,983 kidney transplant recipients with BMIs of 10–60.	39.5	Mean: 48.2	Ordinal: <30, 30–34.9, 35–39.9, ≥40	Before transplantation	HRs from multivariate Cox regression to predict all-cause mortality.	7	Compared to BMIs <30, BMIs of 30–34.9 yield lower mortality, and BMIs ≥35 yield no significantly different mortality.
Streja et al. (2011) [13]	'DaVita' MHD[f] patient cohort data, 2001–2006, plus 'Scientific Registry of Transplant Recipients' data up to 2007, US.	10,090 MHD patients who received kidney transplant and had BMIs of 12–60.	49	Mean: 49 SD: 13	Continuous AND ordinal: <20, 20–21.9, 22–24.9, 25–29.9, 30–34.9, ≥35	Average of BMI in 3 months before transplantation	HR from multivariate Cox regression to predict all-cause mortality.	8	Continuous BMI: BMI has no significant (liner) effect on mortality; Ordinal BMI: Compared to BMIs of 22–24.9, higher or lower BMIs yield no significantly different mortality.

Table 1. (continued)

Study ID	Data sources and settings	Participants	% Female	Age	BMI variable	Time of BMI measurement	Mortality index	Quality score	Take-home message
Aalten et al. (2008) [14]	'Netherlands Organ Transplantation Registration' data, 1984-1997, the Netherlands.	2,187 adult kidney transplant recipients with no graft loss during the first 3 months.	38.90	Mean: 45.9 SD: 13.1	Continuous	Before transplantation	HR from multivariate Cox regression to predict all-cause mortality.	7	BMI has no significant (linear) effect on mortality.
Aalten et al. (2006) [17]	'Netherlands Organ Transplantation Registration' data, 1994–N/A, the Netherlands.	2,067 adult kidney transplant recipients with no graft loss during the first 3 months.	48.3	Mean: 39.7	Continuous and ordinal: <19, 19–21.9, 22–24.9, 25–27.9, 28–30.9, 31–33.9, ≥34	Right before transplantation	HRs from multivariate Cox regression to predict all-cause mortality.	6	Continuous BMI: Higher BMIs may yield higher mortality; Ordinal BMI: BMI has a J-shaped effect on mortality, and BMIs ≥28 yield significantly higher mortality compared to BMIs of 22–25.
Gonzalez-Posada et al. (2006) [18]	32 kidney transplantation centers, 1990–1998, Spain.	3,365 single kidney transplant recipients with no graft loss during the first year.	36.7	Mean: 45.3	Continuous	Right before transplantation	HR from multivariate Cox regression to predict all-cause mortality.	6	BMI has no significant (linear) effect on mortality.
Meier-Kriesche et al. (2002) [19]	'US Transplant Scientific Registry' data plus 'US Renal Data System', 1988–1997, US.	51,927 adult kidney transplant recipients.	N/A[g]	N/A	Ordinal: <18, 18–19.9, 20–21.9, 22–23.9, 24–25.9, 26–27.9, 28–29.9, 30–31.9, 32–33.9, 34–35.9, ≥36	Before transplantation	HRs from multivariate Cox regressions to predict death with functioning graft.	7	BMIs ≥30 yield significantly higher death with functioning graft.

[a] BMI = Body mass index; [b] HR = hazard ratio; [c] y/o = years old; [d] SD = standard deviation; [e] IQR = inter-quartile range; [f] MHD = maintenance hemodialysis; [g] N/A = not available.

Studies of Children

The only identified study of children, Hanevold et al. [16] investigated the association of obesity with mortality in KTRs 2–17 years old (table 1). They defined obesity as BMIs >95% for age, and observed a 3.65 fold (95% CI: 1.46–9.11) and 2.94 fold (95% CI: 1.53–5.63) higher mortality in 6–12 year old obese KTRs from living donors and cadaver donors, respectively, compared to those with normal BMI. However, no significant association between obesity and mortality was observed for children below 6 or above 12 years old.

Studies of Adults

The ten studies with adult participants [9–15, 17–19] did not record BMI in a similar manner (table 1). Four of these studies [13, 14, 17, 18] recorded BMI as a continuous variable, and reported a single HR of mortality for every 1 kg/m^2 increase in BMI. These studies observed no significant link between BMI and mortality, except Aalten et al. (2006) [17], which reported a marginally significant association (HR: 1.05; 95% CI: 1.00–1.09).

