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

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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

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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[1]. 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/m^2)[1]. 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/m^2), normal (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), and obesity (≥30 kg/m^2)[2,3]. Obesity further can be classified into 3 classes of severity: class I obesity (30-34.9 kg/m^2), class II obesity (35-39.9 kg/m^2) and class III obesity (≥40.0 kg/m^2)[2].

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[4]. Many epidemiological studies and their meta-analyses on the association between BMI and mortalities 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[5-7] 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[8,9]. Recently, many researchers apply the umbrella review concept[10], 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[11]. 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 included individual study data available for re-analysis. The detailed process of this screening is shown in Figure 1.

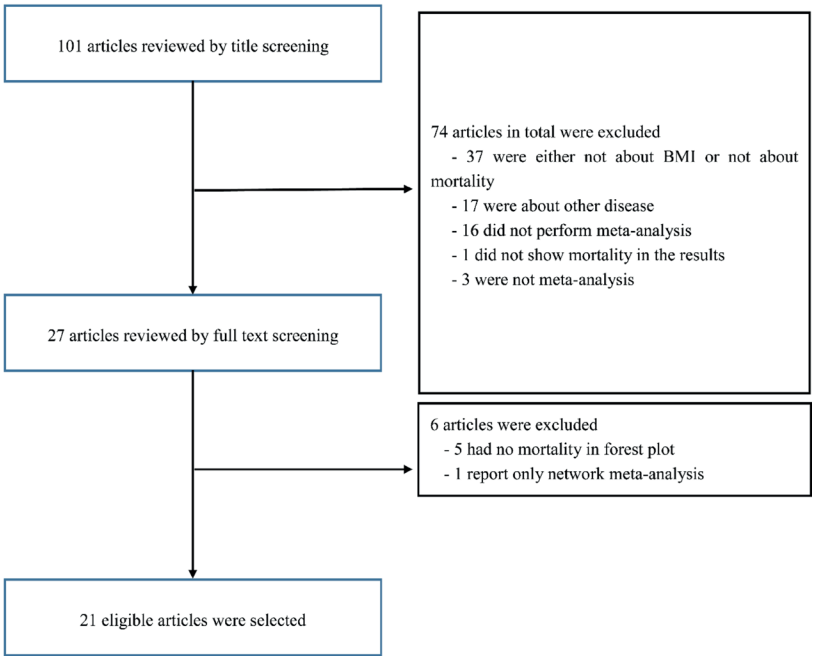

Figure 1. Flow chart of literature search.

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 (I^2>50%), we further evaluated whether such high heterogeneity was caused by the differences in the direction of individual effects[9]. When the number of statistically significant individual studies was the same or greater than the number of individual studies which were not 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

Table I. Association between overweight and morality in cardiovascular diseases; acute coronary syndrome, post-CABG, and post PCI.

Author, Year	No	T	TP	Comparison	Outcome	Death/total	TM	Random effect (reported)	Random effect (re-analyzed)	I^2 (*p*)	E	*p*-value (random)	*p*-value (fixed)	95% PI (random)	Large effect	S	R/N/I†	Co	Evidence
Acute coronary syndrome																			
Niedziela et al[17]	9	C	ACS	Low BMI *vs.* NL	All-cause M	N/A	RR	1.74 (1.47 to 2.05)	1.74 (1.47 to 2.05)	58 (0.016)	<0.01	<0.001	<0.001	1.14 to 2.64	1.38 (1.27 to 1.5)	Y	0/2/7	Y	Weak
Niedziela et al[17]	26	C	ACS	Ob *vs.* NL	All-cause M	N/A	RR	0.6 (0.53 to 0.68)	0.6 (0.53 to 0.68)	85 (<0.001)	0.17	<0.001	<0.001	0.35 to 1.05	0.89 (0.83 to 0.96)	N	18/8/0	Y	Weak
Niedziela et al[17]	26	C	ACS	OW *vs.* NL	All-cause M	N/A	RR	0.7 (0.64 to 0.76)	0.7 (0.64 to 0.76)	82 (<0.001)	0.1	<0.001	<0.001	0.48 to 1.02	0.88 (0.84 to 0.92)	Y	16/10/0	Y	Weak
Niedziela et al[17]	10	C	ACS	SOb *vs.* NL	All-cause M	N/A	RR	0.7 (0.58 to 0.86)	0.7 (0.58 to 0.85)	77 (<0.001)	0.13	<0.001	<0.001	0.38 to 1.3	0.51 (0.45 to 0.57)	N	5/5/0	Y	Weak
Wang et al[5]	10	C	AMI	Ob *vs.* NL	In-hospital M	1091/15171	RR	0.58 (0.51 to 0.67)	0.6 (0.51 to 0.69)	6 (0.386)	0.53	<0.001	<0.001	0.47 to 0.75	0.57 (0.47 to 0.69)	N	4/6/0	Y	Convincing
Wang et al[5]	10	C	AMI	OW *vs.* NL	In-hospital M	1586/21717	RR	0.7 (0.59 to 0.84)	0.7 (0.58 to 0.84)	51 (0.03)	0.2	<0.001	<0.001	0.44 to 1.12	0.77 (0.67 to 0.88)	N	5/5/0	Y	Weak
Wang et al[5]	10	C	AMI	OW *vs.* Ob	In-hospital M	1021/16964	RR	0.82 (0.64 to 1.06)	0.82 (0.64 to 1.06)	47 (0.049)	0.59	0.13	<0.001	0.44 to 1.54	0.73 (0.6 to 0.88)	N	2/8/0	N	No association
Wang et al[5]	11	C	AMI	OW&Ob *vs.* NL	In-hospital M	2025/27673	RR	0.72 (0.57 to 0.9)	0.72 (0.57 to 0.9)	79 (<0.001)	0.71	0.004	<0.001	0.34 to 1.51	0.71 (0.63 to 0.81)	N	7/3/1	Y	Weak
Lamelas et al[18]	19	O	ACS	Ob *vs.* NL	All-cause M	N/A	RR	0.79 (0.71 to 0.88)	0.79 (0.71 to 0.88)	33 (0.08)	0.89	<0.001	<0.001	0.59 to 1.05	0.78 (0.66 to 0.92)	N	6/13/0	Y	Suggestive
Lamelas et al[18]	17	O	ACS	OW *vs.* NL	All-cause M	N/A	RR	0.83 (0.75 to 0.91)	0.83 (0.75 to 0.91)	51 (0.008)	0.33	<0.001	<0.001	0.61 to 1.12	0.8 (0.72 to 0.88)	N	5/12/0	Y	Weak
Post CABG																			
Oreopoulos et al[19]	5	C	Post-CABG	Ob *vs.* NL	All-cause M‡	545/6559	OR	0.88 (0.6 to 1.29)	0.88 (0.6 to 1.29)	64 (0.024)	0.93	0.518	0.186	0.27 to 2.93	0.8 (0.59 to 1.08)	N	1/3/1	Y	No association
Oreopoulos et al[19]	7	C	Post-CABG	Ob *vs.* NL	All-cause M‡	1377/39106	OR	0.63 (0.56 to 0.71)	0.62 (0.55 to 0.7)	0 (0.635)	0.13	<0.001	<0.001	0.53 to 0.73	0.58 (0.49 to 0.69)	N	4/3/0	Y	Convincing
Oreopoulos et al[19]	5	C	Post-CABG	OW *vs.* NL	All-cause M‡	733/10193	OR	0.78 (0.6 to 1)	0.78 (0.61 to 1)	46 (0.116)	0.63	0.047	<0.001	0.38 to 1.58	0.76 (0.61 to 0.95)	N	3/2/0	Y	Weak
Oreopoulos et al[19]	7	C	Post-CABG	OW *vs.* NL	All-cause M‡	1726/50946	OR	0.7 (0.63 to 0.77)	0.7 (0.63 to 0.77)	0 (0.617)	0.65	<0.001	<0.001	0.61 to 0.79	0.72 (0.63 to 0.82)	N	4/3/0	Y	Convincing
Oreopoulos et al[19]	3	C	Post-CABG	SOb *vs.* NL	All-cause M‡	215/2094	OR	1.42 (0.76 to 2.65)	1.42 (0.76 to 2.65)	59 (0.089)	0.54	0.271	0.236	0 to 1130.54	1 (0.7 to 1.42)	N	0/2/1	Y	No association
Oreopoulos et al[19]	4	C	Post-CABG	SOb *vs.* NL	All-cause M‡	310/10542	OR	0.66 (0.51 to 0.86)	0.66 (0.51 to 0.86)	0 (0.731)	0.75	0.002	0.002	0.38 to 1.17	0.77 (0.53 to 1.11)	N	1/3/0	N	Weak
Sharma et al[20]	6	O	Post-CABG	Low BMI *vs.* NL	All-cause M	385/14452	RR	2.66 (1.51 to 4.66)	2.66 (1.51 to 4.67)	63 (0.019)	0.78	<0.001	<0.001	0.49 to 14.53	3.38 (1.86 to 6.14)	N	0/3/3	Y	Weak
Sharma et al[20]	1	O	Post-CABG	Low BMI *vs.* NL	CV M	6/383	RR	0.98 (0.06 to 16.97)	N/A	N/A	N/A	N/A	N/A	NA	0.98 (0.06 to 16.97)	N/A	0/1/0	N/A	N/A
Sharma et al[20]	11	O	Post-CABG	Ob *vs.* NL	All-cause M	1162/31466	RR	0.93 (0.63 to 1.37)	0.93 (0.63 to 1.37)	89 (<0.001)	0.18	0.706	0.018	0.23 to 3.78	2.3 (1.83 to 2.89)	N	3/6/2	N	No association
Sharma et al[20]	2	O	Post-CABG	Ob *vs.* NL	CV M	54/3968	RR	1.57 (0.49 to 5.1)	1.57 (0.48 to 5.1)	73 (0.053)	<0.01	0.453	0.206	NA	0.88 (0.4 to 1.95)	NA	0/1/1	Y	N/A
Sharma et al[20]	11	O	Post-CABG	OW *vs.* NL	All-cause M	1215/34189	RR	0.83 (0.67 to 1.02)	0.83 (0.67 to 1.02)	65 (0.001)	0.51	0.081	<0.001	0.43 to 1.6	0.77 (0.63 to 0.95)	N	4/7/0	N	No association
Sharma et al[20]	2	O	Post-CABG	OW vs NL	CV M	74/6694	RR	1.06 (0.52 to 2.13)	1.05 (0.52 to 2.12)	45 (0.177)	<0.01	0.883	0.923	NA	0.8 (0.46 to 1.4)	NA	0/2/0	Y	N/A
Sharma et al[20]	10	O	Post-CABG	SOb *vs.* NL	All-cause M	555/18984	RR	0.76 (0.55 to 1.04)	0.75 (0.55 to 1.04)	48 (0.046)	0.99	0.087	0.005	0.32 to 1.78	0.59 (0.41 to 0.85)	N	2/7/1	N	No association
Sharma et al[20]	1	O	Post-CABG	SOb *vs.* NL	CV M	13/458	RR	4.07 (1.4 to 11.85)	N/A	N/A	N/A	N/A	N/A	N/A	4.07 (1.4 to 11.85)	N/A	0/0/1	N/A	N/A

