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Does an Obesity Paradox Really Exist After Cardiovascular Intervention?: A Systematic Review and Meta-Analysis of Randomized Controlled Trials and Observational Studies

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Abstract: Several studies have shown the existence of an obesity paradox after Percutaneous Coronary Intervention (PCI). However, other studies have shown its absence. This study sought to perform a systematic review and meta-analysis of studies comparing the mortality risk between high body mass index patients and normal weight patients after PCI.

We have searched PubMed, Embase, and Chinese medical journal for randomized controlled trials (RCTs) and observational studies published between the year 2000 and 2015 by typing the keywords “percutaneous coronary intervention” and “obesity paradox.” The main outcome was “all-cause mortality. RevMan 5.3 software was used to calculate the risk ratio (RR) with 95% confidence interval (CI) to express the pooled effect on discontinuous variables.

Twenty-two studies have been included in this meta-analysis consisting of a total of 242,377 patients with 73,143 normal weight patients, 103,608 overweight, and 65,626 obese patients. Younger age, higher cardiovascular risk factors and the intensive use of medications have mainly been observed among obese patients followed by overweight and normal weight patients respectively. In-hospital, 12 months and ≥ 1 year (long-term) mortality risks were significantly lower in the overweight and obese groups with (RR: 0.67; 95% CI: 0.63–0.72, $P < 0.00001$) and (RR: 0.60; 95% CI: 0.56–0.65, $P < 0.00001$) respectively in the in-hospital follow-up (RR: 0.62; 95% CI: 0.55–0.71 and 0.57; 95% CI: 0.52–0.63, $P < 0.00001$) at 12 months, and (RR: 0.70; 95% CI: 0.64–0.76; $P < 0.00001$) and (RR: 0.80; 95% CI: 0.71–0.91, $P = 0.0006$) respectively for the long-term follow-up after PCI.

This “obesity paradox” does exist after PCI. The mortality in overweight and obese patients is really significantly lower compared to the normal weight patients. However, the exact reasons for this phenomenon need further exploration and research in the future.

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Abbreviations: BMI = body mass index, CAD = coronary artery diseases, DM = diabetes mellitus, PCI = percutaneous coronary intervention, RCTs = randomized controlled trials, RR = risk ratio.

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INTRODUCTION

Nowadays, in a world where fast food has taken a huge position in people’s lifestyle, where tasty and unhealthy food is becoming a priority, and where exercise and physical activities have been restricted due to limited free times, obesity is increasing at a faster rate.^{1–2} People are becoming overweight and obese at a younger age and these people are commonly exposed to several cardiovascular risk factors such as hypertension, Diabetes Mellitus (DM), smoking, and hyperlipidemia.³ Most of these people suffer from coronary artery diseases (CAD) which can, in a more advanced stage, result in acute coronary syndrome.⁴ In most cases, percutaneous coronary intervention (PCI) is the choice of treatment for these patients. These high body mass index (BMI) patients are considered to be at high risk for cardiovascular disorders and hence, several precautions and care have to be taken in their management and treatment, both in the hospital and during the post-discharge period compared to normal weight patients with similar conditions.⁵

Several researches have been carried out and surprisingly, many have shown that after cardiac interventions, the in-hospital and long-term (≥ 1 year) mortality risks in these high BMI patients are lower compared to normal weight patients. Hence, a specific term called the “obesity paradox” has been reserved for this unexpected condition.⁶ Many studies have supported the fact of the existence of this phenomenon. For example, the article published by Lancefield et al in 2010 showed that compared to normal weight patients, overweight and obese patients had a lower in-hospital and 1 year mortality rate after PCI.⁷

However, the existence of this “obesity paradox” is still not so clear. The results and conclusion from a meta-analysis published by Oreopoulos et al in 2008 were still not so clear about the presence of this phenomenon after coronary revascularization.⁸ Several studies have also shown the absence of such a phenomenon after PCI. For example, the article published by Akin et al in 2012 challenged this phenomenon by revealing no evidence of this “obesity paradox” and stated that it may in fact not exist at all.⁹

In recent years, many newer Randomized Controlled Trials (RCTs) and observational studies comparing the mortality rate in overweight and obese patients with that of normal weight patients after PCI have been published. Therefore, by combining previous researches with new ones (from year 2000 to 2015), we aim to perform a meta-analysis to show whether this “obesity paradox” exists or not.

METHODS

Data Sources and Searches

We have searched PubMed, Embase, and Chinese medical journal for RCTs and observational studies by typing the words

“obesity paradox and percutaneous coronary intervention,” and also replacing the word “obesity paradox” by the word “obesity,” “overweight” or, “high BMI.” To further enhance this search, the term “mortality” has also been used. No language restriction was applied.

STUDY SELECTION

Inclusion and Exclusion Criteria

RCTs and observational studies were included if:

They consisted of overweight, obese, and normal weight patients, (b) they reported mortality after cardiac interventions, (c) they were published between the year 2000 and 2015.

RCTs and observational studies were excluded if:

They did not include overweight and/or obese patients together with normal weight patients, (b) they did not compare normal weight patients with overweight and/or obese ones, (c) mortality rate was not among the reported clinical end points, (d) only their abstracts were made available.