Hatamizadeh et al. [11] used a large dataset with 145,470 patients; however, their report was based on a subset of 15,667 elderly patients. They dichotomized

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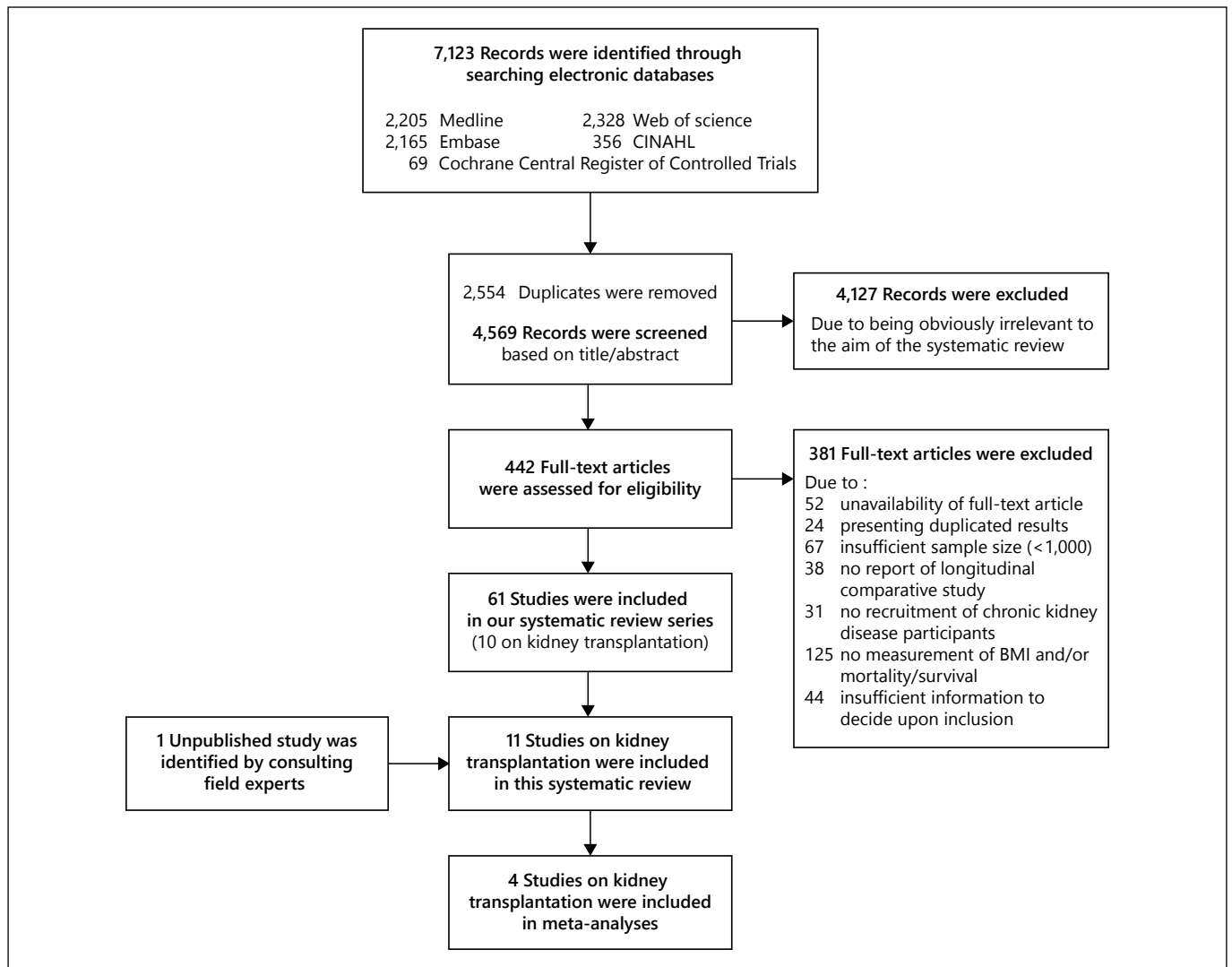
Fig. 1. Study flow diagram.