Continued

Table I *(Continued)*. Association between overweight and morality in cardiovascular diseases; acute coronary syndrome, post-CABG, and post PCI.

Author, Year	No	T	TP	Comparison	Outcome	Death/total	TM	Random effect (reported)	Random effect (re-analyzed)	I^2 (*p*)	E	*p*-value (random)	*p*-value (fixed)	95% PI (random)	Large effect	S	R/N/I†	Co	Evidence
Post PCI																			
Bundhun et al[21]	13	O/R	Post-PCI	Ob *vs.* NL	In-hospital M	2796/115465	RR	0.6 (0.56 to 0.65)	0.62 (0.54 to 0.71)	26 (0.184)	0.84	<0.001	<0.001	0.47 to 0.82	0.59 (0.54 to 0.65)	N	5/8/0	Y	Convincing
Bundhun et al[21]	6	O/R	Post-PCI	Ob *vs.* NL	1-year M	622/13161	RR	0.5 (0.43 to 0.59)	0.5 (0.42 to 0.58)	0 (0.503)	0.88	<0.001	<0.001	0.4 to 0.62	0.46 (0.38 to 0.56)	N	3/3/0	Y	Convincing
Bundhun et al[21]	10	O/R	Post-PCI	Ob *vs.* NL	>1-year M	1424/24083	RR	0.8 (0.71 to 0.91)	0.82 (0.7 to 0.95)	12 (0.33)	0.99	0.007	0.001	0.63 to 1.06	0.8 (0.66 to 0.96)	N	3/7/0	Y	Weak
Bundhun, et al[21]	13	O/R	Post-PCI	OW *vs.* NL	In-hospital M	3289/141263	RR	0.67 (0.63 to 0.72)	0.67 (0.62 to 0.71)	0 (0.734)	0.7	<0.001	<0.001	0.62 to 0.72	0.64 (0.59 to 0.7)	N	6/7/0	Y	Convincing
Bundhun, et al[21]	6	O/R	Post-PCI	OW *vs.* NL	1-year M	883/18583	RR	0.62 (0.55 to 0.71)	0.64 (0.55 to 0.75)	15 (0.319)	<0.01	<0.001	<0.001	0.47 to 0.87	0.54 (0.45 to 0.64)	N	1/5/0	Y	Convincing
Bundhun et al[21]	10	O/R	Post-PCI	OW *vs.* NL	>1-year MC	1931/36974	RR	0.7 (0.64 to 0.76)	0.71 (0.64 to 0.79)	8 (0.365)	0.37	<0.001	<0.001	0.61 to 0.84	0.63 (0.55 to 0.72)	N	3/7/0	Y	Convincing
Li et al[22]	2	C	Post-PCI	Ob *vs.* NL	CV M[s]	N/A	HR	1.16 (0.75 to 1.8)	1.16 (0.75 to 1.79)	0 (0.41)	<0.01	0.498	0.498	NA	1.02 (0.6 to 1.74)	NA	0/2/0	Y	N/A
Li et al[22]	5	C	Post-PCI	Ob *vs.* NL	All-cause M[s]	N/A	HR	0.9 (0.77 to 1.06)	0.9 (0.77 to 1.06)	0 (0.529)	0.9	0.207	0.207	0.69 to 1.17	1.07 (0.8 to 1.43)	N	1/4/0	Y	No association
Li et al[22]	2	C	Post-PCI	OW *vs.* NL	CV M[s]	N/A	HR	1.1 (0.81 to 1.48)	1.09 (0.81 to 1.48)	0 (0.748)	<0.01	0.553	0.553	NA	1.05 (0.71 to 1.56)	NA	0/2/0	Y	N/A
Li et al[22]	5	C	Post-PCI	OW *vs.* NL	All-cause M[s]	N/A	HR	0.75 (0.64 to 0.87)	0.74 (0.64 to 0.87)	30 (0.225)	0.31	<0.001	<0.001	0.51 to 1.09	0.9 (0.72 to 1.12)	N	3/2/0	N	Weak
Li et al[22]	1	C	Post-PCI	UW *vs.* NL	CV M[s]	N/A	HR	1.52 (0.72 to 3.19)	N/A	N/A	N/A	N/A	N/A	N/A	1.52 (0.72 to 3.19)	N/A	0/1/0	N/A	N/A
Li et al[22]	2	C	Post-PCI	UW *vs.* NL	All-cause M[s]	N/A	HR	1.72 (1.11 to 2.66)	1.72 (1.11 to 2.66)	0 (0.821)	<0.01	0.014	0.014	NA	1.67 (1 to 2.78)	NA	0/1/1	Y	N/A
Lin et al[6]	4	C	Post-PCI	Ob *vs.* NL	>3 year M	N/A	HR	0.85 (0.74 to 0.97)	0.85 (0.74 to 0.97)	14 (0.321)	0.71	0.018	0.004	0.58 to 1.24	0.82 (0.71 to 0.95)	N	2/2/0	Y	Weak
Lin et al[6]	10	C	Post-PCI	Ob *vs.* NL	1-2 year M	1262/27188	RR	0.78 (0.64 to 0.94)	0.78 (0.64 to 0.94)	29 (0.173)	0.41	0.01	<0.001	0.5 to 1.2	0.76 (0.59 to 0.98)	N	3/7/0	Y	Weak
Lin et al[6]	7	C	Post-PCI	Ob *vs.* NL	In-hospital M[30]	210/16926	RR	0.52 (0.39 to 0.68)	0.51 (0.39 to 0.68)	0 (0.499)	0.12	<0.001	<0.001	0.36 to 0.74	0.41 (0.28 to 0.61)	N	1/6/0	Y	Convincing
Lin et al[6]	4	C	Post-PCI	OW *vs.* NL	>3 year M	N/A	HR	0.81 (0.69 to 0.94)	0.8 (0.69 to 0.94)	42 (0.159)	0.13	0.005	<0.001	0.47 to 1.39	0.88 (0.75 to 1.03)	N	2/2/0	N	Weak
Lin et al[6]	10	C	Post-PCI	OW *vs.* NL	1-2 year M	1776/41267	RR	0.77 (0.65 to 0.9)	0.77 (0.65 to 0.9)	44 (0.063)	0.27	0.001	<0.001	0.51 to 1.15	0.63 (0.55 to 0.72)	N	3/7/0	Y	Suggestive
Lin et al[6]	7	C	Post-PCI	OW *vs.* NL	30-day M & In-hospital M	267/19368	RR	0.62 (0.49 to 0.79)	0.62 (0.49 to 0.79)	0 (0.468)	0.85	<0.001	<0.001	0.45 to 0.85	0.48 (0.32 to 0.71)	N	1/6/0	Y	Convincing
Lin et al[6]	1	C	Post-PCI	UW *vs.* NL	>3 year M	N/A	HR	1.45 (0.88 to 2.38)	N/A	N/A	N/A	N/A	N/A	N/A	1.45 (0.88 to 2.38)	N/A	0/1/0	N/A	N/A
Lin et al[6]	4	C	Post-PCI	UW *vs.* NL	1-2 year M	960/16213	RR	2.33 (1.87 to 2.91)	2.33 (1.87 to 2.91)	0 (0.84)	0.21	<0.001	<0.001	1.43 to 3.79	2.49 (1.87 to 3.32)	N	0/1/3	Y	Convincing
