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Effect of the Obesity Paradox on Mortality in Patients with Acute Coronary Syndrome: A Comprehensive Meta-analysis of the Literature

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Background: The protective effect of obesity in patients with acute coronary syndrome undergoing percutaneous coronary intervention or bypass surgery has been described as the obesity paradox in the literature.

Aims: In this comprehensive meta-analysis, we aimed to investigate the pooled effect of the obesity paradox on mortality in acute coronary syndrome patients.

Study Design: Systemic meta-analysis and metaregression.

Methods: We searched PubMed, Google Scholar, and the Cochrane Library for eligible studies that compared the mortality rates between body mass index cut-off points in acute coronary syndrome patients. This meta-analysis comprised 54 studies with 534,903 patients. Random- and fixed-effect models were used to calculate pooled effects sizes in the presence of moderately high and low heterogeneity between studies, respectively. A metaregression analysis was used to detect possible causes of heterogeneity. A dose-response meta-analysis was also conducted to detect the association between mortality risk and body mass index.

Results: Overweight patients had lower mortality risk for 30-day (RR =0.69; 0.62-0.76, $p < 0.01$) and long-term (RR =0.73; 0.70-0.77, $p < 0.01$) mortality than normal-weight patients. The 30-day mortality risk was higher in low-weight patients than in normal-weight patients (RR =1.74; 1.39-2.18, $p < 0.01$). Meta-regression could not explain the possible causes of between-study heterogeneity. Patients with body mass index <21.5 kg/m^2 and >40 kg/m^2 had a higher risk of mortality, which was lowest at approximately 30 kg/m^2.

Conclusion: Low-weight and overweight acute coronary syndrome patients had higher mortality risk than normal-weight patients. A U-shaped nonlinear association was detected between body mass index and mortality risk.

INTRODUCTION

The prevalence of obesity has considerably increased worldwide and has become a major social and health issue. Obesity is associated with multiple cardiometabolic abnormalities, such as metabolic syndrome, diabetes mellitus, hypertension, and hyperlipidemia.[1] Moreover, obesity is a major predictor of future cardiovascular and all-cause mortality, accounting for one in every five deaths globally.[2] Although obesity is a predisposing factor for cardiovascular disease, when acute cardiovascular decompensation develops, such as in congestive heart failure, obese patients may have a survival benefit, a phenomenon known as the "obesity paradox".[3] Furthermore, it has been hypothesized that obese persons might have better outcomes following coronary artery bypass surgery.[4] In the current literature, although some studies show favorable cardiovascular outcomes and mortality in obese patients with acute coronary syndrome (ACS), many other investigations reveal a negative cardiovascular impact of obesity. Therefore, in this meta-analysis, we intended to investigate the role of the obesity paradox in mortality in patients with ACS.

MATERIALS AND METHODS

Data Gathering

We conducted the meta-analysis in line with the recommendations of the Cochrane Collaboration. We searched PubMed, Google Scholar, and the Cochrane Library for relevant articles using the following keywords: *obesity, obesity paradox, acute coronary syndrome, percutaneous coronary intervention, ST elevation myocardial infarction, non-ST elevation myocardial infarction, unstable angina,*

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and body mass index (BMI). After deleting duplicate reports, 1,006 out of 1,348 reports were retained. After reviewing the summaries of these papers, we removed 956 of them and left 83 for full-text review. We eliminated 39 studies from the meta-analysis after reviewing the full texts because they had inappropriate research designs or non-ACS populations, utilized inaccurate data to evaluate effect magnitude, or were review articles. Thus, our meta-analysis ultimately included 54 studies (Figure 1).[1-3,5-55] Our meta-analysis was registered in the PROSPERO database (CRD42022355750).

Study Evaluation

All possible studies were systematically explored by two authors (S.F., C.T.) for their applicability and likelihood of bias. The studies were evaluated using the following criteria: i-) studies that assessed mortality based on BMI, ii-) studies that published the mortality data, and iii-) studies that included only patients with ACS. Finally, we removed publications where the effect size and standard error could not be estimated. There were no limitations on sample size, follow-up period, or language.

Quality Assessment and Data Extraction

Two independent authors reviewed published studies that fulfilled the eligibility criteria, while a third reviewer resolved any discrepancies between the two reviewers. The quality of the observational cohort studies included in this analysis was assessed using the Newcastle-Ottawa standard ratings system. Based on the research population, study consistency, and outcome of interest, studies scored up to 9 points on that scale. A score of 0-5 on the Newcastle-Ottawa scale indicates poor quality, whereas a score of 6-9 indicates excellent quality. The Robin-I risk of bias tools, as outlined in the *Cochrane Handbook for Systematic Reviews*, were used to assess the risk of bias of nonrandomized trials.

Clinical Endpoints

Thirty-day and long-term mortality were the main endpoints assessed in this meta-analysis.