BMI values to ≤30 (non-obese) and >30 kg/m^2 (obese), and observed a significantly higher mortality in obese patients ≥75 years old (HR: 1.50, 95% CI: 1.09–2.07). No significant differences in mortality were detected between obese and non-obese patients in age groups 65–70 and 70–75 years. This study [11] analyzed data from the 'Scientific Registry of Transplant Recipients' (SRTR). In order to collect further information about the association of mortality with BMI in KTRs, we accessed this study's dataset and completed a reanalysis. In our reanalysis, categories of BMI were classified according to the WHO BMI classification system [20]. Cox proportional hazards models adjusted for age, gender, race, dialysis vintage, comorbidities (diabetes, angina, chronic

obstructive pulmonary disease, hypertension, peptic ulcer, peripheral vascular disease, and cerebrovascular disease), and pre-transplantation serum creatinine and albumin were used to estimate the association of all-cause mortality with underweight, overweight, and obese classes I, II, and III compared to normal BMI. We additionally estimated the adjusted HRs for outcomes of graft failure and combined mortality or graft failure. J-shaped associations were observed for BMI with all-cause mortality and combined mortality or graft failure, in which underweight, overweight, and all-obese BMI classes were associated with an increased risk of mortality as well as combined mortality or graft failure (fig. 2). Risk of graft failure alone was also significantly higher
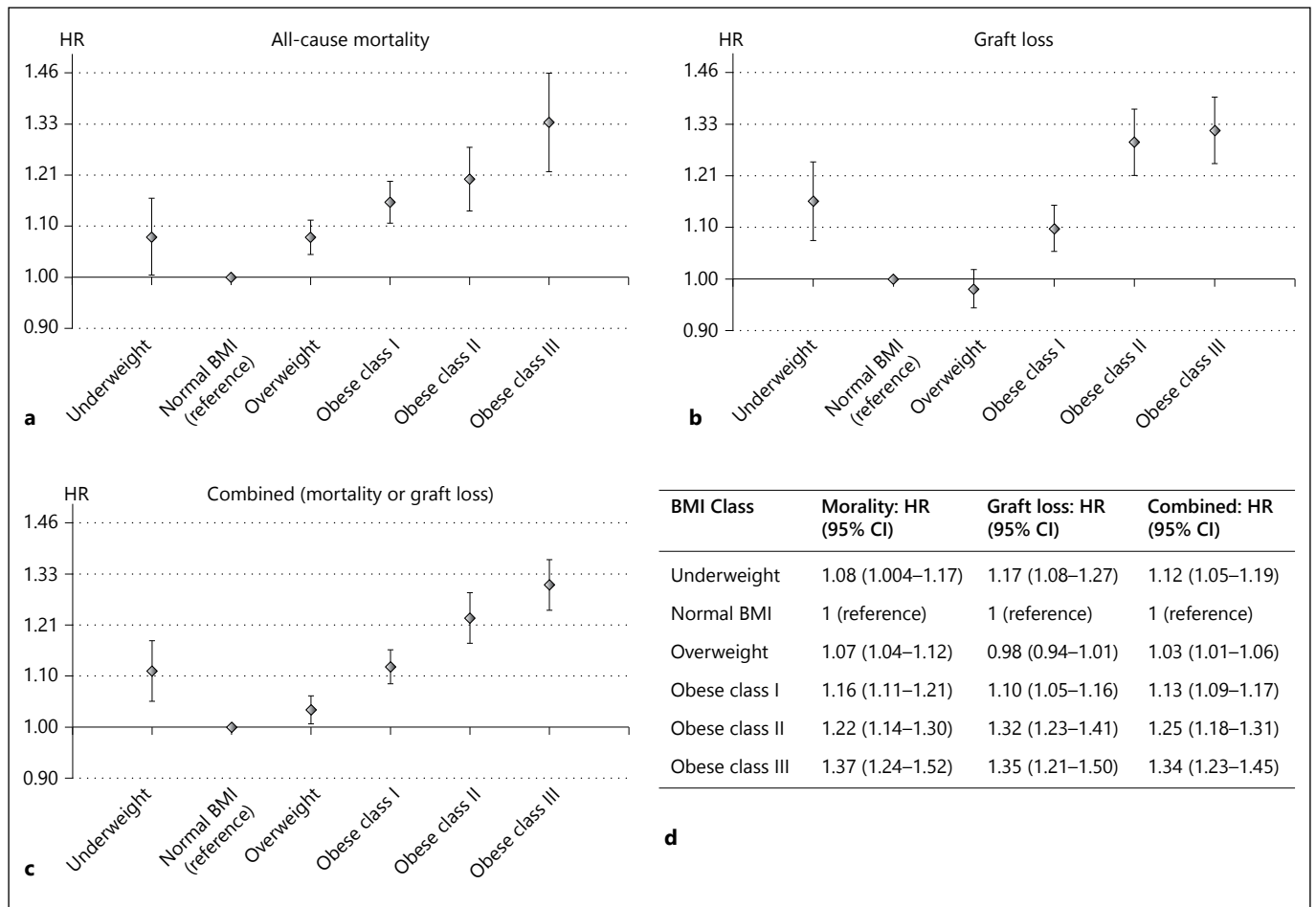
Fig. 2. The results from re-analyzing a report of 'Scientific Registry of Transplant Recipients' data. Re-analysis of the largest reported dataset by Hatamizadeh et al. [11] revealed the adjusted hazard ratios (HRs) of 'all-cause mortality' (**a**), 'graft failure' (**b**), and 'combined mortality or graft failure' (**c**) for underweight, over-weight, and obese classes I, II, and III, compared to the normal BMI. The above categories were defined according to the WHO BMI classification [20]. The vertical axes are in logarithmic scale. The hazard ratios and their 95% confidence intervals (CIs) are tabulated (**d**).