Lin et al[6]	3	C	Post-PCI	UW *vs.* NL	30-day M & In-hospital M	146/5899	RR	3.32 (2.19 to 5.03)	3.32 (2.19 to 5.03)	15 (0.31)	0.3	<0.001	<0.001	0.11 to 99.25	3.83 (2.59 to 5.66)	N	0/1/2	Y	Suggestive
Oreopoulos et al[19]	8	C	Post-PCI	Ob *vs.* NL	All-cause M[l]	1050/16524	OR	0.65 (0.51 to 0.83)	0.66 (0.51 to 0.84)	60 (0.014)	0.11	<0.001	<0.001	0.33 to 1.29	0.6 (0.48 to 0.74)	N	3/5/0	Y	Weak
Oreopoulos et al[19]	4	C	Post-PCI	Ob *vs.*.NL	All-cause M[s]	732/65612	OR	0.63 (0.54 to 0.73)	0.63 (0.54 to 0.72)	0 (0.951)	0.55	<0.001	<0.001	0.46 to 0.86	0.63 (0.53 to 0.75)	N	3/1/0	Y	Convincing
Oreopoulos et al[19]	8	C	Post-PCI	OW *vs.* NL	All-cause M[l]	1298/20085	OR	0.66 (0.55 to 0.79)	0.66 (0.55 to 0.78)	39 (0.121)	0.1	<0.001	<0.001	0.43 to 1	0.51 (0.42 to 0.61)	N	3/5/0	Y	Convincing
Oreopoulos et al[19]	4	C	Post-PCI	OW *vs.* NL	All-cause M[s]	840/83996	OR	0.71 (0.62 to 0.81)	0.71 (0.62 to 0.81)	0 (0.574)	0.53	<0.001	<0.001	0.52 to 0.96	0.73 (0.62 to 0.85)	N	2/2/0	Y	Convincing
Oreopoulos et al[19]	5	C	Post-PCI	SOb *vs.* NL	All-cause M[l]	419/5364	OR	0.62 (0.41 to 0.96)	0.63 (0.41 to 0.96)	52 (0.082)	0.61	0.032	<0.001	0.17 to 2.26	0.46 (0.33 to 0.64)	N	1/4/0	Y	Weak
Oreopoulos et al[19]	4	C	Post-PCI	SOb *vs.* NL	All-cause M[s]	467/39582	OR	0.76 (0.61 to 0.95)	0.77 (0.61 to 0.96)	0 (0.441)	0.88	0.021	0.021	0.47 to 1.26	0.73 (0.56 to 0.95)	N	1/3/0	Y	Weak
Sharma et al[20]	10	O	Post-PCI	Low *vs.* NL BMI	All-cause M	738/36174	RR	2.65 (2.19 to 3.2)	2.65 (2.19 to 3.2)	0 (0.51)	0.58	<0.001	<0.001	2.12 to 3.31	3.31 (2.35 to 4.67)	N	0/6/4	Y	Convincing
Sharma et al[20]	4	O	Post-PCI	Low *vs.* NL BMI	CV M	91/3306	RR	2.76 (1.67 to 4.56)	2.76 (1.67 to 4.56)	0 (0.489)	0.92	<0.001	<0.001	0.91 to 8.32	3.31 (1.35 to 8.12)	N	0/2/2	Y	Suggestive
Sharma et al[20]	24	O	Post-PCI	Ob *vs.* NL BMI	All-cause M	1709/80539	RR	0.66 (0.51 to 0.86)	0.67 (0.52 to 0.86)	79 (<0.001)	0.93	0.002	<0.001	0.22 to 2.01	0.59 (0.48 to 0.72)	N	10/13/1	Y	Weak
Sharma et al[20]	10	O	Post-PCI	Ob *vs.* NL BMI	CV M	373/14319	RR	0.94 (0.62 to 1.44)	0.94 (0.62 to 1.44)	61 (0.006)	0.31	0.78	0.026	0.29 to 3.11	0.53 (0.39 to 0.72)	N	1/8/1	N	No association
Sharma et al[20]	29	O	Post-PCI	OW *vs.* NL BMI	All-cause M	3440/128729	RR	0.68 (0.62 to 0.74)	0.68 (0.62 to 0.74)	23 (0.129)	0.99	<0.001	<0.001	0.54 to 0.86	0.78 (0.67 to 0.9)	N	10/19/0	Y	Convincing
Sharma et al[20]	10	O	Post-PCI	OW *vs.* NL BMI	CV M	530/20822	RR	0.78 (0.66 to 0.93)	0.78 (0.66 to 0.93)	0 (0.85)	0.08	0.006	0.006	0.64 to 0.96	0.69 (0.54 to 0.89)	N	1/9/0	Y	Weak
Sharma et al[20]	8	O	Post-PCI	SOb *vs.* NL BMI	All-cause M	684/43069	RR	0.69 (0.46 to 1.04)	0.69 (0.46 to 1.05)	74 (<0.001)	0.92	0.08	<0.001	0.19 to 2.55	0.73 (0.57 to 0.94)	N	2/6/0	N	No association
Sharma et al[20]	3	O	Post-PCI	SOb *vs.* NL BMI	CV M	82/3087	RR	1.16 (0.66 to 2.03)	1.17 (0.67 to 2.03)	22 (0.279)	0.36	0.587	0.448	0.01 to 120.25	1.66 (0.86 to 3.22)	N	0/3/0	Y	No association
Wang et al[23]	12	O	Post-PCI	Ob *vs.* NL	All-cause M	N/A	RR	0.64 (0.49 to 0.84)	0.64 (0.49 to 0.84)	59 (0.005)	0.16	0.001	<0.001	0.3 to 1.37	0.45 (0.37 to 0.55)	N	4/8/0	Y	Weak
Wang et al[23]	12	O	Post-PCI	OW *vs.* NL	All-cause M	N/A	RR	0.63 (0.56 to 0.71)	0.63 (0.56 to 0.72)	8 (0.372)	0.17	<0.001	<0.001	0.52 to 0.77	0.54 (0.46 to 0.64)	N	4/8/0	Y	Convincing
Wang et al[23]	3	O	Post-PCI	SOb *vs.* NL	All-cause M	N/A	RR	0.54 (0.31 to 0.93)	0.54 (0.31 to 0.93)	0 (0.762)	0.87	0.026	0.026	0.02 to 18.62	0.49 (0.23 to 1.04)	N	0/3/0	N	Weak
Wang et al[23]	4	O	Post-PCI	UW *vs.* NL	All-cause M	N/A	RR	2.52 (1.69 to 3.75)	2.52 (1.69 to 3.75)	0 (0.586)	0.55	<0.001	<0.001	1.05 to 6.03	3.37 (1.9 to 5.98)	N	0/3/1	Y	Convincing

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 obese; 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. [l]long-term (1-5 years), s short term (<30 days), 5 > 5 years, 30 30 day mortality.

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[5,17,18]. One study, which included 9 cohort studies, compared underweight 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[17].

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

Table II. Association between overweight and morality in HF.

