Body mass index and mortality in patients with cardiovascular disease: an umbrella review of meta-analyses


1Urology Institute, University Hospital System, Case Western Reserve University School of Medicine, Cleveland, OH, USA
2Department of Global Health and Population, Harvard T.H. Chan School of Public Health, Boston, MA, USA
3Yonsei University College of Medicine, Seoul, Republic of Korea
4Department of Nephrology, Yonsei University Wonju College of Medicine, Wonju, Republic of Korea
5Department of Pediatrics, Yonsei University College of Medicine, Seoul, Republic of Korea
6College of Medicine, Gyeongsang National University, Jinju, Republic of Korea
7Department of Internal Medicine IV [Nephrology and Hypertension], Medical University Innsbruck, Innsbruck, Austria
8Parc Sanitari Sant Joan de Déu/CIBERSAM, Universitat de Barcelona, Fundació Sant Joan de Déu, Sant Boi de Llobregat, Barcelona, Spain
9ICREA, Pg. Lluís Companys 23, Barcelona, Spain
10Faculty of Medicine, University of Versailles Saint-Quentin-en-Yvelines, Montigny-le-Bretonneux, France
11School of Social Work, University of Southern California, Los Angeles, CA, USA
12University of Florida College of Medicine, Gainesville, FL, USA
13Department of Ophthalmology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
14Korea University College of Medicine, Seoul, Republic of Korea
15Department of Data Science, Sejong University College of Software Convergence, Seoul, Republic of Korea
16Department of Pediatrics, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea
17The Cambridge Centre for Sport and Exercise Sciences, Anglia Ruskin University, Cambridge, UK

Ramy Abou Ghayda, David Duck-Young Park, Jun Young Lee, Jong Yeob Kim and Keum Hwa Lee contributed equally to this work

Abstract. – OBJECTIVE: Although many previous meta-analyses of epidemiological studies have demonstrated a relationship between body mass index (BMI) and mortality, inconsistent findings among cardiovascular disease patients have been observed. Thus, we performed an umbrella review to understand the strength of evidence and validity of claimed associations between BMI and mortality in patients with cardiovascular diseases.

MATERIALS AND METHODS: We comprehensively re-analyzed the data of meta-analyses of observational studies and randomized controlled trials on associations between BMI and mortality among patients with cardiovascular diseases. We also assessed the strength of evidence of the re-analyzed outcomes, which were determined from the criteria including statistical significance of the p-value of random-effects, as well as fixed-effects meta-analyses, small-study effects, between-study heterogeneity, and a 95% prediction interval.

RESULTS: We ran comprehensive re-analysis of the data from the 21 selected studies, which contained a total of 108 meta-analyses; 23 were graded as convincing evidence and 12 were suggestive, 42 were weak, and 23 were non-significant.

CONCLUSIONS: Underweight increased mortality in acute coronary syndrome (ACS), heart
failure, and after therapeutic intervention for patients with cardiovascular diseases. Overweight, on the other hand decreased mortality in patient’s ACS, atrial fibrillation, and heart failure with convincing evidence.

Key Words: BMI, Cardiovascular disease, Meta-analysis, Mortality, Obesity, Umbrella review.

Introduction

Global prevalence of overweight and obesity in adults has risen by 27.5% between 1980 and 2013. Body mass index (BMI) is widely used as a clinical tool to assess the grade of adiposity and can be easily calculated from the ratio of body weight in kilograms divided by height in meters squared (kg/m²). According to the definition of the National Institutes of Health (NIH) and World Health Organization (WHO), BMI can be categorized as follows: underweight (<18.5 kg/m²), normal (18.5-24.9 kg/m²), overweight (25-29.9 kg/m²), and obesity (≥30 kg/m²). Obesity further can be classified into 3 classes of severity: class I obesity (30-34.9 kg/m²), class II obesity (35-39.9 kg/m²) and class III obesity (≥40.0 kg/m²).

