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Meta-analysis of the Relation of Body Mass Index to All-Cause and Cardiovascular Mortality and Hospitalization in Patients with Chronic Heart Failure

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Abstract:

Clinical studies have indicated existence of an "obesity paradox" in patients with chronic heart failure (HF), i.e., reduced mortality among patients who have elevated body mass index (BMI) compared to normal weight reference groups. We aimed to investigate the relationship of BMI with all-cause and cardiovascular (CV) mortality and hospitalization in patients with chronic HF though a systematic review and meta-analysis of the literature. We searched Pub Med, CINAHL, Cochrane CENTRAL, Scopus, and EMBASE databases for studies reporting rate of total mortality, cardiac mortality and risk of hospitalization in patients with HF in various BMI categories [<20 (low); 20-24.9 (normal reference); 25-29.9 (overweight); 30-34.9 (obese); >=35 (severely obese)]. Event rates were compared using a forest plot of relative risk using a random effects model assuming inter-study heterogeneity. Two study authors [AS, AV] independently reviewed the 124 articles and identified 6 for final analyses (N=22807). After mean follow up period of 2.85 years, the risk for adverse events was highest among patients with low BMI: Total mortality RR 1.27 [95% CI 1.17 – 1.37]; CV mortality1.20 [95% CI 1.01 -1.43]; and hospitalization 1.19 [95% CI 1.09 – 1.30]. Risk of CV mortality and hospitalization was lowest in overweight patients (RR0.79 [95% CI 0.70-0.90] and 0.92 [95% CI 0.86-0.97] respectively). Increasing degree of obesity failed to achieve a statistically significant effect on CV mortality (0.82 [0.64-1.05] and 0.71 [0.50-1.01] for obese and severely obese, respectively) and on hospitalization (0.99 [0.92-1.07] and 1.28 [0.88-1.87] for obese and severely obese, respectively). In conclusion, risk of total mortality and CV mortality and hospitalization was highest among chronic HF patients who were underweight as defined by low BMI, whereas risk of CV mortality and hospitalization was lowest in the overweight.

Key words: Body mass index, heart failure

Introduction:

The association between BMI and all- cause and CV mortality and hospitalizations in HF is not fully understood. Due to contradictory results in various studies and lack of definitive data on prognostic value of BMI and its purposeful alteration in HF, the American College of Cardiology Foundation/American Heart Association do not provide any firm recommendations for purposeful weight loss in HF [1]. In the present study, the available evidence is systematically reviewed to examine the association between the most commonly used anthropometric measure of the degree of adiposity, namely the body BMI, with all- cause mortality and CV mortality and hospitalizations among patients with chronic HF.

METHODS

Meta-analysis was performed in accordance with the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines [2]. A checklist of each of the MOOSE criteria and how they were handled in our study is contained in Appendix Table 1.

We systematically searched PubMed, CINAHL, Cochrane CENTRAL, Scopus and Web of Science databases for all studies that reported total mortality, cardiac mortality and rate of hospitalization on the basis of BMI. All relevant combinations of the following keywords related to body mass (for example, BMI, body weight, obesity, overweight, central obesity), total mortality, CV events (for example, cardiac death, CV death, mortality), hospitalization, readmission and presence of HF (systolic HF, diastolic HF, cardiomyopathy, cardiac failure) were included for database search. The search was conducted from the inception of these databases to May 31, 2014. No language or age restrictions were applied.

Clinical studies were included if the studies met the following criteria: (i) inclusion of patients with chronic HF, (ii) reported measures of total mortality, CV mortality and/or rate of hospitalization secondary to congestive HF exacerbation according to BMI.

We could not use the standard categorization of BMI groups because of the inconsistency of across studies. Thus, we arbitrarily assigned the low BMI group when BMI was the lowest and below 20, normal BMI if it was identical or close to 20–24·9, overweight if the BMI group was identical or close to 25–29·9, obesity if it was close or identical to 30–34·9, and severe obesity if BMI was 35 or greater.

Two independent reviewers (AS, AV) screened the titles and abstracts for relevance. Discrepancies between reviewers were discussed until consensus was reached. The manuscripts of selected titles/abstracts were reviewed for inclusion. Using the above selection criteria, two reviewers (AS, AV) independently determined the articles to be included or excluded. Data from the relevant articles were extracted using pre-defined extraction forms. Two independent reviewers (AS, AV) performed the data extraction. Any disagreements in data extraction were discussed until consensus was reached. Events for studies which reported outcome separately for patients with BMI >35 kg/m^2 and > 40 kg/m^2 were combined and reported as severely obese (> 35 kg/m^2).