| BMI Class	Morality: HR (95% CI)	Graft loss: HR (95% CI)	Combined: HR (95% CI)
Underweight	1.08 (1.004–1.17)	1.17 (1.08–1.27)	1.12 (1.05–1.19)
Normal BMI	1 (reference)	1 (reference)	1 (reference)
Overweight	1.07 (1.04–1.12)	0.98 (0.94–1.01)	1.03 (1.01–1.06)
Obese class I	1.16 (1.11–1.21)	1.10 (1.05–1.16)	1.13 (1.09–1.17)
Obese class II	1.22 (1.14–1.30)	1.32 (1.23–1.41)	1.25 (1.18–1.31)
Obese class III	1.37 (1.24–1.52)	1.35 (1.21–1.50)	1.34 (1.23–1.45)

in underweight and all obese BMI classes; however, the overweight class showed a trend toward a lower risk of graft failure (fig. 2).

In addition to our re-analyses, seven included studies [9, 10, 12, 13, 15, 17, 19] used ordinal BMI variables and estimated the HR of mortality for the BMI categories above or below normal BMI (two of these studies [13, 17] also reported associations based on BMIs as a continuous variable). These studies showed either a J-shaped association [17, 19] or no significant association of BMI with mortality [9, 12, 13, 15]. One study [10], however, reported obesity class I to be protective (HR: 0.92, 95% CI: 0.86–0.99). Nevertheless, the reference category in this study was any BMI <30, which combines the underweight, normal BMI, and overweight classes all together.

Meta-Analyses of All-Cause Mortality Results

To estimate the overall association of BMI with mortality, we pooled the results of our re-analysis with the results from three other studies that used ordinal BMI categories. Other studies using ordinal BMI categories were not included in this meta-analysis because they represented only a subset of SRTR data [10, 13], reported insufficient numerical results [17, 19], or inserted insufficient covariates in the Cox proportional hazards model [17]. We did not pool the results from studies with continuous BMI regressors since such regressors could only detect linear relationships.