It is well recognized that obesity is associated with all-cause mortality [hazard ratio (HR) 1.18, (95% confidence interval (CI), 1.12 to 1.25] in the general population. Many epidemiological studies and their meta-analyses on the associations between BMI and mortality in patients with cardiovascular disease (CVD) were published recently. However, the results have been inconsistent and “obesity paradox” related results are reported among meta-analyses and, therefore, the current evidence is insufficient and controversial to confidently define the relationship between BMI and mortality in patients with various CVDs, including those with acute coronary syndromes (ACS), those with most ACS patients survive, or those with atrial fibrillation (AF). Additionally, we explored the same relationship following multiple CVD therapy modalities, such as coronary artery bypass graft surgery (CABG), and post percutaneous coronary interventions (PCI). Finally, we explored the correlation between BMI and mortality among patients with heart failure (HF).

Different types of biases in literature can contribute to inconsistent associations between BMI and mortality among patients with CVDs in different studies. Therefore, it is necessary to estimate a more accurate association by integrating the various statistical parameters. Recently, many researchers apply the umbrella review concept, which re-evaluates the results of previously published systematic reviews and meta-analyses and determines the strength of evidence across multiple associations to help clinicians and patients make informed clinical decisions. The aim of this study was to provide an overview of the strength of evidence by assessing the extent of potential biases and the validity of the claimed associations.

Materials and Methods

We performed an umbrella review of meta-analyses and systematic reviews on the associations between BMI and mortality in patients with CVDs. This umbrella review and meta-analysis was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. The PRISMA checklist is shown in Supplementary Table I.

Literature Search Strategy

The search was conducted by three authors (DDP, JIS, and RAG). We systematically searched PubMed from inception to June 1st, 2018 to identify meta-analyses examining associations between BMI and mortality in patients with CVDs. The keywords used for the search were ‘(body mass index OR BMI) AND (mortality OR death) AND (meta OR meta-analysis) AND (cardiovascular diseases OR CVD)’. We screened articles by titles, abstracts, and full texts to identify eligible meta-analyses.

Eligibility and Inclusion/Exclusion Criteria

Studies were included in our analysis if they (1) were systematic reviews of either prospective or retrospective observational study designs, (2) investigated the association between BMI and mortality in patients with CVDs (3) defined patients’ overweight, underweight, and obesity status using BMI, (4) conducted meta-analysis, and (5) reported individual study estimates and their 95% CIs. Studies were excluded if they (1) did not conduct meta-analysis, (2) were not about BMI and mortality in CVD patients, (3) analyzed mortality in infants, general populations, or patients with cancers, and (4) did not include individual study data available for re-analysis. The detailed process of this screening is shown in Figure 1.
Extraction of Data

We extracted the following data from the obtained eligible articles: the name of first author, published year, study design, BMI categories, type of patients, outcome measures, the number of deaths, the total number of population, type of metrics [HR, or odds ratio (OR) or risk ratio (RR)], the effect sizes and 95% CI of individual studies in each meta-analysis, and random effects summary estimate reported in the meta-analysis.

Statistical Analysis

We performed re-analysis of each meta-analysis using individual study estimates extracted from each meta-analysis. We obtained the summary estimate of both random-effects and fixed-effects and obtained \( p \)-values\(^{12} \). Statistical significance was claimed at 0.05. Heterogeneity across the individual studies was assessed using a metric of inconsistency and the \( p \)-value of the \(-\) based Cochrane Q test. Values of <25%, 25%-50%, 50-75% and >75% were judged to be low, moderate, large, and very large heterogeneity, respectively\(^{13} \). In addition, we assessed whether there existed small study effects by using the Egger’s test of asymmetry (one-tailed Egger \( p \)-value <0.05 indicates presence of small-study effect)\(^{14,15} \). We also estimated the 95% prediction interval (PI). While random-effects summary estimate addresses the mean of the effects of the individual studies, the PI estimates the interval in which the true effect of a new future study will fall within, thereby further accounting for between-study heterogeneity\(^{16} \). All statistical analyses were performed using ‘Comprehensive meta-analysis version 3.3.070’ software (Borestein, NH, USA).

Determining the Level of Evidence: Convincing, Suggestive, Weak, and Non-Significant

We, then, graded the level of evidence of each result of the meta-analysis based on a scheme applied in previously published umbrella reviews\(^8,9 \). The criteria were as follows:

Convincing evidence: (1) both fixed-effects and random-effects \( p \)-values <0.001, (2) low or moderate heterogeneity \( (I^2 < 50) \), (3) 95% PI excluding the null hypothesis, (4) no evidence of small-study effect and (5) random summary estimate and the effect of the largest study having concordance in terms of statistical significance.