Statistical Analysis

All statistics were calculated using R software v. 3.6.3 (R statistical software, Institute for Statistics and Mathematics, Vienna, Austria). The "metabin" function in the "meta" package was used to estimate pooled risk ratios with 95% confidence intervals between the compared groups. The between-study heterogeneity was assessed with the Higgins I^2 and Cochran Q tests. A heterogeneity of <25% was accepted as low, 25%-75% as moderate, and >75% as high. In the presence of moderate to high heterogeneity ($I^2 > 25\%$), the pooled effect size was computed using the random-effect model, whereas in the context of low heterogeneity ($I^2 < 25\%$), the fixed-effect model was calculated. To investigate potential publication bias, Egger's regression test was used and visualized with a funnel plot. When a potential publication bias was detected either with the regression test or funnel plot, a Duval and Tweedie Trim and Fill method was used to obtain a bias-adjusted estimation of the pooled effect size. To identify the likely source of between-study heterogeneity, outlier and influence analyses were conducted. A sensitivity analysis was conducted by excluding outliers and influential studies from the meta-analysis. Furthermore, a metaregression analysis with potential covariates was performed to explain the causes of heterogeneity between studies. Finally, a dose-response meta-analysis was used to evaluate the relationship between BMI and all-cause death. To evaluate statistical significance, a two-tailed *p*-value of 0.05 was utilized.

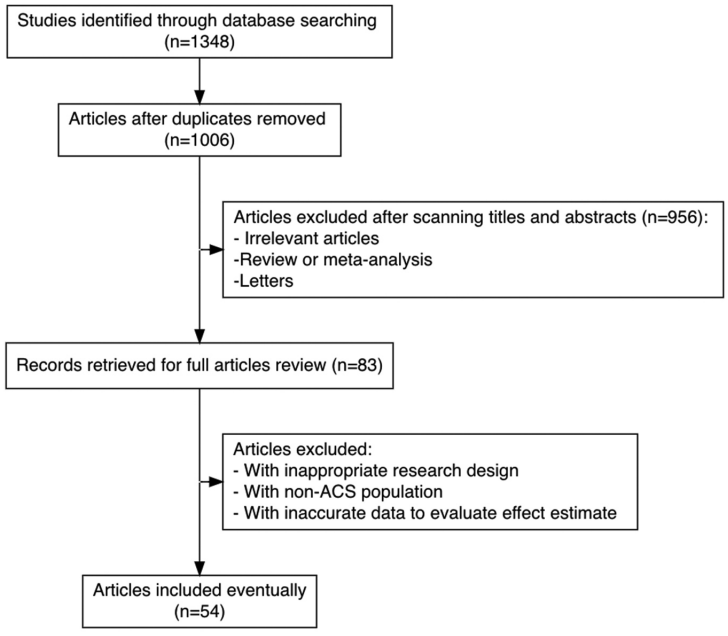


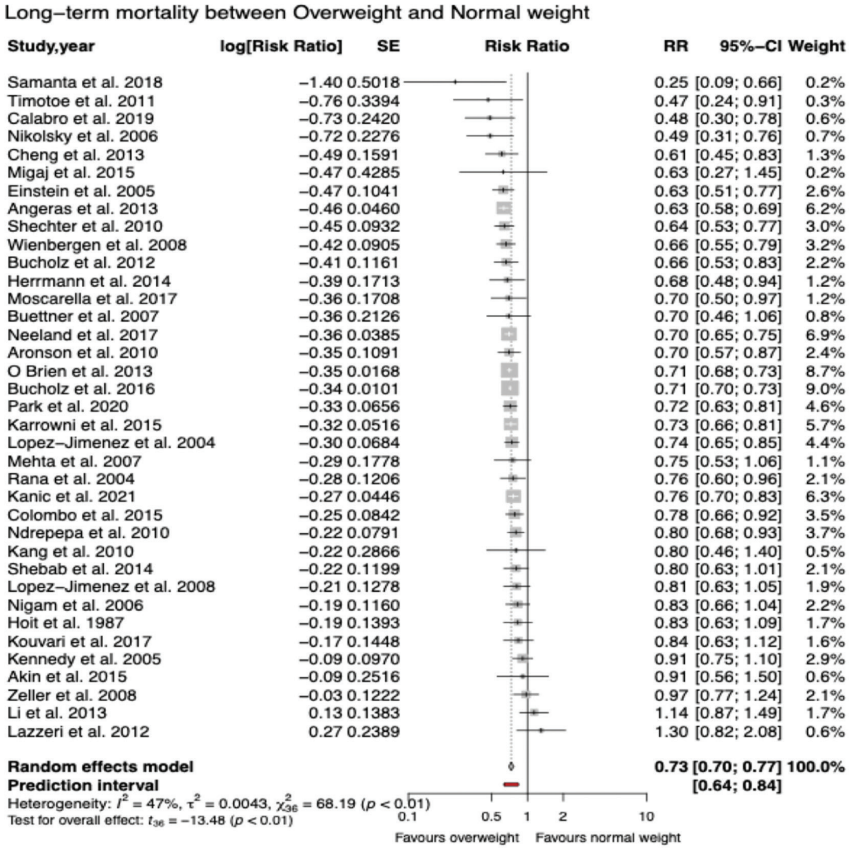
FIG. 1. Flowchart of the study selection for the meta-analysis.

TABLE 1. All Studies Included in the Meta-analysis.