Author, Year	No	T	TP	Comparison	Outcome	Death/total	TM	Random effect (reported)	Random effect (re-analyzed)	I^2 (p)	E	p-value (random)	p-value (fixed)	95% PI (random)	Largest effect	S	R/N/I†	Co	Evidence
Oreopoulos et al[24]	3	R&C	CHF	Ob *vs.* NL	CV M	644/3893	RR	0.6 (0.53 to 0.69)	0.6 (0.52 to 0.69)	0 (0.874)	0.68	<0.001	<0.001	0.24 to 1.49	0.6 (0.52 to 0.69)	N	1/2/0	Y	Suggestive
Oreopoulos et al[24]	9	R&C	CHF	Ob *vs.* NE BMI	All-cause M	5441/15900	RR	0.67 (0.62 to 0.73)	0.67 (0.62 to 0.73)	58 (0.015)	0.11	<0.001	<0.001	0.53 to 0.84	0.73 (0.68 to 0.78)	N	7/2/0	Y	Weak
Oreopoulos et al[24]	3	R&C	CHF	OW *vs.* NL	CV M	891/4580	RR	0.81 (0.72 to 0.92)	0.82 (0.72 to 0.92)	0 (0.85)	0.75	0.001	0.001	0.37 to 1.8	0.82 (0.73 to 0.93)	N	1/2/0	Y	Suggestive
Oreopoulos et al[24]	9	R&C	CHF	OW *vs.* NE BMI	All-cause M	7013/19317	RR	0.84 (0.79 to 0.9)	0.84 (0.79 to 0.9)	56 (0.02)	0.07	<0.001	<0.001	0.71 to 1	0.93 (0.89 to 0.97)	Y	4/5/0	Y	Weak
Oreopoulos et al[24]	3	R&C	CHF	SOb *vs.* NE BMI	All-cause M	1099/4025	RR	0.62 (0.55 to 0.69)	0.62 (0.55 to 0.69)	0 (0.396)	0.11	<0.001	<0.001	0.31 to 1.24	0.59 (0.51 to 0.69)	N	2/1/0	Y	Suggestive
Oreopoulos et al[24]	2	R&C	CHF	UW *vs.* NL	CV M	549/2276	RR	1.2 (1.04 to 1.38)	1.19 (1.03 to 1.38)	0 (0.796)	<0.01	0.018	0.018	NA	1.19 (1.03 to 1.38)	NA	0/1/1	Y	N/A
Oreopoulos et al[24]	4	R&C	CHF	UW *vs.* NL	All-cause M	2758/6169	RR	1.25 (1.19 to 1.31)	1.25 (1.19 to 1.31)	0 (0.697)	<0.01	<0.001	<0.001	1.13 to 1.39	1.27 (1.2 to 1.34)	N	0/2/2	Y	Convincing
Sharma et al[25]	5	O	CHF	LBMI *vs.* NL	CV M	N/A	RR	1.2 (1.01 to 1.43)	1.2 (1.01 to 1.43)	63 (0.029)	0.72	0.039	<0.001	0.68 to 2.13	1.19 (1.03 to 1.38)	N	0/2/3	Y	Weak
Sharma et al[25]	5	O	CHF	LBMI *vs.* NL	All-cause M	N/A	RR	1.27 (1.17 to 1.37)	1.26 (1.17 to 1.37)	0 (0.535)	0.63	<0.001	<0.001	1.12 to 1.43	1.29 (1.14 to 1.46)	N	0/2/3	Y	Convincing
Sharma et al[25]	2	O	CHF	MOb *vs.* NL	CV M	N/A	RR	0.71 (0.5 to 1.01)	0.71 (0.5 to 1.01)	77 (0.035)	<0.01	0.058	<0.001	NA	0.6 (0.49 to 0.74)	NA	1/1/0	N	N/A
Sharma et al[25]	2	O	CHF	MOb *vs.* NL	All-cause M	N/A	RR	0.75 (0.57 to 0.98)	0.74 (0.57 to 0.98)	77 (0.036)	<0.01	0.035	<0.001	NA	0.65 (0.55 to 0.77)	NA	1/1/0	Y	N/A
Sharma et al[25]	5	O	CHF	Ob *vs.* NL	CV M	N/A	RR	0.82 (0.64 to 1.05)	0.82 (0.64 to 1.05)	82 (<0.001)	0.55	0.12	<0.001	0.35 to 1.91	0.75 (0.68 to 0.83)	N	2/2/1	N	No association
Sharma et al[25]	5	O	CHF	Ob *vs.* NL	All-cause M	N/A	RR	0.79 (0.65 to 0.97)	0.8 (0.65 to 0.98)	81 (<0.001)	0.58	0.03	<0.001	0.4 to 1.58	0.75 (0.69 to 0.82)	N	3/1/1	Y	Weak
Sharma et al[25]	6	O	CHF	OW *vs.* NL	CV M	N/A	RR	0.79 (0.7 to 0.9)	0.79 (0.69 to 0.9)	62 (0.023)	0.51	<0.001	<0.001	0.55 to 1.15	0.83 (0.77 to 0.9)	N	4/2/0	Y	Weak
Sharma et al[25]	6	O	CHF	OW *vs.* NL	All-cause M	N/A	RR	0.78 (0.68 to 0.89)	0.78 (0.69 to 0.89)	72 (0.003)	0.32	<0.001	<0.001	0.53 to 1.14	0.86 (0.8 to 0.92)	N	4/2/0	Y	Weak
Lin et al[26]	3	C	HF	≥28 *vs.* 18.5-23.9	All-cause M	N/A	HR	0.47 (0.34 to 0.65)	0.47 (0.34 to 0.65)	0 (0.676)	0.94	<0.001	<0.001	0.06 to 3.76	0.41 (0.26 to 0.64)	N	2/1/0	Y	Suggestive
Lin et al[26]	3	C	HF	15-18.4 *vs.* 18.5-23.9	All-cause M	N/A	HR	1.44 (1.06 to 1.96)	1.44 (1.06 to 1.95)	0 (0.579)	0.5	0.021	0.021	0.2 to 10.48	1.24 (0.82 to 1.88)	N	0/2/1	N	Weak
Lin et al[26]	4	C	HF	24-27.9 *vs.* 18.5-23.9	All-cause M	N/A	HR	0.61 (0.44 to 0.83)	0.61 (0.44 to 0.83)	48 (0.121)	0.6	0.002	<0.001	0.19 to 1.91	0.59 (0.47 to 0.75)	N	3/1/0	Y	Suggestive
Lin et al[26]	8	C	HF	5 unit I in BMI	All-cause M	N/A	HR	0.65 (0.58 to 0.73)	0.65 (0.58 to 0.73)	37 (0.131)	0.17	<0.001	<0.001	0.49 to 0.87	0.79 (0.66 to 0.94)	N	8/0/0	Y	Convincing
Mahajan et al[27]	2	R&C	HF	MOb *vs.* NL	All-cause M	N/A	HR	0.8 (0.77 to 0.83)	0.8 (0.77 to 0.83)	0 (0.848)	<0.01	<0.001	<0.001	NA	0.8 (0.77 to 0.83)	NA	1/1/0	Y	N/A
Mahajan et al[27]	4	R&C	HF	Ob *vs.* NL	CV M	N/A	HR	0.97 (0.72 to 1.33)	0.97 (0.72 to 1.32)	87 (<0.001)	0.22	0.864	<0.001	0.25 to 3.82	0.82 (0.72 to 0.93)	N	2/1/1	N	No association
Mahajan et al[27]	10	R&C	HF	Ob *vs.* NL	All-cause M	N/A	HR	0.79 (0.69 to 0.91)	0.79 (0.69 to 0.91)	95 (<0.001)	0.82	0.001	<0.001	0.49 to 1.27	0.79 (0.77 to 0.81)	N	6/3/1	Y	Weak
Mahajan et al[27]	3	R&C	HF	OW *vs.* NL	CV M	N/A	HR	0.86 (0.79 to 0.94)	0.86 (0.79 to 0.94)	57 (0.099)	0.29	0.001	<0.001	0.34 to 2.21	0.84 (0.82 to 0.86)	N	2/1/0	Y	Weak
Mahajan et al[27]	10	R&C	HF	OW *vs.* NL	All-cause M	N/A	HR	0.88 (0.79 to 0.98)	0.88 (0.78 to 0.98)	91 (<0.001)	0.87	0.021	<0.001	0.62 to 1.24	0.84 (0.82 to 0.86)	N	5/4/1	Y	Weak
Mahajan et al[27]	2	R&C	HF	UW *vs.* NL	CV M	N/A	HR	1.2 (0.61 to 2.39)	1.2 (0.61 to 2.39)	79 (0.029)	<0.01	0.599	0.812	NA	0.88 (0.65 to 1.19)	NA	0/1/1	Y	N/A
Mahajan et al[27]	4	R&C	HF	UW *vs.* NL	All-cause M	N/A	HR	1.4 (1.25 to 1.57)	1.4 (1.25 to 1.57)	12 (0.33)	0.69	<0.001	<0.001	1.03 to 1.9	1.56 (1.33 to 1.83)	N	0/2/2	Y	Convincing
Milajerdi et al[28]	10	O	HF	Hi *vs.* Lo	HF M	N/A	OR	0.69 (0.61 to 0.77)	0.69 (0.61 to 0.77)	84 (<0.001)	0.69	<0.001	<0.001	0.47 to 1	0.67 (0.65 to 0.7)	N	6/4/0	Y	Weak
Milajerdi et al[28]	7	O	HF	Hi *vs.* Lo	HF M	N/A	OR	1.24 (0.65 to 2.37)	1.24 (0.65 to 2.37)	91 (<0.001)	0.88	0.517	0.019	0.13 to 12.04	0.64 (0.47 to 0.87)	N	2/2/3	N	No association
Qin et al[29]	14	C	HF	5 unit I in BMI	All-cause M	13508/46794	HR	0.95 (0.92 to 0.97)	0.95 (0.92 to 0.97)	90 (<0.001)	0.05	<0.001	<0.001	0.86 to 1.04	1.01 (1 to 1.02)	Y	8/5/1	N	Weak
Aune et al[30]	4	C	HF M	5 unit I in BMI	HF M	1015/215657	RR	1.26 (0.85 to 1.87)	1.26 (0.85 to 1.87)	95 (<0.001)	0.53	0.249	<0.001	0.19 to 8.35	1.25 (1.1 to 1.43)	N	1/0/3	N	No association
Zhang et al[31]	4	O	HFpEF	Per 5 unit I in BMI	All-cause M	N/A	HR	0.93 (0.89 to 0.97)	0.93 (0.89 to 0.97)	81 (0.001)	0.54	<0.001	<0.001	0.76 to 1.13	0.89 (0.87 to 0.91)	N	4/0/0	Y	Weak
Zhang et al[31]	7	O	HFpEF	Per 5 unit I in BMI	All-cause M	N/A	HR	0.96 (0.92 to 1)	0.96 (0.93 to 1)	95 (<0.001)	0.06	0.033	0.412	0.85 to 1.09	1.01 (1 to 1.02)	Y	4/2/1	N	No association