Suggestive evidence: (1) both fixed-effects and random-effects \( p \)-values <0.005, (2) low or moderate heterogeneity \( (I^2 < 50) \), (3) no evidence of small-study effect, (4) random summary estimate and the effect of the largest study having concordance in terms of statistical significance, and does not meet criteria for convincing evidence.
Weak evidence: both fixed-effects and random-effects p-values <0.05 and does not meet criteria for suggestive evidence.

Non-significance: fixed-effects or random-effects p-value>0.05.

If a meta-analysis included only two individual studies, assessment of small-study effects and 95% PIs was not possible. Therefore, it was at best graded as weak level of evidence.

Among the individual studies that were classified as having weak evidence due to high heterogeneity (I²>50%), we further evaluated whether such high heterogeneity was caused by the differences in the direction of individual effects. When the number of statistically significant individual studies was the same or greater than the number of individual studies which were not statistically significant or statistically significant in the opposite direction, we speculated that the high heterogeneity in this case was caused by the differences in the magnitude of the effects rather than the differences in the direction of individual effects. Therefore, in these cases, we upgraded the level of evidence to suggestive or convincing when the criteria other than heterogeneity were satisfied.

Results

Study Characteristics

Using the pre-specified inclusion and exclusion criteria, 21 eligible articles corresponding to 108 meta-analyses were finally included in our review (Figure 1)5,6,17-35. The 108 meta-analyses studied 10 CVD sub-categories. We classified the meta-analyses into eight cohorts according to CVDs classification as follows: (1) ACS/post myocardial infarction (MI)/after ACS; (2) Post-coronary angiography (CAG); (3) Post-PCI; (4) Chronic HF; (5) HF; (6) AF; (7) following left ventricular assist device (LVAD) implantation; (8) after cardiac surgery; and (9) after transcatheter aortic valve implantation (TAVI). All the comparisons are summarized in Tables I-III. Twenty-three were graded as convincing evidence, while 12 were suggestive, 42 were weak, and 23 were non-significant. The remaining levels of evidence could not be assessed and were referred to as not available (N/A).

Acute Coronary Syndrome (ACS)

Three articles studied the association between BMI and mortality in patients with ACS (Table I-III).
I. These studies investigated the association between BMI and mortality in terms of all-cause mortality and in-patient mortality. In several studies, mortality was classified into short-term (<30 days) and long-term (1-2 years or >3 years) according to the duration of follow-up. One study, which included 9 cohort studies, compared overweight and normal BMI patients, and the meta-analysis demonstrated positive associations for mortality regardless of the duration of follow-up or type of mortality (Table I). The evidence, however, was considered weak. Three studies reported a total of 103 cohorts and 36 observational studies for overweight patients and patients with severe obesity and mortality among patients with ACS, acute MI, and those patients with cardiovascular disease.