No study reported the corresponding HRs for all WHO obese classes [20] separately (except our re-analysis of SRTR data). Therefore, for each study, we estimated
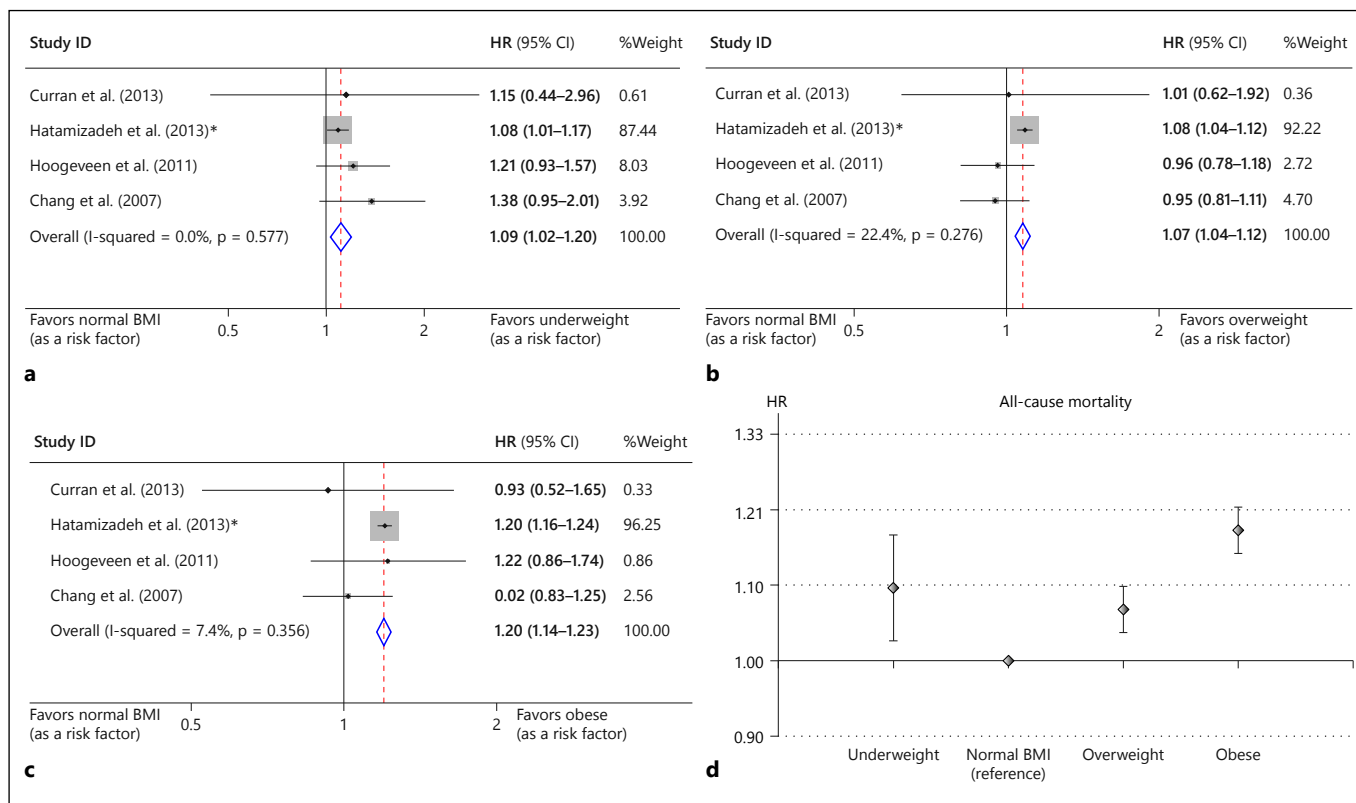
Fig. 3. Meta-analyses of hazard ratios of all-cause mortality. **a–c** Illustrate the meta-analysis of the hazard ratios (HRs) of all-cause mortality in 'underweight', 'overweight', and 'obese' BMI classes, respectively, compared to normal BMI. The three BMI cut-points between the 'underweight', 'normal BMI, 'overweight', and 'obese' classes were 18.5 [11, 15] or 20 [9, 12], 25, and 30, respectively. The horizontal axes are in logarithmic scale. **d** Puts the results of **a–c** together, showing the pooled hazard ratios of all-cause mortality (in logarithmic scale). * Results are derived from re-analyzing Hatamizadeh et al. [11] data.

a single-pooled HR for obese classes I to III all together. We then pooled the results across all 4 studies and observed all abnormal BMI classes to be associated with an increased risk of all-cause mortality compared to the normal BMI class (fig. 3).

Post-Hoc Meta-Analyses of Graft Failure and Combined Outcome

The same four studies [9, 11, 12, 15] either reported [9, 12, 15] or provided data [11] to estimate HRs of graft failure. In the pooled analysis, underweight and obese classes were associated with a higher risk of graft failure, while overweight showed almost the same risk of graft failure as normal BMI (fig. 4).

For combined mortality or graft failure, we pooled HRs from the same studies except from the study by Hoogeveen et al. [12] and observed the risk of the combined outcome to be higher in underweight, overweight, and all obese BMI classes compared to the normal BMI class (fig. 5).

Sensitivity Analyses

Since the results of re-analyzing SRTR data – reported by Hatamizadeh et al. [11] – gained large weights in our meta-analyses, we repeated the meta-analyses while assigning equal weight to the meta-analyzed studies. Pooled results showed similar trends toward higher mortality in underweight (HR: 1.20, 95% CI: 0.92–1.56) and obese (HR: 1.08, 95% CI: 0.91–1.29) classes compared to the normal BMI class. However, this particular analysis showed a similar risk of mortality in the overweight class and the normal BMI class (HR: 1.00, 95% CI: 0.85–1.16). (see online suppl. appendix: Forest plots 1.A–1.C; for all online suppl. material, see www.karger.com/doi/10.1159/000367812).