Study	Year	Country	Number of patients	BMI categories	Follow-up time	Outcomes	Age (mean, years)	Male sex	NOS
Lopez-Jimenez et al.[5]	2004	USA	2,277	<25, 2-5-29.9, >30	10 years	Long-term mortality	NA	57.6	8
Rana et al.[6]	2004	USA	1,898	18.5-24.9, 25-29.9, 30-34.9, >35	3.7 years	Long-term mortality	61.4	69.4	8
Eisenstein et al.[7]	2005	United Kingdom	15,071	18.5-24.9, 25-29.9, 30-34.9, >35	1 year	Long-term mortality, 30-day mortality	59.3	72.7	9
Nikolsky et al.[8]	2006	USA	2,035	<25, 25-29.9, >30	1 year	Long-term mortality, 30-day mortality	59.6	73.1	9
Buettner et al.[9]	2007	Germany	1,676	<18.5, 18.5-24.9, 25-29.9,30-34.9, >35	3 years	Long-term mortality, 30-day mortality	64.8	71.4	8
Mehta et al.[10]	2007	USA	2,325	<25, 25-29.9, >30	1 year	Long-term mortality, in-hospital mortality	60.2	73.8	8
Lopez-Jimenez et al.[11]	2008	USA	2,318	<20, 20-24.9, 25-29.9, 30-40, >40	median 29 months	Long-term mortality	60.9	55.9	9
Wienbergen et al.[12]	2008	Germany	10,534	18.5-24.9, 25-29.9, >30	1 year	Long-term mortality, in-hospital mortality	65.8	70.2	8
Aronson et al.[13]	2010	Israel	2,157	<18.5, 18.5-20.9, 21-23.4, 23.5-24.9, 25-26.4, 26.5-27.9, 28-29.9, 30-34.9, >35	mean 26 months	Long-term mortality	61.1	78.7	8
Shechter et al.[14]	2010	USA	5,751	<18.5, 18.5-24.9,25-29.9, >30	1 year	Long-term mortality, 30-day mortality	63.2	60.4	7
Timóteo et al.[15]	2011	Portugal	539	<25, 25-29.9, >30	1 year	Long-term mortality, in-hospital mortality	61.8	77.4	7
Bucholz et al.[16]	2012	USA	6,359	18.5-24.9, 25-29.9, 30-34.9, >35	1 year	Long-term mortality, 30-day mortality	59.7	67.4	7
Lazzeri et al.[17]	2012	Italy	864	<20, 20-25, 25-29.9, >30	1 year	Long-term mortality, in-hospital mortality	60.2	81.9	7
Herrmann et al.[18]	2014	USA	4,477	<24.5, 24.5-27.08, 27.08-30.12, >30.12	3 years	Long-term mortality	60.9	61.2	8
Colombo et al.[19]	2015	Germany	4,054	18.5-24.9, 25-29.9, >30	12 years	Long-term mortality	60.4	76.1	8
Kang et al.[20]	2010	South Korea	3,824	<18.5, 18.5-23, 23-27.5, >27.5	1 year	Long-term mortality, 30-day mortality	61.1	75.7	9
Moscarella et al.[21]	2017	Spain	1,421	<25, 25-29.9, >30	5 years	Long-term mortality	61.2	83	9
Ndrepepa et al.[22]	2010	Germany	9,146	12.8-24.3, 24.3-26.4, 26.4-29.1, >29.1	1 year	Long-term mortality	66.3	73.9	7
Zeller et al.[23]	2008	France	2,229	<24, 24-28, >28	1 year	Long-term mortality	67	73.4	7
Nigam et al.[24]	2006	USA	894	<25, 25-29.9, >30	10 years	Long-term mortality	63.1	68.9	9
Hoit et al.[25]	1987	USA	1,760	<25, 25-29.9, >30	1 year	Long-term mortality, in-hospital mortality	63.1	75.4	7
Kennedy et al.[26]	2005	Sweden	5,388	<22, 22-24.9, 25-29.9, >30	median 30 months	Long-term mortality	67.3	71.3	9
O Brien et al.[27]	2013	Denmark	37,655	<18.5, 18.5-24.9, 25-29.9, 30-34.9, 35-39.9, >40	3 years	Long-term mortality	77.6	48.1	9
Fukuoka et al.[3]	2019	Japan	1,634	<20, 20-24.9, >25	2 years	Long-term mortality, 30-day mortality	68	78.6	8
Cheng et al.[28]	2013	Taiwan	1,298	<18.5, 18.5-24, 24-27, >27	5 years	Long-term mortality, 30-day mortality	63.6	82.7	7
Bucholz et al.[29]	2016	USA	124,981	18.5-24.9, 25-29.9, 30-34.9, >35	1 year	Long-term mortality	75.8	56.9	8
Angeras et al.[1]	2013	Sweden	38,667	<18.5, 18.5-21, 21-23.5, 23.5-25, 25-26.5, 26.5-28, 28-30, 30-35, >35	3.5 years	Long-term mortality	67	77.4	8

TABLE 1. Continued.