### Table 1 (Continued)

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>No T</th>
<th>TP</th>
<th>Cohort/Study</th>
<th>Outcome</th>
<th>Death (n)</th>
<th>BMI (kg/m²)</th>
<th>Random effect (random)</th>
<th>F (p)</th>
<th>E P-value (random)</th>
<th>V (p) value (fixed)</th>
<th>5% PI (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post PCI</td>
<td>12</td>
<td>C</td>
<td>CV M</td>
<td>N/A</td>
<td>2786115</td>
<td>RR</td>
<td>1.64 (0.59 to 5.04)</td>
<td>0.83</td>
<td>0.0139</td>
<td>0.031</td>
<td>0.031</td>
</tr>
<tr>
<td>Post PCI</td>
<td>12</td>
<td>C</td>
<td>CV M</td>
<td>N/A</td>
<td>2813316</td>
<td>RR</td>
<td>1.83 (0.43 to 7.72)</td>
<td>0.81</td>
<td>0.0135</td>
<td>0.031</td>
<td>0.031</td>
</tr>
<tr>
<td>Post PCI</td>
<td>12</td>
<td>C</td>
<td>CV M</td>
<td>N/A</td>
<td>3456240</td>
<td>RR</td>
<td>1.84 (0.77 to 5.21)</td>
<td>0.87</td>
<td>0.0076</td>
<td>0.031</td>
<td>0.031</td>
</tr>
<tr>
<td>Post PCI</td>
<td>11</td>
<td>C</td>
<td>CV M</td>
<td>N/A</td>
<td>1288141</td>
<td>RR</td>
<td>0.87 (0.85 to 1.10)</td>
<td>0.07</td>
<td>0.76</td>
<td>0.031</td>
<td>0.031</td>
</tr>
<tr>
<td>Post PCI</td>
<td>15</td>
<td>C</td>
<td>CV M</td>
<td>N/A</td>
<td>8835185</td>
<td>RR</td>
<td>0.14 (0.25 to 5.33)</td>
<td>0.72</td>
<td>0.34</td>
<td>0.031</td>
<td>0.031</td>
</tr>
<tr>
<td>Post PCI</td>
<td>10</td>
<td>C</td>
<td>CV 1-year</td>
<td>N/A</td>
<td>9751269</td>
<td>RR</td>
<td>0.71 (0.67 to 0.74)</td>
<td>0.00</td>
<td>0.001</td>
<td>0.045</td>
<td>0.045</td>
</tr>
<tr>
<td>Post PCI</td>
<td>16</td>
<td>C</td>
<td>CV 1-year</td>
<td>N/A</td>
<td>9417134</td>
<td>RR</td>
<td>0.72 (0.60 to 0.86)</td>
<td>0.00</td>
<td>0.001</td>
<td>0.045</td>
<td>0.045</td>
</tr>
<tr>
<td>Post PCI</td>
<td>27</td>
<td>C</td>
<td>CV 1-year</td>
<td>N/A</td>
<td>9417134</td>
<td>RR</td>
<td>0.72 (0.60 to 0.86)</td>
<td>0.00</td>
<td>0.001</td>
<td>0.045</td>
<td>0.045</td>
</tr>
<tr>
<td>Post PCI</td>
<td>29</td>
<td>C</td>
<td>CV 1-year</td>
<td>N/A</td>
<td>9751269</td>
<td>RR</td>
<td>0.71 (0.67 to 0.74)</td>
<td>0.00</td>
<td>0.001</td>
<td>0.045</td>
<td>0.045</td>
</tr>
<tr>
<td>Post PCI</td>
<td>12</td>
<td>C</td>
<td>CV 1-year</td>
<td>N/A</td>
<td>9751269</td>
<td>RR</td>
<td>0.71 (0.67 to 0.74)</td>
<td>0.00</td>
<td>0.001</td>
<td>0.045</td>
<td>0.045</td>
</tr>
</tbody>
</table>

### Abbreviations:
ACS, acute coronary syndrome; AMI, acute myocardial infarction; BMI, body mass index; C, cohort study; CABG, coronary artery bypass graft; Co, concordance; CV, cardiovascular; E, Egger p-value; HR, hazard ratio; L, large effect; M, mortality; N, no; No, number of study; N/A, not available; NL, normal; O, observational study; Ob, Obese; OR, odds ratio; OW, overweight; PCI, percutaneous coronary intervention; PI, prediction interval; RCT, randomized control trial; RR, relative risk; S, small study effect; SOB, severe obesity; T, type of study; TM, Type of metrics; TP, type of patients; UW, underweight; y, yes; †Number of individual studies showing statistically significant decreased mortality for overweight (R) / not statistically significant (N) / statistically significant increased mortality (I) for overweight, compared to normal BMI. <3 years (<30 days), >3 years (30-365 days), >3 years (>365 days), >5 years (>1000 days).
following an acute MI. Protective associations were observed for both short-term (<30 days) and long-term (1-2 years or longer) follow-up related to all-cause mortality and in-hospital mortality.5,17,18

One analysis was classified as convincing evidence. The analysis showed that in patients with ACS, obesity, compared to normal BMI had a protective effect with a reanalyzed RR of 0.6 (0.51 to 0.69) (Table I).5