Abbreviations: BMI, body mass index; C, cohort; Co, concordance; CHF, chronic heart failure CV, cardiovascular; E, Egger p-value; EF, ejection fraction; Hi vs Lo, Highest vs lowest category of post-HF diagnosis BMI ;HF, heart failure; HR, hazard ratio; I, increase; LBMI, low BMI (<20); MOb, Morbid obese;N, no; N/A, not available; O, Observational; OR, odds ratio; P, preserved; R&C, RCT/cohort; RCT, randomized control trial; RR, relative risk; S, small-study effect; 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.

following an acute MI. Protective associations were observed for both short-term (<30days) 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[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 III. Association between overweight and morality in transcatheter aortic valve implantation, cardiac surgery, atrial fibrillation and left ventricular assist device.

Author, Year	No	T	TP	Comparison	Outcome	Death/total	TM	Random effect (reported)	Random effect (re-analyzed)	I^2(*p*)	E	*p*-value (random)	*p*-value (fixed)	95% PI (random)	Largest effect	S	R/N/I†	Co	Evidence
Sannino et al[32]	3	C	TAVI	<20.0 *vs.* 20-24.9	30 days M	N/A	HR	1.61 (0.57, 4.53)	1.61 (0.57, 4.54)	71% (0.03)	0.40	0.366	0.122	0, 201229	1.54 (0.87, 2.73)	N	0/2/1	Y	Non-significant
Sannino et al[32]	6	C	TAVI	>30.0 *vs.* 20-24.9	30 days M	N/A	HR	0.87 (0.65, 1.16)	0.87 (0.65, 1.16)	58% (0.04)	0.33	0.348	0.194	0.39, 1.93	0.98 (0.94,1.02)	N	1/5/0	Y	Non-significant
Sannino et al[32]	5	C	TAVI	<20.0 *vs.* 20-24.9	All-cause M	N/A	HR	1.68 (1.09, 2.59)	1.68 (1.09, 2.59)	60% (0.04)	0.19	0.019	0.000	0.41, 0.83	1.25 (0.78, 2.00)	N	0/2/3	N	Weak
Sannino et al[32]	7	C	TAVI	>30.0 *vs.* 20-24.9	All-cause M	N/A	HR	0.79 (0.67, 0.93)	0.80 (0.66, 0.96)	0% (0.55)	0.11	0.015	0.015	0.61, 1.04	0.74 (0.57, 0.96)	N	2/5/0	Y	Weak
Mariscalco et al[33]	19	C	CS	UW *vs.* NL	30 days M	6064/141815	RR	1.77 (1.30, 2.42)	1.75 (1.34, 2.29)	78% (<0.01)	0.39	0.000	0.000	0.69, 4.47	1.93 (1.72, 2.16)	N	1/11/7	Y	Weak
Mariscalco et al[33]	27	C	CS	OW *vs.* NL	30 days M	12692/383146	RR	0.73 (0.66, 0.81)	0.73 (0.67, 0.80)	62% (<0.01)	0.07	0.000	0.000	0.55, 0.98	0.65 (0.62, 0.67)	N	9/18/0	Y	Weak
Mariscalco et al[33]	17	C	CS	Ob I *vs.* NL	30 days M	8659/246016	RR	0.76 (0.67, 0.86)	0.76 (0.67, 0.86)	62% (<0.01)	0.02	0.000	0.000	0.52, 1.10	0.61 (0.58, 0.65)	Y	5/12/0	Y	Weak
Mariscalco et al[33]	4	C	CS	Ob II *vs.* NL	30 days M	4956/122924	RR	0.65 (0.60, 0.71)	0.70 (0.56, 0.88)	42% (0.16)	0.19	0.002	0.000	0.31, 1.60	0.65 (0.59, 0.70)	N	2/2/0	Y	Suggestive
Mariscalco et al[33]	5	C	CS	Ob III *vs.* NL	30 days M	4782/110391	RR	0.83 (0.74, 0.94)	0.83 (0.74, 0.94)	0% (0.87)	0.20	0.002	0.002	0.68, 1.02	0.84 (0.74, 0.96)	N	1/4/0	Y	Suggestive
Zhu et al[34]	5	R&C	Afib	Ob *vs.* NL	CV M	N/A	RR	0.99 (0.79 to 1.24)	0.99 (0.79 to 1.24)	5 (0.381)	0.9	0.926	0.943	0.65 to 1.5	1.17 (0.83 to 1.65)	N	0/5/0	Y	No association
Zhu et al[34]	7	R&C	Afib	Ob *vs.* NL	All-cause M	N/A	RR	0.84 (0.64 to 1.1)	0.84 (0.64 to 1.1)	86 (<0.001)	0.59	0.202	<0.001	0.35 to 2	0.73 (0.65 to 0.82)	N	3/3/1	N	No association
Zhu et al[34]	5	R&C	Afib	OW *vs.* NL	CV M	N/A	RR	0.79 (0.58 to 1.08)	0.79 (0.58 to 1.08)	57 (0.053)	0.55	0.142	0.048	0.3 to 2.08	0.88 (0.67 to 1.15)	N	1/4/0	Y	No association
Zhu et al[34]	7	R&C	Afib	OW *vs.* NL	All-cause M	N/A	RR	0.78 (0.62 to 0.96)	0.78 (0.62 to 0.96)	82 (<0.001)	0.8	0.021	<0.001	0.38 to 1.57	0.67 (0.58 to 0.77)	N	5/1/1	Y	Weak
Zhu et al[34]	2	R&C	Afib	UW *vs.* NL	CV M	N/A	RR	2.49 (1.38 to 4.5)	2.49 (1.38 to 4.5)	0 (0.369)	<0.01	0.003	0.003	NA	2.91 (1.47 to 5.76)	NA	0/1/1	Y	N/A
Zhu et al[34]	3	R&C	Afib	UW *vs.* NL	All-cause M	N/A	RR	2.61 (2.21 to 3.09)	2.61 (2.21 to 3.09)	0 (0.557)	0.09	<0.001	<0.001	0.88 to 7.76	2.74 (2.26 to 3.33)	N	0/0/3	Y	Suggestive
Khan et al[35]	4	O	ALVAD	Ob *vs.* non-Ob	ST all-cause M	1828/5143	RR	0.79 (0.73 to 0.86)	0.79 (0.73 to 0.86)	0 (0.392)	0.81	<0.001	<0.001	0.66 to 0.95	0.78 (0.7 to 0.86)	N	2/2/0	Y	Convincing
Khan et al[35]	10	O	ALVAD	Ob *vs.* non-Ob	LT all-cause M	7308/16050	RR	0.94 (0.88 to 1.00)	0.95 (0.9 to 1.01)	44 (0.066)	0.68	0.082	<0.001	0.83 to 1.09	0.92 (0.89 to 0.95)	N	3/7/0	N	No association
Khan et al[35]	8	O	ALVAD	Ob *vs.* non-Ob	1-year all-cause M	4980/15254	RR	0.95 (0.87 to 1.04)	0.87 (0.79 to 0.96)	69 (0.002)	0.66	0.008	<0.001	0.66 to 1.15	0.82 (0.78 to 0.87)	N	3/5/0	Y	Weak
Khan et al[35]	5	O	ALVAD	Ob *vs.* non-Ob	2-year all-cause M	6787/14944	RR	0.95 (0.89 to 1.01)	0.95 (0.89 to 1.01)	55 (0.062)	0.46	0.117	<0.001	0.79 to 1.14	0.92 (0.89 to 0.95)	N	1/4/0	N	No association
Khan et al[35]	3	O	ALVAD	Ob *vs.* non-Ob	3-year all-cause M	241/870	RR	0.84 (0.61 to 1.15)	0.84 (0.61 to 1.15)	43 (0.173)	0.98	0.284	0.155	0.04 to 18.78	0.99 (0.69 to 1.41)	N	1/2/0	Y	No association