Study	Year	Country	Number of patients	BMI categories	Follow-up time	Outcomes	Age (mean, years)	Male sex	NOS
Samanta et al.[30]	2018	Australia	380	18.5-24.9, 25-29.9, >30	1 year	Long-term mortality	58	80	7
Park et al.[31]	2020	Korea	6,978	<18.5, 18.5-22.9, 23-24.9, 25-29.9, >30	median 5 years	Long-term mortality	62.9	63.2	9
Migaj et al.[32]	2015	Poland	341	18.5-24.9, 25-29.9, >30	18 months	Long-term mortality	64.2	73.9	8
Shebab et al.	2014	United Arab Emirates	4,379	<25, 25-29.9, >30	NA	Long-term mortality, in-hospital mortality	56.6	80.3	7
Kouvari et al.[34]	2017	Greece	1,000	<25, 25-29.9, >30	10 years	Long-term mortality, in-hospital mortality	64.7	76.1	8
Calabrò et al.[2]	2019	Italy	1,209	<25, 25-29.9, >30	2 years	Long-term mortality	66.1	72.6	9
Akin et al.[35]	2015	Germany	890	<25, 25-29.9, >30	1 year	Long-term mortality, in-hospital mortality	63.1	76.9	8
Li et al.[36]	2013	China	1,429	18.5-24, 24-28, >28	1 year	Long-term mortality	NA	NA	8
Karrowni et al.[37]	2015	USA	6,346	18.5-24.9, 25-29.9, 30-34.9, >35	7 years	Long-term mortality	NA	NA	7
Kanic et al.[38]	2021	Slovenia	6,496	<18.5, 18.5-24.9, 25-29.9, 30-34.9, 35-39.9, >40	12 years	Long-term mortality, 30-day mortality	64.4	69	8
Neeland et al.[39]	2017	USA	19,499	18.5-24.9, 25-29.9, 30-34.9, 35-39.9, >40	3 years	Long-term mortality	74.1	62	8
Diercks et al.[40]	2005	USA	80,845	<18.5, 18.5-24.9,25-29.9, 30-34.9, 35-39.9, >40	In-hospital	In-hospital mortality	67.3	60.4	8
Goldberg et al.[41]	2006	USA	3,513	<25, 25-29.9, 30-34.9, >35	In-hospital	In-hospital mortality	70.4	57.2	8
Iakobishvili et al.[42]	2006	Israel	164	<25, 25-29.9, >30	30 days	30-day mortality	62	75	7
Wells et al.[43]	2006	USA	284	<20, 20-24.9, 25-29.9, 30-34.9, >35	In-hospital	In-hospital mortality	57.5	68.3	7
Mehta et al.[44]	2008	USA	7,630	20-24.9, 25-29.9, >30	In-hospital	In-hospital mortality	62.8	74.5	8
Hadi et al.[45]	2009	United Arab Emirates	7,843	<25, 25-29.9, >30	In-hospital	In-hospital mortality	NA	NA	7
Mahaffey et al.[46]	2010	USA	9,837	<20, 20-24.9, 25-29.9,30-34.9, >35	30 days	30-day mortality	67.6	66.2	8
Das et al.[47]	2011	USA	49,329	18.5-24.9, 25-29.9, 30-34.9, 35-39.9, >40	In-hospital	In-hospital mortality	62.2	70.5	8
Camprubi et al.[48]	2012	Spain	824	<25, 25-29.9, >30	In-hospital	In-hospital mortality	65.8	73.5	7
Witassek et al.[49]	2014	Switzerland	5,833	<18.5, 18.5-24.9, 25-29.9, 30-34.9, >35	In-hospital	In-hospital mortality	62.8	91.7	8
Kosuge et al.[50]	2008	Japan	3,076	<20, 20-24.9, 25-29.9, >30	In-hospital	In-hospital mortality	66.1	74.1	7
Mobeirek Abdulelah et al.[51]	2014	Saudi Arabia	3,469	<25, 25-29.9, 30-39.9, >40	In-hospital	In-hospital mortality	57.9	77.6	8
Ratwatte et al.[52]	2020	Australia	8,503	<18.5, 18.5-24.9, 25-29.9, 30-39.9, >40	In-hospital	In-hospital mortality	64	72	8
Kim et al.[53]	2021	Korea	2,489	<18.5, 18.5-23, 23-27.5, >27.5	In-hospital	In-hospital mortality	84.3	54.6	8
Yokoyamo et al.[55]	2019	Japan	517	<21.9, 21.9-24, 24-26, >26	6 years	Long-term mortality	65.6	78.3	8
Kim et al.[54]	2019	Korea	10,568	<22, 22-26, >26	1 year	Long-term mortality	61.8	75.9	8