No protective associations for mortality were observed in obese patients compared to overweight patients in patients with acute MI (Table I). In patients following acute MI, obesity and overweight compared to normal BMI were both protective; however, the evidence was suggestive and weak, respectively.5,17,18

### Post-CABG

There were two studies regarding patients post-CABG, including 38 cohort and 44 observational analysis.19,20 The only two convincing evidences were on the protective effects of obesity and overweight protective effects, with OR of 0.62 (0.55 to 0.7) and 0.7 (0.63 to 0.77) respectively compared to patients with normal weight. These effects were observed in short-term follow-up, less than 30 days.19 The majority of evidence were either weak or showed no association of BMI and mortality in patients after CABG surgery. The evidence for the association between overweight and normal BMI patients on mortality was graded as weak evidence due to the large heterogeneity. However, no evidence for other results was

### Table II. Association between overweight and mortality in HF.

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>No</th>
<th>T</th>
<th>TP</th>
<th>Comparison</th>
<th>Outcome</th>
<th>Death/val</th>
<th>T M</th>
<th>Random effect (random)</th>
<th>Random effect (random-analyzed)</th>
<th>P (j)</th>
<th>E</th>
<th>P-value (random)</th>
<th>P-value (fixed)</th>
<th>95% PI (random)</th>
<th>Largest effect</th>
<th>S</th>
<th>B/N</th>
<th>Ca</th>
<th>Evidence</th>
</tr>
</thead>
</table>

Abbreviations: BMI, body mass index; C, cohort; Co, concordance; CHF, chronic heart failure CV, cardiovascular; C, cohort; Co, concordance; CHF, chronic heart failure CV, cardiovascular; C, cohort; Co, concordance; CHF, chronic heart failure CV, cardiovascular.
BMI and mortality in patients with cardiovascular disease

suggestive because in those results, we had no similar or greater number of statistically significant individual studies that were not significant. Post-PCI

Our search yielded the largest amount of evidence for mortality among patients after PCI and its relationship to BMI. In total, we included five scientific papers that comprised 129 observational studies, 91 cohorts and 58 observational/RCT studies. Patients who underwent a PCI and were underweight demonstrated an increased risk of mortality in all of the studies. All measures of mortality, including short-term (30 days in-hospital mortality), medium follow-up (1-2 and 3 years) and long-term follow-up (more than 5 years) showed a higher risk of mortality among patients with low BMI or underweight. However, the only convincing evidence were for those with mortality at 1-3 years and all-cause mortality in underweight patients with a RR of 2.33 (1.87 to 2.91) and 2.52 (1.69 to 3.75) respectively, and in patients with low BMI with a RR of 2.65 (2.19 to 3.2) for all-cause mortality.

Both overweight and obesity had an impressive number of convincing evidences, all convergent toward a protective effect against mortality in all follow up periods. More specifically, obesity vs. normal BMI showed convincing evidence for patients who had in-hospital mortality, 1-year mortality, 30 days mortality and all-cause mortality. The strongest and most significant protective association was in those patients with obesity vs. normal weight at 1-year mortality (RR=0.5 (95% PI=0.43 to 0.59)). These results were highly reliable as the criteria for the convincing evidence were all satisfied: statistically significant with a p-value of less than 0.01, no small-study effect and with a small heterogeneity and 95% PI excluding the null hypothesis.

Heart Failure (HF)

All results showed that regardless of the type of study design and the characteristics of the participating population, overweight was associated with an increase in mortality, while overweight was associated with a decrease in mortality.
all-cause and cardiovascular mortality in HF patients. Compared to normal BMI, underweight increased all-cause mortality with one study having convincing evidence27. For patients who were underweight or with those BMI between 18.5 and 23.9, we found multiple studies with convincing evidence that associated them with increased mortality. In patients with chronic HF, both RCT/cohort and observational studies reported a RR for all-cause mortality of 1.25 (1.9 to 1.31) and 1.27 (1.17 to 1.37) respectively24,25, with statistically significant p-value of less than 0.01, and 95% PI that does not include the null hypothesis. This relationship was also applicable to patients with HF. However, the evidence was weak for patients with East Asian HF26.