Mix 2.0 Pro (Biostat XL) software was used to analyze the data. A random-effects model with inverse variance weighting was used to calculate pooled relative risks (and 95% CI). We assessed the three outcomes: total mortality, CV mortality and rate of hospitalization. Heterogeneity between studies was assessed using Cochrane's Q test and I^2 statistic, which denotes the percentage of total variation across studies that is a result of heterogeneity rather than

chance. Heterogeneity was considered significant if the p value was less than 0.05. Publication bias was assessed by Begg's test and Egger's regression test. The influence of individual studies was examined by removing each study sequentially to assess the degree to which the meta-analysis estimate depends on a particular study (exclusion sensitivity analysis).

RESULTS

Six studies met inclusion/exclusion criteria (N=22,807) (Figure 1) [3-8]. Follow-up duration was from 1.5 years to 4.1years. Details of the studies are summarized in Table 1. Obese patients were younger than normal and low BMI patients on average by 4 and 7 years, respectively (Table 2).

The low BMI group had the greatest risk for total mortality, with a relative risk (RR) of 1.27 (95% confidence interval [CI] 1.17 – 1.37), while overweight, obese and severely obese groups had lower relative risks of 0.78 [0.68-0.89], 0.79 [0.65-0.97], and 0.75 [0.57-0.98], respectively (Figures 2, 3 and Table 3). Heterogeneity analysis was significant across overweight ($p=0.003$, $I^2=72\%$), obese ($p<0.001$, $I^2=81\%$) and severely obese ($p=0.04$, $I^2=77\%$) groups. There was no heterogeneity across the low BMI group ($p=0.54$, $I^2=0\%$).

The low BMI group had the greatest risk for CV mortality (RR = 1.20 [1.01 -1.43]), while overweight had decreased risk compared with normal (0.79 [0.70-0.90]), and did not differ significantly from obese and severely obese groups (0.82 [0.64-1.05] and 0.71 [0.50-1.01], respectively [Figures 3, 4 and Table 3]). Heterogeneity analysis was significant across overweight ($p=0.03$, $I^2=60\%$), obese ($p<0.001$, $I^2=82\%$) and severely obese ($p=0.04$, $I^2=77\%$) groups. There was no heterogeneity across the low BMI group ($p=0.57$, $I^2=0\%$).

The risk for hospitalization secondary to HF exacerbation was highest in the low BMI group (1.19 [1.09 – 1.30]) and lowest in overweight group (0.92 [0.86-0.97]). The obese (0.99 [0.92-1.07]) and severely obese group (1.28 [0.88-1.87]) did not have significantly different risk (Figures 3, 5 and Table 3). There was no significant heterogeneity among the low BMI (p=0.31, I^2 =17%), overweight (p=0.31, I^2 =17%) and obese groups (p=0.59, I^2 =0%),but significant heterogeneity was present across the studies in the severely obese group (p =0.005, I^2 =87%).

DISCUSSION

Our results indicate that in patients with chronic HF, the risk of all-cause and CV mortality and hospitalization was highest among those with low BMI at the end of a mean follow up period of 2.85 years and lowest in the overweight BMI group. This finding is counterintuitive and supports the presumption of a strong "obesity (or 'overweight') paradox" (Figure 4).

Our results also show that, unlike less severe degrees of obesity, which seem to be associated with an obesity paradox, severe obesity is associated with quite poor overall CV outcomes, suggesting that the apparent protective effect of adiposity tends to disappear at more extreme levels of obesity. This finding is consistent with previous studies; conceivably, it could be due to deleterious effect of extreme obesity on central and peripheral hemodynamics, as well as on cardiac structure and function [9, 10, 11]. Nonetheless, Oreopoulos et al reported lower all-cause mortality and CV mortality among HF patients who were overweight compared to normal weight patients [10]. However, to our knowledge, our study is the first meta-analysis to comprehensively evaluate the association between BMI, the most commonly used anthropometric parameter to assess the degree of adiposity, with all- cause and CV mortality and risk of hospitalization among patients with chronic HF. Our results demonstrate that increased

total mortality among underweight patients can be explained by the increased rates of CV mortality, as opposed to mortality from non-CV causes, including cancer. Recently, Shah et al confirmed existence of a global obesity paradox in patients with acutely decompensated HF, reporting lower 1-year mortality among patients with acute decompensated HF who have higher BMI despite heterogeneity in biochemical and clinical profiles, thus demonstrating that a lower BMI effectively defines risk of long-term mortality independently of other clinical and of biochemical indices [12].