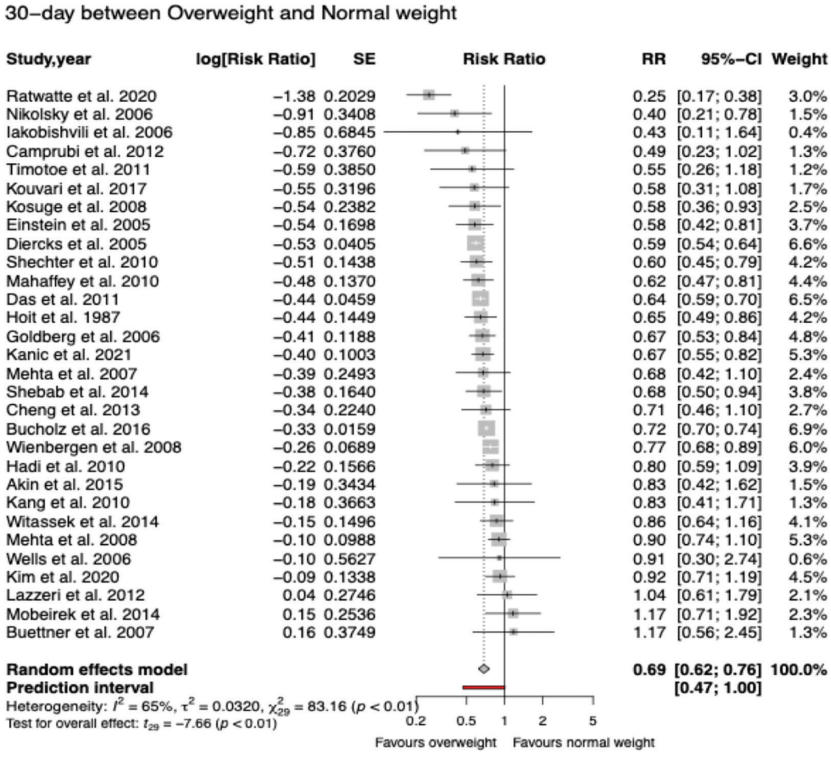
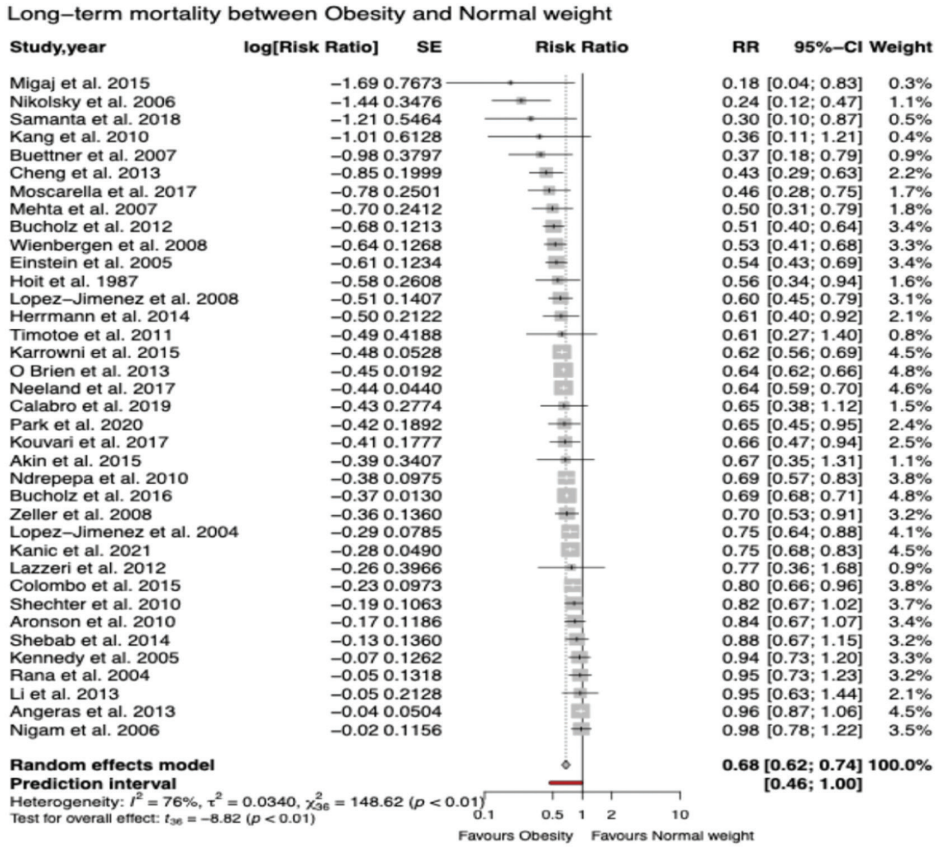


FIG. 2. Forest plots of pooled effect sizes between overweight and normal-weight patients for 30-day and long-term mortalities.