Abbreviations: Afib, atrial fibrillation; ALVAD , after LVAD inplantation; BMI, body mass index; C, cohort; CS, cardiac surgery; CV, cardiovascular; HR, hazard ratio; LVAD, left ventricular assist device; LT, long term; M, mortality; N, number; No, number of studies; N/A, not available; NL, normal; Ob, obese; P, preserved; R&C, RCT & cohort study; RCT, randomized control trial; RR, relative risk, S, small number of studies; ST, short term; T, type of metrics; TAVI, trans-catheter aortic valve implantation, 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.

suggestive because in those results, we had no similar or greater number of statistically significant individual studies compared to individual studies that were not significant[19].

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[6,19,20,22,23]. 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-hospitals 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 patient with low BMI or underweight. However, the only convincing evidence were for those with a 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[6,23], and in patients with low BMI with a RR of 2.65 (2.19 to 3.2) for all-cause mortality[20].

Both overweight and obesity had an impressive number of convincing evidences, all convergent toward a protective effect against mortality in all follow up periods[6,19-21,23]. 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[21]. Severe obesity did not have a valid protective effect vis-à-vis mortality in patient following PCI. All of the studies showed either weak evidence or no association with a non-statistical significance (*p*-values greater than 0.01) and 95% PI that includes the null hypothesis.

Heart Failure (HF)

All results showed that regardless of the type of study design and the characteristics of the participating population, underweight was associated with an increase in mortality, while overweight was associated with a decrease in

all-cause and cardiovascular mortality in HF patients. Compared to normal BMI, underweight increased all-cause mortality with one study having convincing evidence[27]. 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 increase 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) respectively[24,25], 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 HF[26].

In all studies among patients with chronic HF, the RR pointed towards a protective effect of obesity in term of all-cause and cardiovascular mortality[24,25]. However, none of the evidence was convincing. Moreover, one cohort study showed no association[25]. 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[24]. 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 mortality[30]. 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 association[31]. 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 evidences, respectively. Finally, for East Asian HF patients[26], 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 BMI[26].

Transcatheter Aortic Valve Implantation (TAVI)

One meta-analysis evaluated the association between BMI and mortality based on short term and long-term survival[32]. 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 evidence[33]. 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 group[34]. 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 BMI[35]. 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 underweight 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 evidences. 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[36,37]. 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[38]. 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[39].

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[10,40]. 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[8,9,36,37]. 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[41]. To note, obesity by itself is an independent predictor for CVDs even if it is not associated with any risk factors[42]. Historically, and up until the writing of this report, clinicians, rightfully so, consider obesity as detrimental for both CVD primary and secondary preventions efforts[42]. 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"[43-45]. This paradox has been proven repeatedly in other conditions such as hypertension and patients with congenital heart diseases[46].

The landmark Framingham study and a large body of evidence have laid ground to linking obesity as a strong risk factor for HF[47]. 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 systematic inflammation[43,48]. However, despite this gloomy association, scientists have explored a potential paradoxical protective effect[49] and growing body of research is showing survival benefits in obese patients with HF[19,50,51]. Even though the underlying physiological process is far from being comprehended[46]. The increase in lean muscle might play a central role in the protective process by increasing cardio-respiratory fitness index[52,53].

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[54,55]. However, comparable to those patients with HF, obesity was found to be paradoxically beneficial with more favorable prognosis[56-58]. The same shift in body composition is also thought to be at the roots of the described protective effects[46]. In addition to the benefits of increasing lean muscle mass, increase adiposity in obese patients have been proposed to provide protective properties[59] especially in those sub-set of patients with minimal systemic inflammation[60].

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[61]. Although more research is needed, several observational study also showed correlation between low BMI and cardiovascular disease[51,62]. Sarcopenia (involuntary weight loss), cardiac cachexia, and increased catabolic status were possible mechanisms of poor prognosis in lower BMI patients[63-65]. Our study also showed six convincing evidence that low BMI (or underweight) 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[66,67]. 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 survivals[68,69]. Similarly, supporting this hypothesis, low levels of leptin and adiponectin, such as cardiac cachexia, weight and adipose loss, have been associated with reduced survivals[68,70-73].

To note, BMI itself may not be an accurate measurement for adiposity or body composition since it also reflects lean body mass[74]. 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[74]. 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[75].

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[17] 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

obesity, whereas in other systemic reviews and meta-analysis, patients with BMI ≥30 were defined as high BMI[76]. 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.

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The authors' responsibilities were as follows— R.A.G., D.D.P. and J.I.S. formulated the research question and wrote and reviewed the report. D.D.P., J.Y.L. and J.I.S. did the literature search, extracted and selected articles, completed meta-analysis and wrote the report. All authors (R.A.G., J.Y.L., D.D.P., J.Y.K., K.H.L., S.H.H., J.W.Y., J.S.K., G.H.J., A.K., A.K., L.J., H.O, H.L., J.M.Y., M.S.K., S.W.L., D.K.Y., L.S., and J.I.S.) contributed to writing of the paper. The corresponding author had the final responsibility for the decision to submit for publication.

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References

1) Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, Mullany EC, Biryukov S, Abbafati C, Abera SF, Abraham JP, Abu-Rmeileh NM, Achoki T, AlBuhairan FS, Alemu ZA, Alfonso R, Ali MK, Ali R, Guzman NA, Ammar W, Anwari P, Banerjee A, Barquera S, Basu S, Bennett DA, Bhutta Z, Blore J, Cabral N, Nonato IC, Chang JC, Chowdhury R, Courville KJ, Criqui MH, Cundiff DK, Dabhadkar KC, Dandona L, Davis A, Dayama A, Dharmaratne SD, Ding EL, Durrani AM, Esteghamati A, Farzadfar F, Fay DF, Feigin VL, Flaxman A, Forouzanfar MH, Goto A, Green MA, Gupta R, Hafezi-Nejad N, Hankey GJ, Harewood HC, Havmoeller R, Hay S, Hernandez L, Husseini A, Idrisov BT, Ikeda N, Islami F, Jahangir E, Jassal SK, Jee SH, Jeffreys M, Jonas JB, Kabagambe EK, Khalifa SE, Kengne AP, Khader YS, Khang YH, Kim D, Kimokoti RW, Kinge JM, Kokubo Y, Kosen S, Kwan G, Lai T, Leinsalu M, Li Y, Liang X, Liu S, Logroscino G, Lotufo PA, Lu Y, Ma J, Mainoo NK, Mensah GA, Merriman TR, Mokdad AH, Moschandreas J, Naghavi M, Naheed A, Nand D, Narayan KM, Nelson EL, Neuhouser ML, Nisar MI, Ohkubo T, Oti SO, Pedroza A, Prabhakaran D, Roy N, Sampson U, Seo H, Sepanlou SG, Shibuya K, Shiri R, Shiue I, Singh GM, Singh JA, Skirbekk V, Stapelberg NJ, Sturua L, Sykes BL, Tobias M, Tran BX, Trasande L, Toyoshima H, van de Vijver S, Vasankari TJ, Veerman JL, Velasquez-Melendez G, Vlassov VV, Vollset SE, Vos T, Wang C, Wang X, Weiderpass E, Werdecker A, Wright JL, Yang YC, Yatsuya H, Yoon J, Yoon SJ, Zhao Y, Zhou M, Zhu S, Lopez AD, Murray CJ, Gakidou E. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2014; 384: 766-781.