Several hypotheses have been proposed to explain obesity paradox in chronic HF [9, 13]. Clearly, HF is a catabolic state and cardiac cachexia is an independent predictor of CV mortality in patients with advanced HF [14]. Patients with higher BMI also have high- energy reserve (higher body fat and lean mass), which help them to deal effectively with the high-energy requirement of HF. Alternatively, low BMI may be a marker of the severity of HF which, by itself, is the basis of outcome.

Cytokines and neuroendocrine profiles of chronic HF patients who are overweight/obese differ from those who are underweight and might play a modulating role [15-20]. Soluble tumor necrosis factor-alpha (TNFα) receptor level has been shown to be correlated significantly with both BMI and percentage body fat, which could exert a protective role by neutralizing the circulating TNF in overweight/obese patients [15, 20]. Chronic HF patients in edematous states have higher circulating levels of bacterial lipopolysaccharide (LPS) [21], which acts as a very strong immune activator due to its ability to release of pro inflammatory cytokines from circulating immune competent cells [17, 21]. Higher levels of circulating lipoproteins found in overweight/obese HF patients may bind and then detoxify lipopolysaccharides and have a potential anti-inflammatory effect [15, 14, 21].

In our study obese patients were younger than normal patients and than low BMI patients, on average by 4 and 7 years, respectively. This could be due to early onset of HF among obese patients secondary to high prevalence of CAD, CV risk factors and metabolic derangement secondary to obesity [9, 10, 13, 16]. In addition, HF patients with higher BMI typically have higher arterial blood pressure than their leaner counterparts, which allow them to tolerate more cardio-protective medications, potentially at higher doses, including beta blockers, renin angiotensin aldosterone system (RAAS) inhibitors, and mineralocorticoid receptor antagonists [9, 16]. Obese patients also have demonstrated an attenuated response to the RAAS, which may lead to a better HF prognosis [9, 16].

Parameters of central obesity, like waist circumference and waist-to –hip ratio, are more closely associated with progression of atherosclerosis and adverse CVD events as compared with BMI [22-24]. This could be due to failure of BMI as an anthropometric parameter to adequately assess distribution and degree of adiposity; also, BMI cannot differentiate between adipose tissue and lean body mass [25, 26]. Low BMI not only reflects low adiposity but also potentially lower body lean mass, which has been associated with poor cardiorespiratory fitness and muscular fitness, -both of which predict poor clinical outcomes [13, 27-29].

Our study, however, also has several potential limitations. First, the prevalence of various associated comorbidities, including detailed data on various CV risk factors and duration and severity of HF and etiology of HF among various categories of BMI, was not reported, and, hence, could not be analyzed in the present meta- analysis. Thus, it remains unclear whether our findings can be attributed to more advanced disease in patients with low BMI. Studies included in our analysis have not taken into consideration any unintentional weight loss among patients; therefore, we cannot rule out the possibility of residual confounding effects in our study. Further,

our study did not evaluate the impact of targeted weight reduction in various BMI categories, thus it is not clear if targeted weight loss in morbidly obese patient of weight gain in underweight patients is beneficial or not. These issues need to be addressed in randomized control trial before making any specific recommendations. Second, higher levels of physical activities has been shown to improve cardiovascular risk profile and poor cardiorespiratory fitness is a strongly associated with adverse clinical outcomes in chronic HF patients [30, 31]. However, as studies included in our meta-analysis did not report the data on physical activities on patients or its impact on clinical outcome, we were unable to assess this important question in our present study. Third, not all studies included in our analysis classified their patients using the standard BMI categories. In addition, parameters of central adiposity, estimation of body fat and lean body mass (or non-fat mass) were not provided in the studies included in our analysis, precluding assessment of the relationship between these important body composition parameters with various end points. Fourth, average follow up in our study was 2.85 years, which might not be long enough to evaluate the negative impact of obesity on various clinical end points.