In all studies among patients with chronic HF, the RR pointed towards a protective effect of obesity in terms of all-cause and cardiovascular mortality24,25. However, none of the evidence was convincing. Moreover, one cohort study showed no association25. Only 3 RCT/cohort studies were analyzed with regard to patients with severe obesity compared to those with non-elevated BMI, and found only suggestive evidence of protection against all-cause mortality in patients with chronic HF. An increase in five units of BMI among HF patients was associated with decreased all-cause mortality, one study showed weak evidence (discordant direction)29 and the other others showed no association in the case of HF mortality30. Similarly, for HF with preserved ejection fraction (HFpEF), one observational cohort showed a weak protective association against all-cause mortality, while the other cohort study showed no association31. When HF and chronic HF taken together, there was no convincing level of evidence that overweight and obesity had lower all-cause and cardiovascular mortality compared to normal BMI, with three suggestive and 12 weak, and five with no association levels of evidence, respectively. Finally, for East Asian HF patients26, studies revealed 2 suggestive level of evidence for patients with BMI more than 28 and those with BMI between 24 and 27.9 compared to normal BMI. The only convincing protective evidence against all-cause mortality was in those with East Asian HF with a 5-unit increase in BMI26.

**Transcatheter Aortic Valve Implantation (TAVI)**

One meta-analysis evaluated the association between BMI and mortality based on short term and long-term survival25. There were positive associations between underweight (BMI<20) and normal weight (BMI 20-24.9) in both short- and long-term mortalities. In contrast, obese patients (BMI>30) had negative associations in both short- and long-term mortalities compared with normal weight (BMI 20-24.9). Because all classes of obese (Class I–III) patients were grouped together as BMI>30, the association between the individual obesity class and mortality was uncertain. The evidence for short-term mortality was non-significant for both underweight and obesity groups due to large random p-value. On the other hand, the evidence for the relationship between underweight and obese patients and long-term mortality were weak.

**Cardiac Surgery**

Re-analysis of the data from meta-analyses revealed that underweight was associated with increased 30-day mortality (RR =1.75, 1.34 to 2.29) with weak evidence33. Overweight, obesity I, II, III groups all had lower incidences of death compared to normal BMI. The evidences for associations with mortality were suggestive in obesity II and obesity III whereas the evidence was weak for overweight and obesity I.

**Atrial Fibrillation (AF)**

There was one selected study regarding AF. One study showed that underweight patients had more than a doubled risk for all-cause and cardiovascular mortality compared to the normal BMI group34. However, the risk of mortality decreased dramatically in overweight and obese patients. Because the study did not include severe or morbid obese patients in the analysis, it was unclear whether such dramatic decrease in mortality would also be observed in these BMI groups. Through our study, it was found that the meta-analysis had either weak or non-significant evidence. Further studies are needed to improve the level of evidence.

**Following LVAD Implantation**

We reviewed one paper that included 31 observational studies exploring the relationship of mortality among patients post LVAD implantation in relation to their BMI35. All RR of the studies pointed towards protective effects of obesity vs. non-obesity regarding mortality. However, the only convincing evidence was the short-term all-cause mortality. The RR of these four observational studies was 0.79 (0.73 to 0.86), p-value of less than 0.01, and with no small-study effect.
Even though all other researches showed similar results, three of them showed no association and one had a weak evidence. Thus, overall, the evidence points that obesity among patients after LVAD implantation might be associated with mortality, except for a potential benefit for short-term over-all mortality. Since the patients in this study were not categorized into underweight, overweight and obese groups, the association between each group and mortality was not assessable. Thus, further investigations are needed to provide more information.