In addition, the risk of graft failure was higher in underweight (HR: 1.29, 95% CI: 1.04–1.59) and obese (HR: 1.25, 95% CI: 1.05–1.48) classes, and a trend existed toward a higher graft failure in the overweight (HR: 1.09, 95% CI: 0.94–1.27) compared to the normal BMI class.
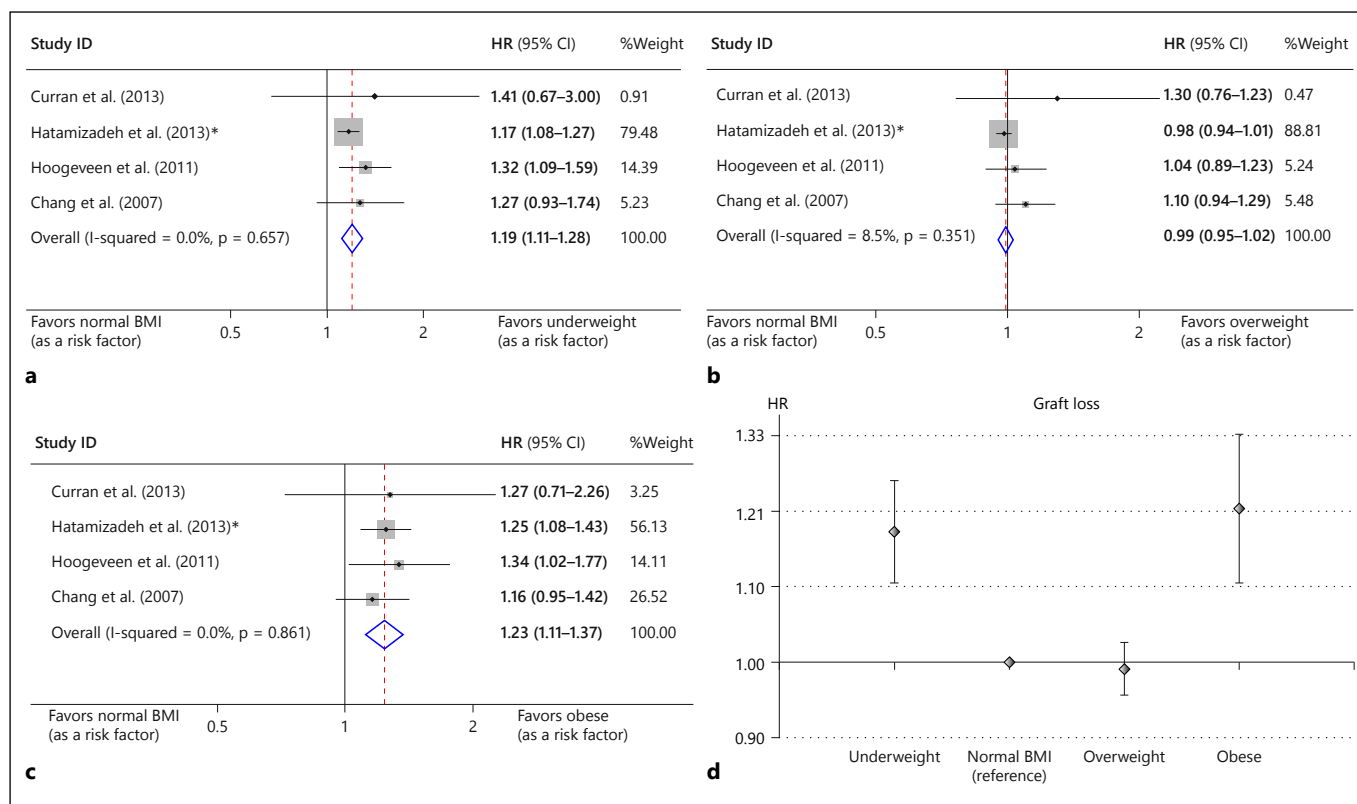
Fig. 4. Meta-analyses of hazard ratios of graft failure. **a–c** Illustrate the meta-analysis of the hazard ratios (HRs) of graft failure in 'underweight', 'overweight', and 'obese' BMI classes, respectively, compared to normal BMI. The cut-points between the 'underweight', 'normal BMI, 'overweight', and 'obese' classes were the same as those shown in figure 3. Graft failure was defined as re-initiation of dialysis or re-transplantation (patients who died before graft failure were censored). The horizontal axes are in logarithmic scale. **d** Puts the results of **a–c** together, showing the pooled hazard ratios of graft failure (in logarithmic scale). * Results are derived from re-analyzing Hatamizadeh et al. [11] data.