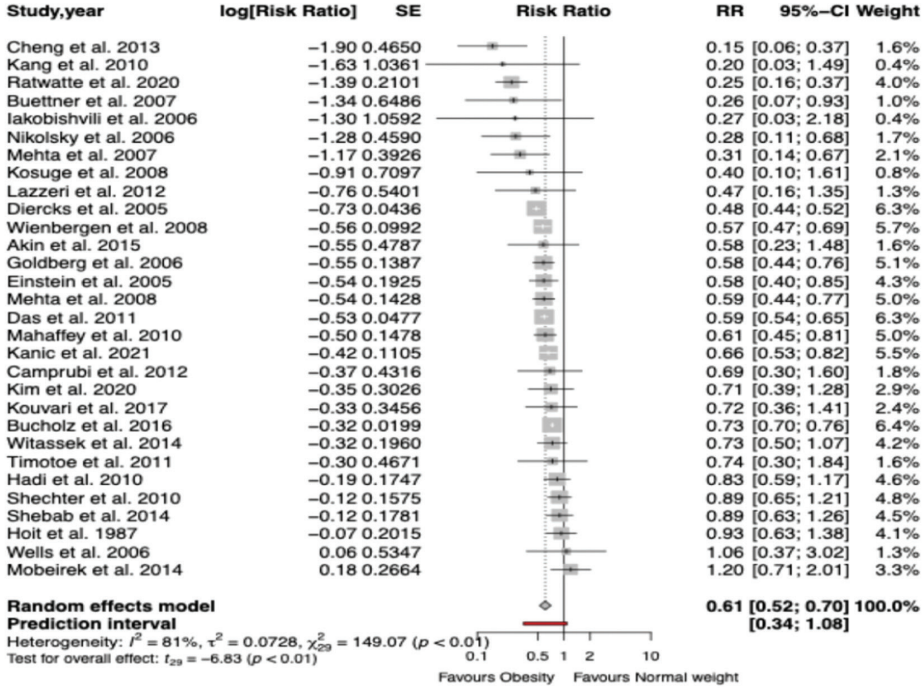


FIG. 3. Forest plots of pooled effect sizes between obese and normal-weight patients for 30-day and long-term mortalities.

RESULTS

This meta-analysis consisted of 54 studies with 534,903 patients. The quality assessments of all studies were adequate (Table 1). All of the studies except one (Nikolsky et al.[8]) had a moderate risk of bias due to the selection of participants (Supplementary File 1). The overweight patients had lower 30-day (RR =0.69, 0.62-0.76, $p < 0.01$, $I^2 = 65\%$) and long-term mortality (RR =0.73, 0.70-0.77, $p < 0.01$, $I^2 = 47\%$) than patients with normal weight (Figure 2). The 30-day and long-term mortalities were lower in obese patients than in normal-weight patients (RR =0.61, 0.52-0.70, $p < 0.01$, I^2 =81%, RR =0.68, 0.62-0.74, $p < 0.01$, $I^2 = 76\%$; respectively) (Figure 3). Patients with low weight had higher mortality rates than patients with normal weight for 30-day and long-term mortality (RR =1.74, 1.39-2.18, $p < 0.01$, $I^2 = 40\%$, RR =2.06, 1.61-2.65, $p < 0.01$, $I^2 = 92\%$; respectively) (Figure 4). Three studies (Nikolsky et al.,[8] Nigam et al.,[24] and Angeras et al.[1]) were detected as outliers, and Angeras et al.[1] was an influential study in the comparison of long-term mortality between obese and normal-weight persons. In the sensitivity analysis, the pooled effect was still significant after removing these three studies, but with a lower heterogeneity (RR =0.67, 0.62-0.73, $p < 0.001$; $I^2 = 60.9\%$). There may have been publication bias in the pooled estimate of long-term mortality between obesity and normal weight, which had a small study effect (Supplementary file 2). To address the bias, a bias-adjusted estimation was recalculated using the Duval and Tweedie Trim and Fill method. A bias-adjusted estimate was recalculated by adding six studies for missing studies and the result did not change (RR =0.68, 0.63-0.74, $p < 0.001$, $I^2 = 59.5$). Three studies (Cheng et al.,[28] Mobeirek Abdulelah et al.,[51] and Ratwatte et al.[52]) were detected as outliers, and Diercks et al.[40] was an influential study for the comparison of 30-day mortality between obesity and normal weight. The effect estimate did not change after removing these studies, but with a lower heterogeneity (RR =0.66, 0.60-0.72, $p < 0.001$, $I^2 = 48.7\%$). The study reported by O Brien et al.[27] in 2015 was detected as an outlier study, and Angeras et al.[1] and Park et al.[31] were influential studies for long-term mortality between low and normal-weight patients. Therefore, we recalculated the pooled effect size after removing these studies. There was still a significant higher risk of mortality in the long term between patients with low and normal weight (RR = 1.96, 1.45-2.65, $p = 0.0009$; $I^2 = 68\%$).