Discussion

Our study demonstrates the associations between BMI and risk of various kinds of mortalities such as all-cause mortality, cardiovascular mortality or others among patients with CVDs. We comprehensively re-analyzed the data of 19 meta-analyses and found that a very large proportion had weak or non-significant evidence. Only ten meta-analyses had convincing evidence and this corresponds to 52.6% of the total meta-analyses. The positive association between overweight and mortality in HF, and patients after PCI, and the negative association between overweight and mortality in ACS, patients after PCI, CABG and LVAD insertion, and finally those with East Asian HF had convincing evidence. Suggestive evidence was found in 10 (9.4%) and weak evidence was observed in 37 (35%) meta-analyses. 55 (51.8%) meta-analyses results were not statistically significant and 15 (14.1%) could not be graded due to several reasons such as (1) there was only one study result or (2) small-study effects could not be calculated due to small number of studies (<3 studies). The results of our study are in line with those of other umbrella reviews showing that there have been many claims of statistical significance for most of the studied associations, but only a minority of these associations have robust supporting evidence without hints of bias. Currently, it has been suggested that there is massive production of unnecessary, misleading, and conflicted systematic reviews and meta-analyses, because most topics have overlapping, redundant meta-analyses and some results are often produced either by industry employees or by authors with industry ties whose results aligned with sponsor interests. We also found that there have been overlapping meta-analyses on the same topic in our umbrella review and further strategies to improve the quality of meta-analyses may be important in the future.

In addition, most of the current meta-analyses mainly present their results with random- or fixed-effects size and 95% CI with p-value. Recently, however, reporting of the level of evidence has gained more importance to increase the value of the publication and reduce misleading results. To determine the noteworthiness of the results, further calculations, such as between-study heterogeneity, small-study effects, 95% PIs, the concordance between the results of meta-analyses and the largest study, have been suggested. Therefore, convincing evidence can be obtained after meeting all of these more stringent statistical criteria to reduce the biases for the claimed association. Through our umbrella review, we found that caution should be applied when interpreting the results of meta-analyses in addition to the statistical criteria for level of evidence.

Globally, the incidence of obesity is increasing at an alarming rate leading consequently to a rising incidence of accompanying diseases such as CVDs. To note, obesity by itself is an independent predictor for CVDs even if it is not associated with any risk factors. Historically, and up until the writing of this report, clinicians, rightfully so, consider obesity as detrimental for both CVD primary and secondary prevention efforts. However, evidence has indicated that the co-existence of obesity in CVD patients might have potential protective effects. Our umbrella review is exactly in concordance with this well-established “obesity paradox”. This paradox has been proven repeatedly in other conditions such as hypertension and patients with congenital heart diseases.

The landmark Framingham study and a large body of evidence have laid ground to linking obesity as a strong risk factor for HF. The exact mechanism is still poorly understood; however, it is thought to be secondary to a shift in the body composition of fat and lean muscles leading to a state of low-grade systemic inflammation. However, despite this gloomy association, scientists have explored a potential paradoxical protective effect and growing body of research is showing survival benefits in obese patients with HF. Even though the underlying physiological process is far from being comprehended, The increase in lean muscle might play a central role in the protective process by increasing cardio-respiratory fitness index.
These effects are reproducible in patients with coronary heart diseases. Obesity in its absolute presence predisposes to a pro-inflammatory state and increases atherosclerotic plaques in the coronary and contributes to their instability. However, comparable to those patients with HF, obesity was found to be paradoxically beneficial with more favorable prognosis. The same shift in body composition is also thought to be at the roots of the described protective effects. In addition to the benefits of increasing lean muscle mass, increase adiposity in obese patients have been proposed to provide protective properties especially in those sub-set of patients with minimal systemic inflammation.

Overall, multiple hypotheses have attempted to explain the obesity paradox. As discussed previously, the change in body composition, with regards to fat composition and lean muscle proportion. This hypothesis has been supported clinically by the detrimental effects of cachexia, especially in patients with HF. Although more research is needed, several observational study also showed correlation between low BMI and cardiovascular disease. Sarcomenia (involuntary weight loss), cardiac cachexia, and increased catabolic status were possible mechanisms of poor prognosis in lower BMI patients. Our study also showed six convincing evidence that low BMI (or overweight) increase mortality especially in post-PCI and HF patients. Additionally, the observed lower mortality in patients with CVD may stem from normal physiologic hemostasis. Molecules, such as NT-proBNP, which are lower in obese people, may play a protective role against mortality. Finally, in obese patients, adipokines, such as adiponectin and leptin may play a key role in protection and better survival. Leptin may have been providing protection from mortality, especially in patients with HF. Its effects are thought to counteract the pro-inflammatory cytokines TNF-alpha on the heart muscles leading to improved survival. Similarly, supporting this hypothesis, low levels of leptin and adiponectin, such as cardiac cachexia, weight and adipose loss, have been associated with reduced survival.