Trends toward an increased risk of combined mortality or graft failure were observed in the underweight (HR: 1.23, 95% CI: 0.99–1.52), overweight (HR: 1.06, 95% CI: 0.92–1.21), and obese classes (HR: 1.12, 95% CI: 0.94–1.33), compared to normal BMI class (see online suppl. appendix: Forest plots 2.A–3.C).

Risk of Reporting Bias

Egger's tests – of association between the HRs with the accuracy of HRs – detected no significant reporting bias for all-cause mortality results (p: 0.228, 0.185, 0.264, for the underweight, overweight, and obese HRs, respectively). Among the graft failure results, the Egger's test was significant for the overweight HRs (p: 0.206, 0.047, 0.780, for the underweight, overweight, and obese HRs, respectively). For the combined mortality or graft failure, Egger's test detected no reporting bias (p: 0.401, 0.338, 0.473, for the underweight, overweight, and obese HRs, respectively).

Discussion

Our results indicate that in adult KTRs, both extremes (low and high) PreT-BMI are associated with increased mortality and graft failure, and the presence of an obesity survival paradox is not observed in this population. In children, obesity seems to yield higher mortality. However, the effect of being underweight was not investigated. We did not include the HRs from continuous BMI predictors in our meta-analyses since the first-order trend cannot pick up any non-linear, for instance, J-shaped relationship between BMI and mortality. Our sensitivity analyses confirmed the results of our main meta-analyses except for the association of the overweight class with mortality and graft failure.

Many pre-transplant factors may affect post-transplant outcomes [21] including BMI [13]. Obesity is associated with an unexpected survival advantage in hemodi-

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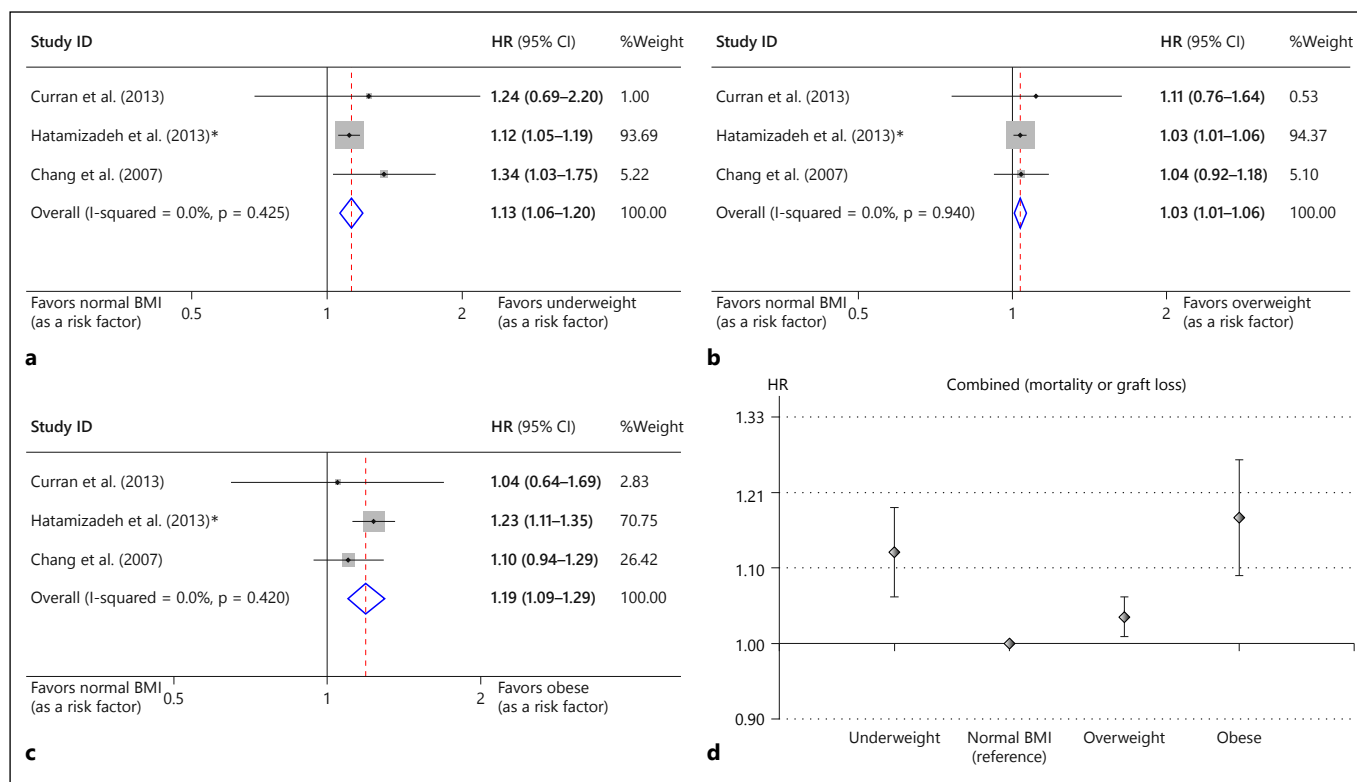
Fig. 5. Meta-analyses of hazard ratios of combined mortality or graft failure. **a–c** Illustrate the meta-analysis of the hazard ratios (HRs) of combined mortality or graft failure in 'underweight', 'overweight', and 'obese' BMI classes, respectively, compared to normal BMI. The cut-points between the 'underweight', 'normal BMI, 'overweight', and 'obese' classes were the same as those shown in figure 3. The horizontal axes are in logarithmic scale. **d** Puts the results of **a–c** together, showing the pooled hazard ratios of combined mortality or graft failure (in logarithmic scale). * Results are derived from re-analyzing Hatamizadeh et al. [11] data.