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FIGURE LEGENDS:

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow sheet

Figure 2. Forest plot of total mortality for all studies

Figure 3. Total mortality, cardiac mortality and hospitalization in all studies

Figure 4. Forest plot of CV mortality for all studies

Figure 5. Forest plot of hospitalization in all studies

Table 1. Baseline characteristics of studies

Author	Sample Size	Mean Age (years)	Male	Follow up (years)	NYHA Class	Study population	Post hoc analysis
Kenchaiah et al	7599	66	68%	3	II-IV	CHARM[a]	+
Lavie et al	206	54	81%	1.5	I-III	Single center study	*
Curtis et al	7767	64	75%	3	I-IV	DIG[b]	+
Hamaguchi et al	2488	70	60%	2.1	I-IV	JCARE-CARD[c]	+
Nochioka et al	972	68	65%	3.4	I-IV	CHART[d]	+
Haass et al	4109	72	n/a	4.1	II-IV	I-PRESERVE[e]	+

*: single center study; a: Candesartan in Heart failure - Assessment of mortality and morbidity (CHARM); b: Digitalis Investigation Group (DIG) trial; c: Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD);d: Japanese HF patients in the Chronic Heart Failure Analysis and Registry in the Tohoku District (CHART) study; e: Irbesartan in HF and PRESERVed Ejection fraction (I-PRESERVE)

Table 2. Mean age of patients in various BMI categories

BMI group	Mean age (in years)
<20	70.6
20–24·9	67.7
25-29.9	66.2
30-34.9	63.1
≥35	64.3

BMI: Body Mass Index

BMI	<20	20-24.9	25-29.9	30-34.9	≥35
Total mortality	1.27 [1.17 – 1.37]	1	0.78 [0.68-0.89]	0.79 [0.65-0.97]	0.75 [0.57-0.98]
CV mortality	1.20 [1.01 - 1.43]	1	0.79 [0.70-0.90]	0.82 [0.64-1.05	0.71 [0.50-1.01]
Hospitalization	1.19 [1.09 – 1.30]	1	0.92 [0.86-0.97]	0.99 [0.92-1.07]	1.28 [0.88-1.87]