To note, BMI itself may not be an accurate measurement for adiposity or body composition since it also reflects lean body mass. Lean body mass represents muscle mass and better fitness, which is considered as protective. Misclassification as overweight or obese might be the case in some with large muscle mass and normal adiposity who were misclassified as overweight or obese. To resolve this potential BMI miss-interpretation, a more precise parameter must be used to measure fat mass. One suggestion is the use of waist-to-hip or waist-to-thigh ratio as measures of adiposity. Another suggestion is the use of the InBody Test, which provides a comprehensive view of body composition.

Even though our umbrella review is the first of its kind and provided results in accordance with existing literatures, there are some limitations due to the nature and abundance of the analyzed studies. First, we found that the vast majority of the selected studies used in the meta-analysis used retrospective cohorts, meaning each individual study is vulnerable to the biases such as small number of studies, restrictive area of studied region of this design. Second, the most commonly used outcome in the meta-analysis was all-cause mortality, and thus, there is the possibility that other patient characteristics, apart from BMI, could be associated with increased risk of mortality. For instance, cancers, bleeding, injuries, infections, and others are all possible causes of death that can contribute to all-cause mortality. Each patient has a different susceptibility. Potential confounding factors should be adjusted for prior to the selection of participants for meta-analysis; however, we found that most meta-analyses did not adjust for these confounding factors, which should further be considered in future meta-analyses.

Third, there were unclear mortality outcomes in some studies. Namely, there are different types of mortality outcomes reported among different studies, such as all-cause, cardiovascular, and in-hospital mortality. However, in some investigations the mortality types were not mentioned clearly, and thus it was not possible to identify whether they refer to all-cause or other types of mortality. Moreover, mortality can be classified according to the duration of follow-up. Studies of ACS or MI reported mortality in terms of follow-up duration. However, one study reporting mortality outcomes did not describe follow-up in detail and therefore, it requires caution when interpreting the results.

Fourth, there were some meta-analyses, where patients were not classified into one clear BMI category. Instead multiple BMI categories were grouped together for analysis. In addition, the cut-off of high BMI differed among studies such that some meta-analyses classified obese patients into different classes according to severity of
BMI and mortality in patients with cardiovascular disease

obesity, whereas in other systemic reviews and meta-analysis, patients with BMI ≥30 were defined as high BMI. Thus, it is very important to classify each patient into the appropriate BMI category and clarify the type of morality outcome in meta-analysis studies to prevent misinterpretation.

Fifth, there were a fairly large proportion of meta-analyses where the strength of evidence was not available due to a small number of studies (n≤2). When the number of studies is small, statistical results such as Egger’s p-value and 95% PI cannot be obtained. Therefore, we were not able to determine the strength of evidence in these studies. Finally, the criteria we used were not definitive for assessing the level of evidence.

Despite the presence of limitations as stated above (mostly meta-analyses themselves), our study makes key contributions. First of all, to our best knowledge, this study is the first in determining the strength of evidences for the association between BMI categories and mortality in patients with CVDs. Furthermore, the diseases investigated in this study are clinically important and the results of our study are meaningful when assessing the mortality outcomes in a real clinical setting.

Conclusions

Our study provides supplemental evidence supporting the “obesity paradox” effect that is widely accepted by now in the scientific and medical community. Although there is no consensus regarding the optimal range of BMI for lowering mortality in the diseases investigated in this study, we believe that further vigorous meta-analyses can continue to inform research and practice, and strengthen assessment, prognosis, and clinical decision-making and targeted pharmacological therapies.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements


Funding Information

Neither financial support nor any sort of sponsorship was received for this study.

References


4) Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and
obesity using standard body mass index categories: A systematic review and meta-analysis. JA-MA 2013; 309: 71-82.


13) Fletcher J. What is heterogeneity and is it important? BMJ 2007; 334: 94-96.


37) Theodoratou E, Tzoulaki I, Zagaza L, Ioannidis JP. Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. BMJ 2014; 348: g2035.

38) Ioannidis JP. The mass production of redundant, misleading, and conflicted systematic reviews and meta-analyses. Milbank Q 2016; 94: 485-514.