alysis patients, including those on kidney transplantation waitlists [4]. However, in KTRs, obesity shows an increased mortality risk. The paradoxical effect observed in these two populations is potentially due to contrasting long-term and short-term consequences of obesity: while obesity increases long-term cardiovascular mortality, it may attenuate short-term mortality associated with malnutrition, inflammation, and protein-energy wasting [22]. Since hemodialysis patients rarely live long enough to exhibit the long-term consequences of obesity, the short-term benefits of obesity may outweigh the long-term risks in this population. On the other hand, kidney transplantation substantially increases the longevity of these patients [23] and possibly provides sufficient time for obesity to cause its long-term adverse effects [22]. Unlike obesity, being underweight seems to be consistently associated with increased mortality with similar long-term and short-term consequences, and therefore no paradoxical or differing results are observed between the two populations of patients.

This systematic review has several strengths: we searched multiple databases using sensitive search strategies. Moreover, we only included large studies (with ≥1,000 participants) that provided higher accuracy and lower likelihood of being published selectively. Furthermore, we selected the studies and assessed their quality in duplicate. Our re-analysis of SRTR data (reported by Hatamizadeh et al. [11]) yielded highly precise results, that is, narrow CIs that gained large weights in our meta-analyses. Although these results were statistically homogeneous with the results of the other meta-analyzed studies [9, 12, 15], we performed sensitivity analyses to ascertain that assigning equal weight to the meta-analyzed studies would yield similar results. However, our study has the inherent limitations of the systematic reviews of observational studies. Although the included studies were large and robust, their results were adjusted for no more than the known confounders. In addition, we cannot rule out the possibility of bias in the pooled HRs of graft failure due to competing risks since KTRs may die from other

causes before developing graft failure. Moreover, the cut-point between the underweight and the obese classes was defined slightly differently in the meta-analyzed studies (18.5 [11, 15] vs. 20 [9, 12]). Furthermore, we had a significant Egger's test – indicating a potential reporting bias – for a set of HRs testing the association of being overweight with graft failure. However, graft failure was neither our main pre-specified outcome nor targeted in our searches. Therefore, this significant Egger's test does not imply the possibility of reporting bias in our pooled results regarding all-cause mortality (our main outcome).

In conclusion, we observed a 'back-to-normal' phenomenon [22], in which being underweight and obese at transplantation was linked to higher mortality in KTRs. However, the impact of being overweight on survival in this population is still unclear. Furthermore, our findings do not suggest that kidney transplantation candidates should be selected based on their BMIs. Kidney transplantation still improves the survival of end-stage renal disease patients substantially, including those who are obese [24]. In addition, our study does not support weight reduction in waitlisted candidates as these patients are still on dialysis and obesity has potential survival benefits in this population [4]. Rather, our findings support the need for randomized controlled trials examining the impact of weight modification on hard outcomes in waitlisted transplant candidates.

Disclosure Statement

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