BMI: Body Mass Index

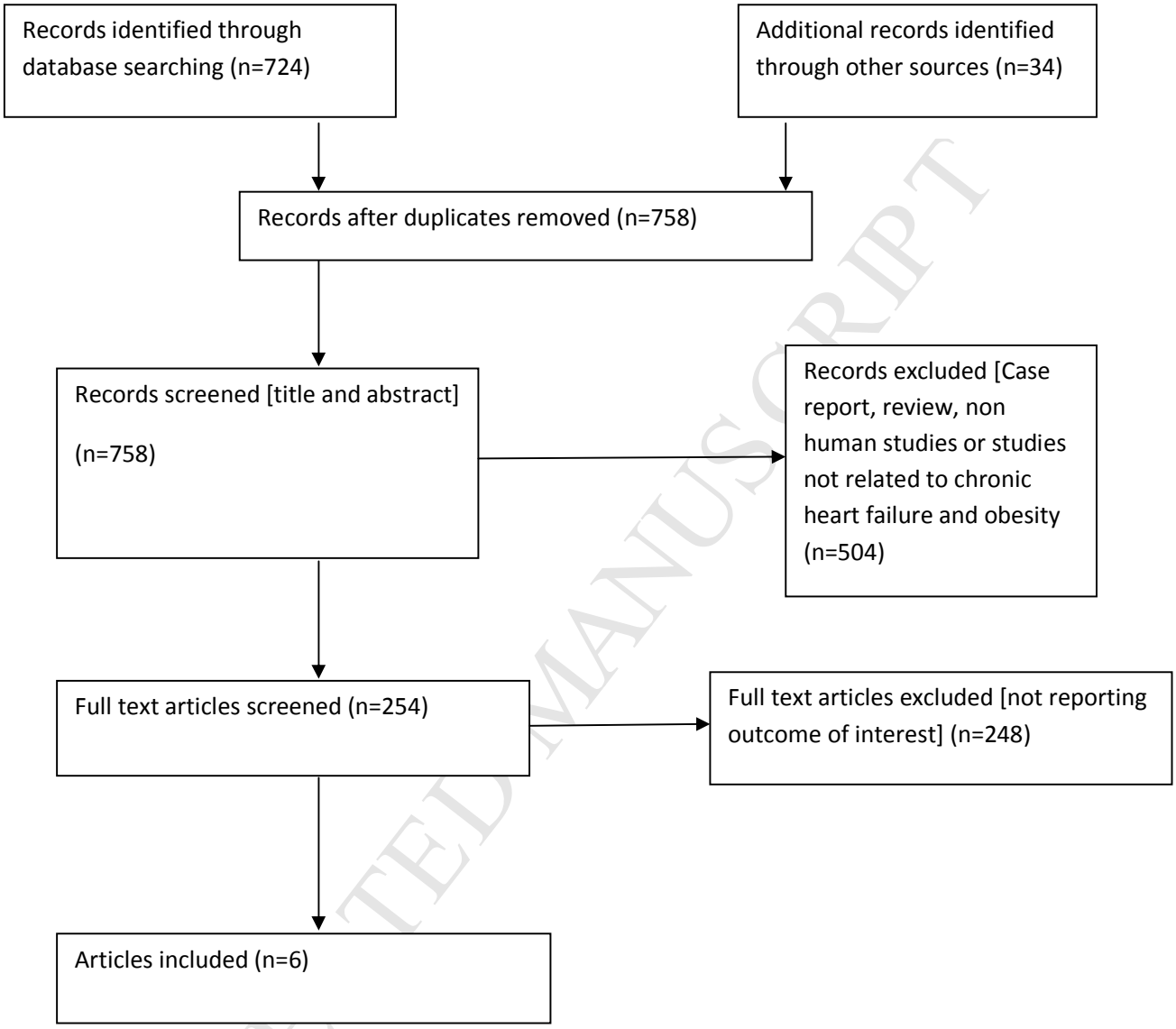
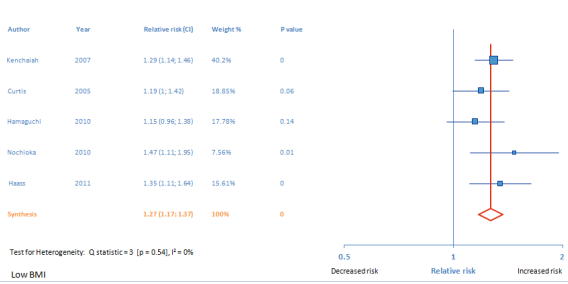


Figure 1. PRISMA Flowsheet



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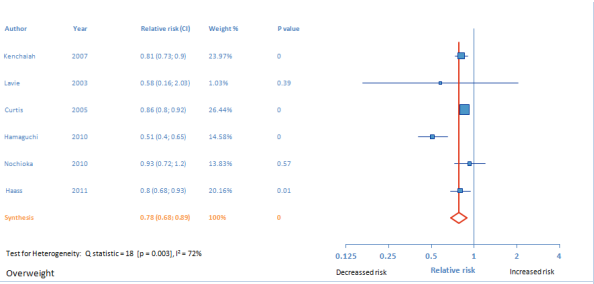
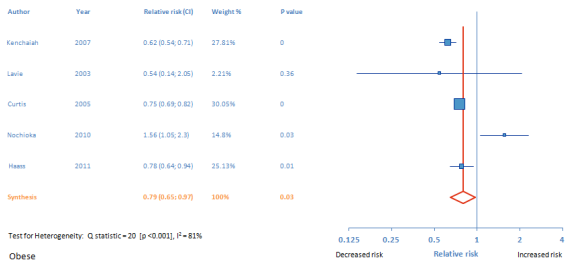
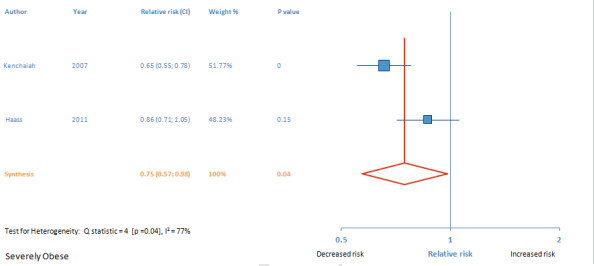