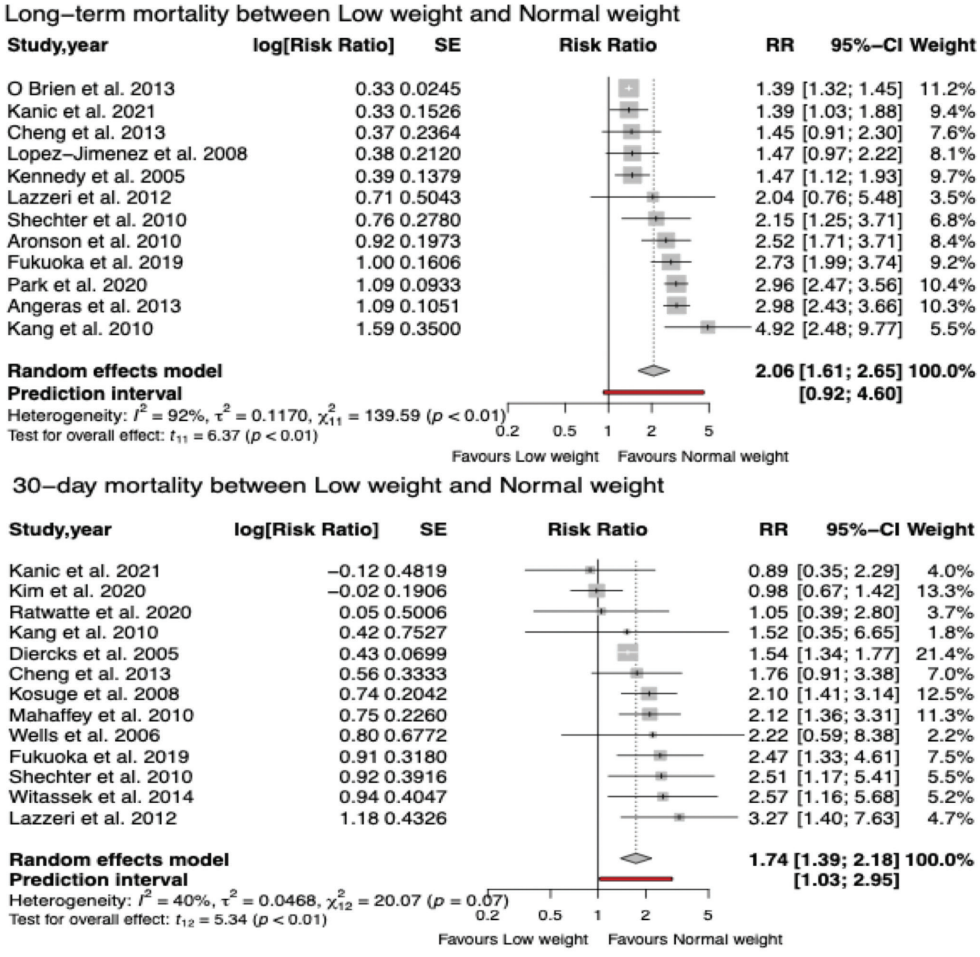


FIG. 4. Forest plots of pooled effect sizes between low-weight and normal-weight patients for 30-day and long-term mortalities.

Metaregression

A metaregression analysis was used to evaluate the underlying cause of between-study heterogeneity. We used covariates such as age, hypertension, diabetes mellitus, hyperlipidemia, prior MI, study year, ethnicity, follow-up time, male sex, cigarette smoking, congestive heart failure, cancer, and chronic obstructive pulmonary disease for the metaregression analysis. However, there was high multicollinearity between variables except for age, study year, follow-up time, and ethnicity. Thus, metaregression was conducted with these variables and none of them was detected as an underlying cause of heterogeneity for 30-day mortality between obese and normal-weight patients. For long-term mortality, only follow-up time seemed to contribute to the heterogeneity between obese and normal-weight patients as it explained 33.4% of the heterogeneity ($p = 0.013$).

Dose-response Meta-analysis

A dose-response meta-analysis was conducted to detect the association between BMI and all-cause mortality as proposed by Orsini et al.[56] and Greenland and Longnecker[57] Due to a nonlinear relationship between BMI and all-cause mortality, a two-stage dose response meta-analysis with restricted cubic splines and three knots (0.35, 0.65, and 0.95) was used (Figure 5). There was a U-shaped nonlinear diagram, with higher mortality risk for BMI < 21.5 kg/m^2 and >40 kg/m^2, whereas the lowest mortality risk was detected at approximately 30 kg/m^2.

DISCUSSION

This meta-analysis demonstrated that overweight patients with ACS had lower 30-day and long-term mortality rates compared to normal-weight patients with ACS. In addition, patients with low weight had a higher mortality risk compared to normal-weight patients following ACS during the 30-day follow-up. Despite the presence of high between-study heterogeneity for outcomes between obese and normal weight patients for 30-day and long-term mortality and between low weight and normal-weight patients for long-term mortality, which could not be explained by the metregression analysis, the results appear to have an important effect on routine clinical practice with the inclusion of >500,000 patients with ACS.

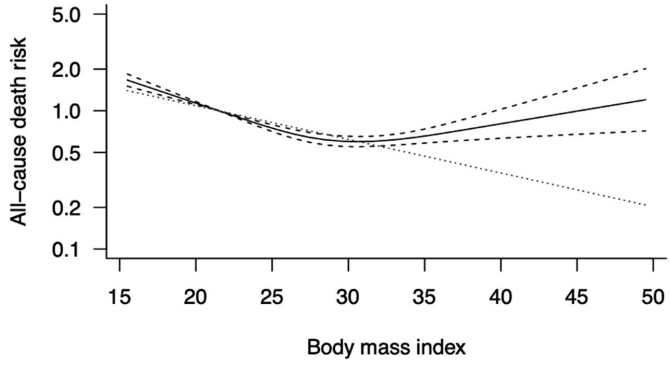


FIG. 5. Restricted cubic spline for detecting the association between body mass index and mortality risk.