2) National Institutes of Health. Clinical guidelines for the identification, evaluation, and treatment of overweight and obesity in adults-the evidence report. Obes Res 1998; 6: 51S-209S.

3) World Health Organization. Physical status: The use and interpretation of anthropometry: report of a WHO Expert Committee. World Health Organization, 1995.

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. JAMA 2013; 309: 71-82.

5) Wang L, Liu W, He X, Chen Y, Lu J, Liu K, Cao K, Yin P. Association of overweight and obesity with patient mortality after acute myocardial infarction: a meta-analysis of prospective studies. Int J Obes (Lond) 2016; 40: 220-228.
6) Lin GM, Li YH, Lin CL, Wang JH, Han CL. Relation of body mass index to mortality among patients with percutaneous coronary intervention in the drug-eluting stent era: a systematic review and meta-analysis. Int J Cardiol 2013; 168: 4459-4466.
7) Padwal R, McAlister FA, McMurray JJ, Cowie MR, Rich M, Pocock S, Swedberg K, Maggioni A, Gamble G, Ariti C, Earle N, Whalley G, Poppe KK, Doughty RN, Bayes-Genis A. The obesity paradox in heart failure patients with preserved versus reduced ejection fraction: a meta-analysis of individual patient data. Int J Obes (Lond) 2014; 38: 1110-1114.
8) Jeong GH, Lee KH, Kim JY, Eisenhut M, Kronbichler A, van der Vliet HJ, Hong SH, Shin JI, Gamerith G. Effect of statin on cancer incidence: an umbrella systematic review and meta-analysis. J Clin Med 2019; 8: 819.
9) Choi EK, Park HB, Lee KH, Park JH, Eisenhut M, van der Vliet HJ, Kim G, Shin JI. Body mass index and 20 specific cancers: re-analyses of dose-response meta-analyses of observational studies. Ann Oncol 2018; 29: 749-757.
10) Ioannidis JP. Integration of evidence from multiple meta-analyses: a primer on umbrella reviews, treatment networks and multiple treatments meta-analyses. CMAJ 2009; 181: 488-493.
11) Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009; 339: b2700.
12) Sacks HS, Berrier J, Reitman D, Ancona-Berk VA, Chalmers TC. Meta-analyses of randomized controlled trials. N Engl J Med 1987; 316: 450-455.
13) Fletcher J. What is heterogeneity and is it important? BMJ 2007; 334: 94-96.
14) Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, Carpenter J, Rucker G, Harbord RM, Schmid CH, Tetzlaff J, Deeks JJ, Peters J, Macaskill P, Schwarzer G, Duval S, Altman DG, Moher D, Higgins JP. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011; 343: d4002.
15) Kyrgiou M, Kalliala I, Markozannes G, Gunter MJ, Paraskevaidis E, Gabra H, Martin-Hirsch P, Tsilidis KK. Adiposity and cancer at major anatomical sites: umbrella review of the literature. BMJ 2017; 356: j477.
16) Graham PL, Moran JL. Robust meta-analytic conclusions mandate the provision of prediction intervals in meta-analysis summaries. J Clin Epidemiol 2012; 65: 503-510.
17) Niedziela J, Hudzik B, Niedziela N, Gasior M, Gierlotka M, Wasilewski J, Myrda K, Lekston A, Polonski L, Rozentryt P. The obesity paradox in acute coronary syndrome: a meta-analysis. Eur J Epidemiol 2014; 29: 801-812.
18) Lamelas P, Schwalm JD, Quazi I, Mehta S, Devereaux PJ, Jolly S, Yusuf S. Effect of body mass index on clinical events after acute coronary syndromes. Am J Cardiol 2017; 120: 1453-1459.
19) Oreopoulos A, Padwal R, Norris CM, Mullen JC, Pretorius V, Kalantar-Zadeh K. Effect of obesity on short- and long-term mortality postcoronary revascularization: a meta-analysis. Obesity (Silver Spring) 2008; 16: 442-450.
20) Sharma A, Vallakati A, Einstein AJ, Lavie CJ, Arbab-Zadeh A, Lopez-Jimenez F, Mukherjee D, Lichstein E. Relationship of body mass index with total mortality, cardiovascular mortality, and myocardial infarction after coronary revascularization: evidence from a meta-analysis. Mayo Clin Proc 2014; 89: 1080-1100.
21) Bundhun PK, Li N, Chen MH. Does an obesity paradox really exist after cardiovascular intervention?: a systematic review and meta-analysis of randomized controlled trials and observational studies. Medicine (Baltimore) 2015; 94: e1910.
22) Li YH, Lin GM, Lin CL, Wang JH, Han CL. Relation of body mass index to mortality among patients with percutaneous coronary intervention longer than 5 years follow-up: a meta-analysis. Int J Cardiol 2013; 168: 4315-4318.
23) Wang ZJ, Gao F, Cheng WJ, Yang Q, Zhou YJ. Body mass index and repeat revascularization after percutaneous coronary intervention: a meta-analysis. Can J Cardiol 2015; 31: 800-808.
24) Oreopoulos A, Padwal R, Kalantar-Zadeh K, Fonarow GC, Norris CM, McAlister FA. Body mass index and mortality in heart failure: a meta-analysis. Am Heart J 2008; 156: 13-22.
25) Sharma A, Lavie CJ, Borer JS, Vallakati A, Goel S, Lopez-Jimenez F, Arbab-Zadeh A, Mukherjee D, Lazar JM. Meta-analysis of the relation of body mass index to all-cause and cardiovascular mortality and hospitalization in patients with chronic heart failure. Am J Cardiol 2015; 115: 1428-1434.
26) Lin GM, Li YH, Yin WH, Wu YW, Chu PH, Wu CC, Hsu CH, Wen MS, Voon WC, Wang CC, Yeh SJ, Lin WS. The obesity-mortality paradox in patients with heart failure in Taiwan and a collaborative meta-analysis for East Asian patients. Am J Cardiol 2016; 118: 1011-1018.
27) Mahajan R, Stokes M, Elliott A, Munawar DA, Khokhar KB, Thiyagarajah A, Hendriks J, Linz D, Gallagher C, Kaye D, Lau D, Sanders P. Complex interaction of obesity, intentional weight loss and heart failure: a systematic review and meta-analysis. Heart 2020; 106: 58-68.

28) Milajerdi A, Djafarian K, Shab-Bidar S, Speakman JR. Pre- and post-diagnosis body mass index and heart failure mortality: a dose-response meta-analysis of observational studies reveals greater risk of being underweight than being overweight. Obes Rev 2018; 20: 252-261.

29) Qin W, Liu F, Wan C. A U-shaped association of body mass index and all-cause mortality in heart failure patients: A dose-response meta-analysis of prospective cohort studies. Cardiovasc Ther 2017; 35: e12232.

30) Aune D, Sen A, Norat T, Janszky I, Romundstad P, Tonstad S, Vatten LJ. Body mass index, abdominal fatness, and heart failure incidence and mortality: a systematic review and dose–response meta-analysis of prospective studies. Circulation 2016; 133: 639-649.

31) Zhang JX, Liu YX, Xia CL, Chu P, Qu XL, Zhu LL, Chen SL. Risks of incident heart failure with preserved ejection fraction in Chinese patients hospitalized for cardiovascular diseases. J Geriatr Cardiol 2019; 16: 885-893.

32) Sannino A, Schiattarella GG, Toscano E, Gargiulo G, Giugliano G, Galderisi M, Losi MA, Stabile E, Cirillo P, Imbriaco M, Grayburn PA, Trimarco B, Esposito G. Meta-analysis of effect of body mass index on outcomes after transcatheter aortic valve implantation. Am J Cardiol 2017; 119: 308-316.

33) Mariscalco G, Wozniak MJ, Dawson AG, Serraino GF, Porter R, Nath M, Klersy C, Kumar T, Murphy GJ. Body mass index and mortality among adults undergoing cardiac surgery: a nationwide study with a systematic review and meta-analysis. Circulation 2017; 135: 850-863.

34) Zhu W, Wan R, Liu F, Hu J, Huang L, Li J, Hong K. Relation of body mass index with adverse outcomes among patients with atrial fibrillation: a meta-analysis and systematic review. J Am Heart Assoc 2016; 5: e004006.