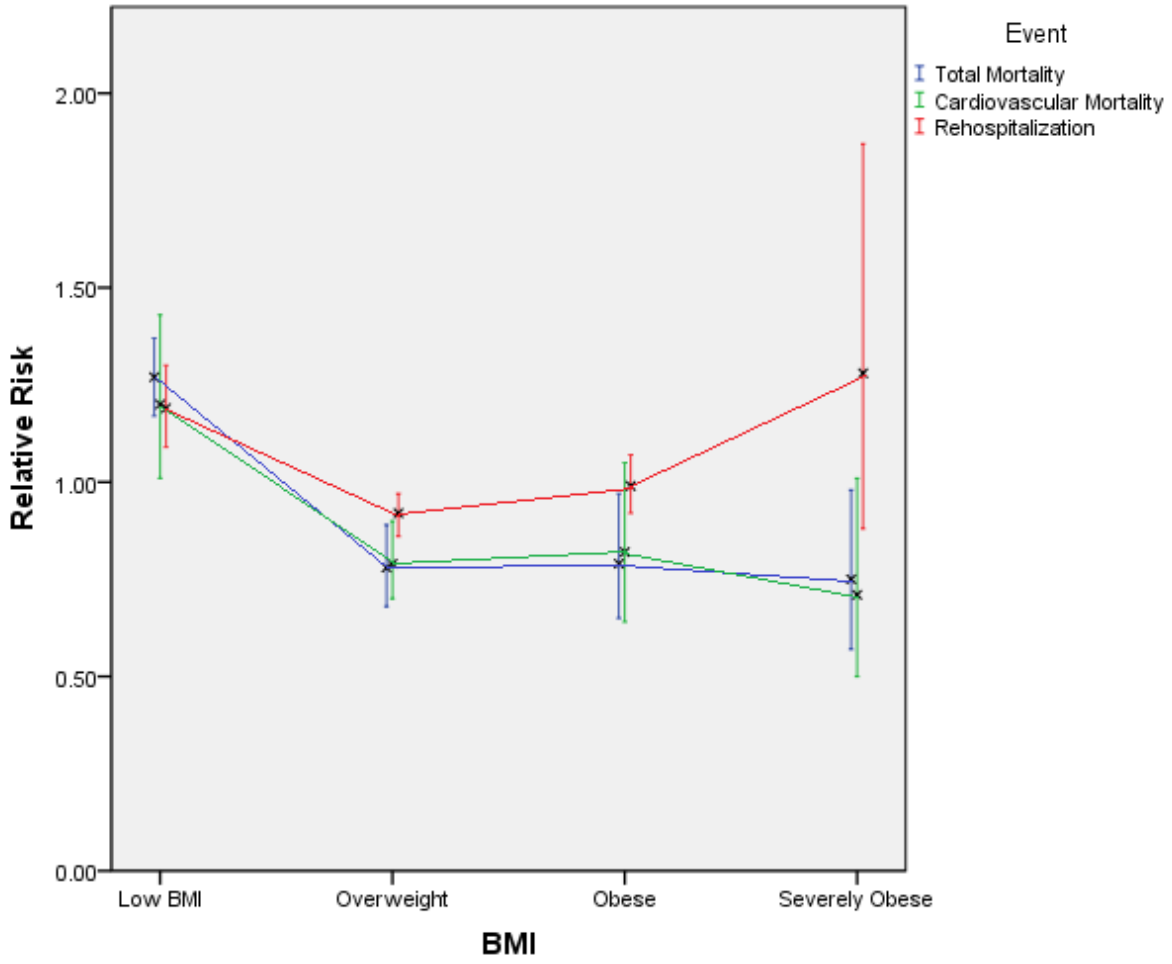
Overweight

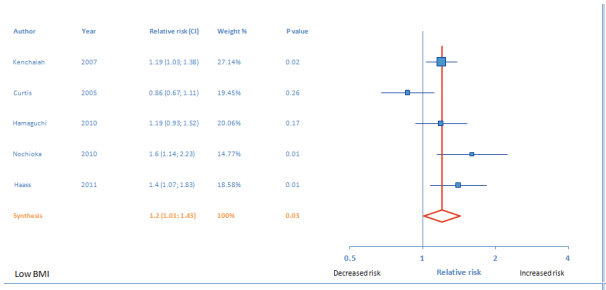


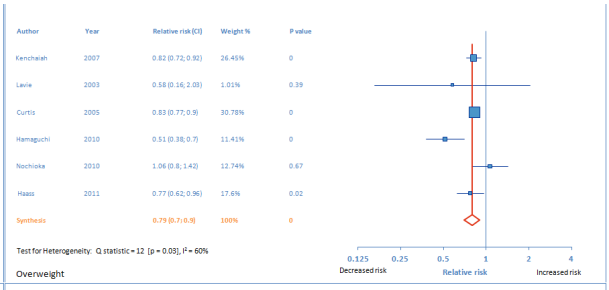
Obese

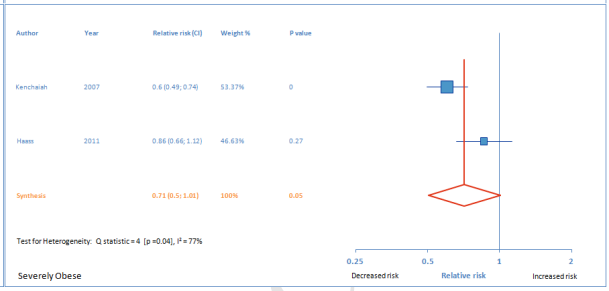


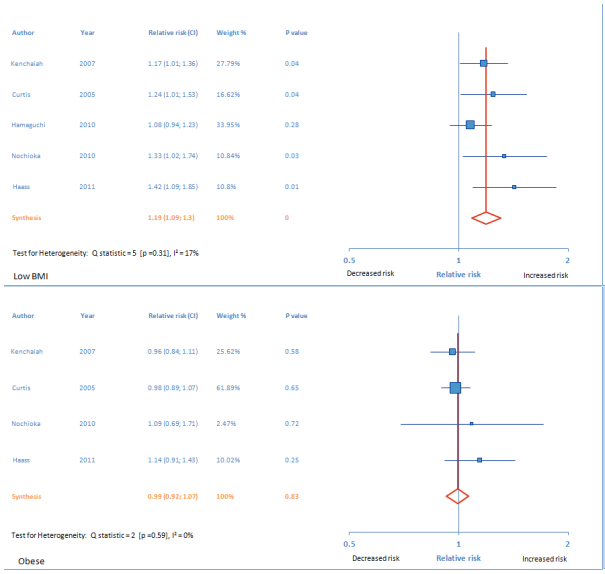
Severely Obese



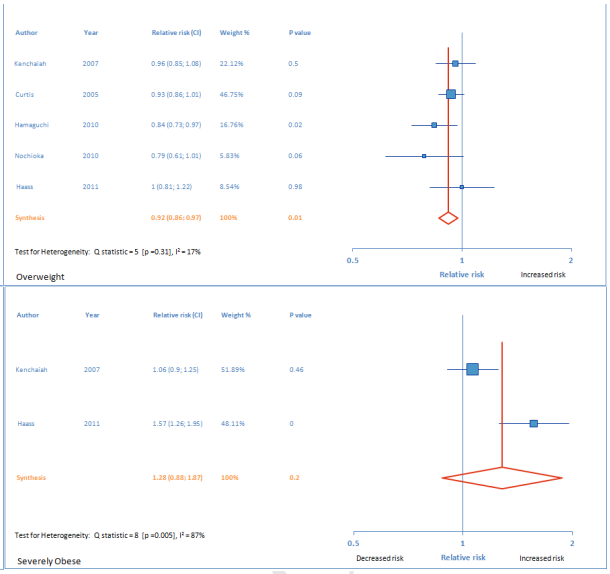








Low BMI



Overweight

Obese

Severely Obese

MOOSE (Meta-analysis Of Observational Studies in Epidemiology) Checklist

Title: Relationship of body mass index (BMI) with total mortality, cardiac mortality and risk of hospitalization in patients with chronic heart failure

Abhishek Sharma, MD; Carl J. Lavie, MD; Jeffrey S. Borer, MD; Ajay Vallakati, MD; Sunny Goel, MD; Francisco Lopez-Jimenez, MD, MSc; Armin Arbab-Zadeh, MD, Ph.D; Debabrata Mukherjee, MD, MS; Jason Lazar, MD, MPH