There may be several potential explanations for the protective effects of being obese or overweight compared to having a normal weight in both the short- and long-term follow-up periods for patients with ACS. Adipose tissue might have cardioprotective benefits because of the production of leptin and adiponectin, which have anti-inflammatory, antiapoptotic, and antihypertrophic properties.[38] Additionally, elevated levels of cannabinoids in overweight patients play a cardioprotective role in reperfusion by causing vasodilatation in the heart and preventing arrhytmias.[9] Obesity is associated with lower platelet levels compared to a normal weight, and this prominently influences the pathogenesis and outcomes in ACS patients.[9,38] The distribution of fat may be more influential than overall adiposity, since visceral fat has been associated with negative outcomes.[58,59] Visceral adipose tissue enhances systemic inflammation in a low-grade manner by causing the elevated syntheses of proinflammatory cytokines, proatherosclerotic adipokines, and cardiodepressant adipokines, which results in a higher cardiometabolic risk.[60,61] Thus, waist circumference, not only BMI, should be evaluated for cardiovascular risk. However, only one study in this meta-analysis had information about the waist circumference of patients. Cardiovascular disease has an increased catabolic effect on overall metabolism, and obesity may play an important role in protecting the metabolic reserve.[62] In addition, patients with ACS may be exposed to longer hospitalization and multiple high-risk coronary interventions, which could easily weaken the metabolic endurance in patients with low reserve.[63,64] Lastly, elevated serum triglyceride levels were observed in obese patients and might play a protective role against sudden cardiac death.[16]

In our study, patients with lower weights were found to have a higher 30-day and long-term mortality risk compared to normal-weight patients. It has been reported that low-weight patients have a higher prevalence of comorbidities compared to normal-weight patients. Cancer, chronic inflammatory disease, and diastolic and systolic heart failure may be the underlying reason for the higher mortality risk in low-weight patients compared to normal-weight ones. The confounding factors in the studies included in this meta-analysis may have influenced the results. Thus, overweight and obese patients should target healthier lifestyles with a combination of exercise and diet instead of losing lean mass while reducing weight. The cutoff values of BMI classes varied minimally between studies. However, a dose-response meta-analysis was conducted to overcome the effect of these differences and presented the association between BMI and mortality on a continuous scale. A similar dose-response meta-analysis was conducted by Mei et al.[65] with 15 studies including patients who underwent percutaneous coronary intervention.[65] The results were in accordance with those of the current study; the mortality risk was higher in low-weight patients with a nadir of risk between 27 and 32 kg/m^2, and it showed an upward trend after 32 kg/m^2.

The most recent meta-analysis regarding the effect of BMI in patients with ACS was presented by Lamelas et al.,[66] whose report included an investigation published before 2014 with 18

studies including 137,975 patients. Unlike the previous meta-analysis, in the current analysis, not only obese and overweight patients with ACS but also low-weight patients with ACS were compared with normal-weight patients. This appears to be one of the notable strengths of the current study. Moreover, such an extensive comparison allowed us to perform a dose-response meta-analysis. After including 38 investigations in the dose-response meta-analysis, it became evident that a BMI higher than 40 kg/m^2 and lower than 21.5 kg/m^2 might be associated with higher mortality risks, and the lowest mortality risk might be near a BMI of 30 kg/m^2. Moreover, a pooled analysis using either hazard ratio or odds ratio for the calculation of pooled effect size as risk ratio can cause serious errors, in which hazard ratio cannot be converted to risk ratio and is also not pooled with odds ratio. This mistake was unfortunately made by Lamelas et al.;[66] however, it was noted and accounted for in the current meta-analysis. Patients with low-weight and obese patients, especially those with a BMI over 40 kg/m^2, should be followed up closely. Instead of gaining or losing weight in these patient groups, a healthier diet and physical activity are more important for the secondary prevention of cardiovascular disease and mortality.

There were several limitations in our meta-analysis. First, relatively few studies compared 30-day and long-term mortality according to BMI in patients with ACS. However, all studies were included in this meta-analysis in order to obtain more precise results. Second, there was high heterogeneity in the analysis of the studies due to the methodological sampling, BMI stratification, missing data, and factors considered for adjustment. Third, because few studies reported adjusted relative risks (odds and hazard ratios), we could not calculate pooled effect sizes using these parameters. Fourth, due to the presence of high heterogeneity for 30-day and long-term mortality between obese and normal-weight patients, and for long-term mortality between low- and normal-weight patients, which could not be explained by the metaregression analysis, we could not present precise conclusions for these outcomes in this meta-analysis. Fifth, the cutoff BMI values slightly differed in some studies, which might have led to between-study heterogeneity for effect sizes. Sixth, the lack of information regarding the waist circumferences of patients was another limitation. Seventh, because it has been reported that BMI was not strongly associated with mortality in physical active patients, the lack of information about physical activity or fitness status of patients in this meta-analysis was the last limitation.[67] However, we were able to overcome this limitation by performing a dose-response meta-analysis. Overweight ACS patients had lower 30-day and long-term mortality, and low-weight ACS patients had higher 30-day mortality risk than normal-weight patients. Moreover, the mortality risk was higher with BMI lower than 21.5 kg/m^2 and higher than 40 kg/m^2, and was lowest at approximately 30 kg/m^2 based on the dose-response meta-analysis.

Ethics Committee Approval: Ethics committee approval was not needed since this was a meta-analysis of the literature.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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