35) Khan MS, Yuzefpolskaya M, Memon MM, Usman MS, Yamani N, Garan AR, Demmer RT, Colombo PC. Outcomes associated with obesity in patients undergoing left ventricular assist device implantation: a systematic review and meta-analysis. ASAIO J 2020; 66: 401-408.

36) Tsilidis KK, Kasimis JC, Lopez DS, Ntzani EE, Ioannidis JP. Type 2 diabetes and cancer: umbrella review of meta-analyses of observational studies. BMJ 2015; 350: g7607.

37) Theodoratou E, Tzoulaki I, Zgaga 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.

39) Park JH, Eisenhut M, van der Vliet HJ, Shin JI. Statistical controversies in clinical research: Overlap and errors in the meta-analyses of microRNA genetic association studies in cancers. Ann Oncol 2017; 28: 1169-1182.

40) Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P. Summarizing systematic reviews: Methodological development, conduct and reporting of an umbrella review approach. Int J Evid Based Healthc 2015; 13: 132-140.

41) World Health Organization. Obesity and overweight fact sheet. Available at: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.

42) Lavie CJ, Arena R, Alpert MA, Milani RV, Ventura HO. Management of cardiovascular diseases in patients with obesity. Nat Rev Cardiol 2018; 15: 45-56.

43) Carbone S, Lavie CJ, Arena R. Obesity and heart failure: focus on the obesity paradox. Mayo Clin Proc 2017; 92: 266-279.

44) Elagizi A, Kachur S, Lavie CJ, Carbone S, Pandey A, Ortega FB, Milani RV. An overview and update on obesity and the obesity paradox in cardiovascular diseases. Prog Cardiovasc Dis 2018; 61: 142-150.

45) Lavie CJ, De Schutter A, Parto P, Jahangir E, Kokkinos P, Ortega FB, Arena R, Milani RV. Obesity and prevalence of cardiovascular diseases and prognosis—the obesity paradox updated. Prog Cardiovasc Dis 2016; 58: 537-547.

46) Carbone S, Canada JM, Billingsley HE, Siddiqui MS, Elagizi A, Lavie CJ. Obesity paradox in cardiovascular disease: where do we stand? Vasc Health Risk Manag 2019; 15: 89-100.

47) Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG, Kannel WB, Vasan RS. Obesity and the risk of heart failure. N Engl J Med 2002; 347: 305-313.

48) Ballak DB, Stienstra R, Tack CJ, Dinarello CA, van Diepen JA. IL-1 family members in the pathogenesis and treatment of metabolic disease: Focus on adipose tissue inflammation and insulin resistance. Cytokine 2015; 75: 280-290.

49) Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Woo MA, Tillisch JH. The relationship between obesity and mortality in patients with heart failure. J Am Coll Cardiol 2001; 38: 789-795.

50) Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. J Am Coll Cardiol 2009; 53: 1925-1932.

51) Kenchaiah S, Pocock SJ, Wang D, Finn PV, Zornoff LA, Skali H, Pfeffer MA, Yusuf S, Swedberg K, Michelson EL, Granger CB, McMurray JJ, Solomon SD. Body mass index and prognosis in patients with chronic heart failure: insights from the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program. Circulation 2007; 116: 627-636.

52) Carbone S, Popovic D, Lavie CJ, Arena R. Obesity, body composition and cardiorespiratory fitness in heart failure with preserved ejection fraction. Future Cardiol 2017; 13: 451-463.

53) Ventura HO, Carbone S, Lavie CJ. Muscling up to improve heart failure prognosis. Eur J Heart Fail 2018; 20: 1588-1590.

54) De Rosa R, Vasa-Nicotera M, Leistner DM, Reis SM, Thome CE, Boeckel JN, Fichtlscherer S, Zeiher AM. Coronary atherosclerotic plaque characteristics and cardiovascular risk factors- Insights from an optical coherence tomography study. Circ J 2017; 81: 1165-1173.

55) Lovren F, Teoh H, Verma S. Obesity and atherosclerosis: mechanistic insights. Can J Cardiol 2015; 31: 177-183.

56) De Schutter A, Lavie CJ, Milani RV. The impact of obesity on risk factors and prevalence and prognosis of coronary heart disease-the obesity paradox. Prog Cardiovasc Dis 2014; 56: 401-408.

57) Romero-Corral A, Montori VM, Somers VK, Korinek J, Thomas RJ, Allison TG, Mookadam F, Lopez-Jimenez F. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. Lancet 2006; 368: 666-678.

58) Lavie CJ, Carbone S, Agarwal MA. An obesity paradox with myocardial infarction in the elderly. Nutrition 2018; 46: 122-123.

59) Lavie CJ, De Schutter A, Patel DA, Romero-Corral A, Artham SM, Milani RV. Body composition and survival in stable coronary heart disease: impact of lean mass index and body fat in the "obesity paradox". J Am Coll Cardiol 2012; 60: 1374-1380.

60) De Schutter A, Kachur S, Lavie CJ, Boddepalli RS, Patel DA, Milani RV. The impact of inflammation on the obesity paradox in coronary heart disease. Int J Obes (Lond) 2016; 40: 1730-1735.

61) Marques MB, Langouche L. Endocrine, metabolic, and morphologic alterations of adipose tissue during critical illness. Crit Care Med 2013; 41: 317-325.

62) Park D, Lee J-H, Han S. Underweight: another risk factor for cardiovascular disease? A cross-sectional 2013 Behavioral Risk Factor Surveillance System (BRFSS) study of 491,773 individuals in the USA. Medicine 2017; 96: e8769.

63) Anker SD, Ponikowski P, Varney S, Chua TP, Clark AL, Webb-Peploe KM, Harrington D, Kox WJ, Poole-Wilson PA, Coats AJ. Wasting as independent risk factor for mortality in chronic heart failure. Lancet 1997; 349: 1050-1053.

64) Berry C, Clark AL. Catabolism in chronic heart failure. Eur Heart J 2000; 21: 521-532.

65) Anker SD, Negassa A, Coats AJ, Afzal R, Poole-Wilson PA, Cohn JN, Yusuf S. Prognostic importance of weight loss in chronic heart failure and the effect of treatment with angiotensin-converting-enzyme inhibitors: an observational study. Lancet 2003; 361: 1077-1083.

66) Dorner TE, Rieder A. Obesity paradox in elderly patients with cardiovascular diseases. Int J Cardiol 2012; 155: 56-65.

67) Clerico A, Giannoni A, Vittorini S, Emdin M. The paradox of low BNP levels in obesity. Heart Fail Rev 2012; 17: 81-96.

68) Kistorp C, Faber J, Galatius S, Gustafsson F, Frystyk J, Flyvbjerg A, Hildebrandt P. Plasma adiponectin, body mass index, and mortality in patients with chronic heart failure. Circulation 2005; 112: 1756-1762.

69) Feldman AM, Combes A, Wagner D, Kadakomi T, Kubota T, Li YY, McTiernan C. The role of tumor necrosis factor in the pathophysiology of heart failure. J Am Coll Cardiol 2000; 35: 537-544.

70) Filippatos GS, Tsilias K, Venetsanou K, Karambinos E, Manolatos D, Kranidis A, Antonellis J, Kardaras F, Anthopoulos L, Baltopoulos G. Leptin serum levels in cachectic heart failure patients. Relationship with tumor necrosis factor-alpha system. Int J Cardiol 2000; 76: 117-122.

71) McGaffin KR, Moravec CS, McTiernan CF. Leptin signaling in the failing and mechanically unloaded human heart. Circ Heart Fail 2009; 2: 676-683.

72) Hascoet S, Elbaz M, Bongard V, Bouisset F, Verdier C, Vindis C, Genoux A, Taraszkiewicz D, Perret B, Galinier M, Carrié D, Ferrières J, Ruidavets JB. Adiponectin and long-term mortality in coronary artery disease participants and controls. Arterioscler Thromb Vasc Biol 2013; 33: e19-29.

73) Wannamethee SG, Whincup PH, Lennon L, Sattar N. Circulating adiponectin levels and mortality in elderly men with and without cardiovascular disease and heart failure. Arch Intern Med 2007; 167: 1510-1517.

74) Nuttall FQ. Body mass index: obesity, BMI, and health: a critical review. Nutr Today 2015; 50: 117-128.

75) Wells JCK, Fewtrell MS. Measuring body composition. Arch Dis Child 2006; 91: 612-617.

76) Lafranca JA, JN IJ, Betjes MG, Dor FJ. Body mass index and outcome in renal transplant recipients: a systematic review and meta-analysis. BMC Med 2015; 13: 111.