Criteria		**Brief description of how the criteria were handled in the meta-analysis**
Reporting of background should include		
√	Problem definition	Clinical studies have indicated existence of an obesity paradox in patients with chronic heart failure (HF) i.e. reduced mortality among patients who have elevated body mass index (BMI) compared to normal weight reference groups. We aim to investigate the relationship of body mass index (BMI) with total mortality, cardiac mortality and risk of hospitalization in patients with chronic HF.
√	Hypothesis statement	Lower BMI is associated with worse clinical outcome in patients with chronic HF.
√	Description of study outcomes	Total mortality, cardiac mortality and risk of hospitalization
√	Type of study designs used	We include various retrospective and prospective comparative studies reporting total mortality, cardiac mortality and the risk of hospitalization among various BMI categories in patients with chronic HF.
√	Study population	We placed no restriction.
Reporting of search strategy should include		
√	Qualifications of searchers	The credentials of the two investigators AS and AV are indicated in the author list.

√	Search strategy, including time period included in the synthesis and keywords	PubMed (1965 – May 31, 2014) EMBASE (1974 – May 31, 2014) CINAHL (1982- May 31, 2014) Web of Science (1965- May 31, 2014) Cochrane Collaboration Central Register of Controlled Trials (- May 31, 2014)
√	Databases and registries searched	PubMed; EMBASE; CINAHL; Web of Science; Cochrane CENTRAL
√	Search software used, name and version, including special features	We did not employ a search software
√	Use of hand searching	We hand-searched bibliographies of retrieved papers for additional references
√	List of citations located and those excluded, including justifications	Details of the literature search process are outlined in the flow chart
√	Method of addressing articles published in languages other than English	No language restriction was applied while searching various databases. Google translation was used to article published in language other than English.
√	Method of handling abstracts and unpublished studies	We contacted few authors for unpublished studies.
√	Description of any contact with authors	We contacted few authors who have reported few but not all outcome of interest.
Reporting of methods should include		
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria were described in the methods section.
√	Rationale for the selection and coding of data	Data extracted from each of the studies were relevant to the population characteristics, study design, and outcomes.
√	Assessment of confounding	Methods section. The influence of individual studies was examined by removing each study at a time to assess the

		degree to which meta-analysis estimate depends on a particular study (exclusion sensitivity analysis). Publication bias was assessed by Begg's test and Egger's regression test. A random-effects model with inverse variance weighting was used to calculate the pooled correlation co-efficient and the corresponding confidence interval.
√	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Described in the methods section.
√	Assessment of heterogeneity	Heterogeneity of the studies were explored within two types of study designs using Cochrane's Q test of heterogeneity and I^2 statistic that provides the relative amount of variance of the summary effect due to the between-study heterogeneity.
√	Description of statistical methods in sufficient detail to be replicated	Description of methods of meta-analyses, sensitivity analyses, and assessment of publication bias are detailed in the methods section.
√	Provision of appropriate tables and graphics	Figures 1-5. Tables 1-3.
Reporting of results should include		
√	Graph summarizing individual study estimates and overall estimate	Figures 2-5.
√	Table giving descriptive information for each study included	Table 1.
√	Results of sensitivity testing	Results. The influence of individual studies was examined by removing each study at a time to assess the degree to which meta-analysis estimate depends on a particular study (exclusion sensitivity analysis).
√	Indication of statistical uncertainty of findings	95% confidence intervals were presented with all summary estimates, I^2 values and results of sensitivity analyses
Reporting of discussion should include		
√	Quantitative assessment of bias	Sensitivity analyses indicate heterogeneity in strengths of

		association due to most common biases in observational studies.
√	Justification for exclusion	We excluded studies that had not reported total mortality, cardiac mortality and the risk of hospitalization among various BMI categories in patients with chronic HF.
√	Assessment of quality of included studies	We discussed the results of the sensitivity and heterogeneity analyses
Reporting of conclusions should include		
√	Consideration of alternative explanations for observed results	We discussed the potential failure of BMI as an anthropometric parameter to adequately assess degree and distribution of adiposity. We also discussed other potential biases including the potential unmeasured confounders that may have caused residual confounding.
√	Generalization of the conclusions	Risk of total mortality, cardiac mortality and hospitalization was highest among chronic heart failure patients who were underweight patients as defined by low BMI
√	Guidelines for future research	We recommend future studies to - Investigate this association and explore potential underlying mechanisms - Investigate other anthropometric parameters like waist to hip ratio, waist circumference to assess degree of adiposity and assessing prognosis in HF patients.
√	Disclosure of funding source	None