DEFINITIONS

According to the World Health Organization and National Heart, Lung, and Blood Institute, the patient population was divided into

- Normal weight patients with a BMI of 18.5 to 24.9 kg/m²
- Overweight patients with a BMI of 25.0 to 29.9 kg/m²
- Obese patients with a BMI of > 30 kg/m²¹⁰
- High BMI patients included both overweight and obese patients.
- Mortality included both cardiac and noncardiac deaths; that is, all-cause death. All-cause death was assumed in studies where “death” had not well been classified or defined.
- In hospital mortality was defined as death within the period of stay in the hospital after cardiac interventions.
- Mortality during a follow-up period of 12 months described the number of death from the period after hospital discharge until 12 months. Mortality at 12 months was considered in the long-term category.
- Long-term mortality was defined as death at 1 year or more after cardiac interventions.

Data Extraction and Quality Assessment

The authors PKB and NL independently checked all the data and then the eligibility and methodological quality of each eligible study were assessed carefully. Several information have been retrieved, and information regarding those included studies and the characteristics/features of the patients involved, intervention strategies, and the corresponding clinical outcomes reported in these studies were systematically extracted. The follow-up periods have also been carefully classified or separated into in-hospital mortality, mortality during a 12-month period and long-term mortality. Any disagreement raised during this data extraction and quality assessment has been carefully discussed between these 2 authors, and if they could not reach a decision, it was discussed and resolved by the third author (MHC). Assessment of the bias risks within the studies were conducted with the components recommended by the Cochrane Collaboration.¹¹

OUTCOME

In-hospital mortality, mortality during a 12 months follow-up period and, long-term (≥1 year) mortality were considered as the main outcomes for this study.

Methodological and Data Analyses

Recommendations of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement have been used during the study selection, data collection, data analysis, and, reporting of the results. The assessment of heterogeneity across the studies was performed using the (a) Cochran Q-statistic whereby a “*P* value” <0.05 was considered statistically significant and, (b) Cochran *I*²-statistic which represented the percentage of the total variation across studies that is due to heterogeneity rather than chance whereby an *I*² value of 0% indicated no heterogeneity, and an increased heterogeneity was indicated by a larger value. If *I*² was < 50%, a fixed effect was used. However, if *I*² was >50%, a random effect has been used. Funnel plots were assessed for publication bias. We calculated weighted risk ratios (RR) and 95% confidence intervals (CIs) for categorical variables. The pooled analyses were performed with RevMan 5.3 software. Ethical approval was not necessary as this study is a Systematic Review and Meta-Analysis.

RESULTS

Study and Patients Characteristics

Based upon titles and abstracts, we have identified 3564 publications from PubMed, Embase, and Chinese medical journal. After excluding the duplicates, 2522 articles were remaining. A total of 2400 publications have been eliminated since they were irrelevant to our topic. However, 122 full-text articles were assessed for eligibility. Another 100 articles were eliminated because they were either meta-analyses, case reports, or letters to the editor, data for the control/normal weight patients were not available, mortality was not among the reported outcomes or discontinuous data were not available. Finally, 22 articles that satisfied our inclusion criteria were selected for this meta-analysis. The study selection including the flow of the process for identifying potentially eligible trials and the reasons for inclusion and exclusion has been represented in Figure 1.

The characteristics of the 22 studies that met the eligibility criteria are displayed in Tables 1 and 2. Table 1 shows the baseline features and Table 2 shows the criteria for the inclusion and exclusion of patients in these 22 studies. Table 2 also shows the reported outcomes and follow-up periods of each study. This meta-analysis consists of a total of 242,377 patients with 73,143 normal weight patients, 103,608 overweight, and 65,626 obese patients.

Two studies, Minutello (2004)¹⁵ and Das (2012),²² consisted of the highest population of overweight and obese patients among all of the trials with a total of 69,501 and 37,549 patients respectively. Obese patients were the youngest among all the other categories of patients in all of the studies. Moreover, male patients were higher in all of the studies as compared to female patients. One study (Ibrahim 2012) had the highest number of hypertensive obese patients (91.2%).⁹ Most of the obese patients suffered from diabetes mellitus. The baseline features of the included studies have been represented in Table 1.

The inclusion and exclusion criteria, total number of participants, and follow-up period of each study included in our meta-analysis have been shown in Table 2.

Total number of patients has been calculated as the normal weight + overweight + obese patients.

The follow-up period was during the stay in hospital (in-hospital follow-up), follow-up during a 12 months period,

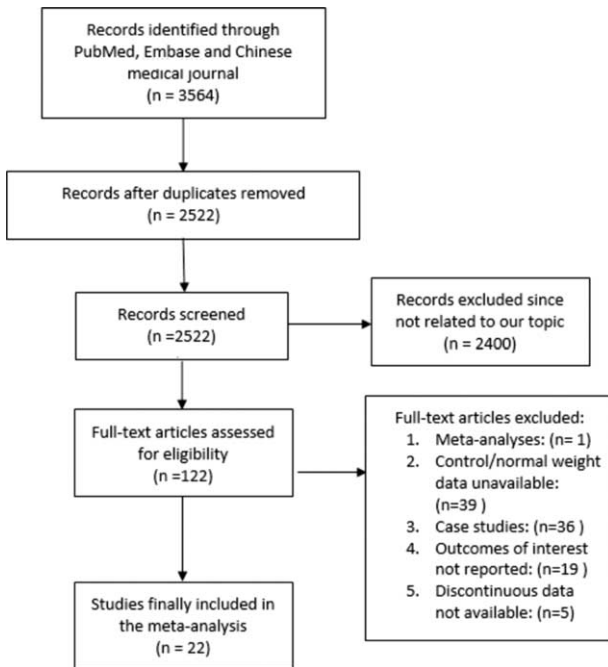


FIGURE 1. The flow diagram of the study selection. The study selection including the flow of the process for identifying potentially eligible trials and the reasons for inclusion and exclusion has been represented. We have followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement for our study. From 3564 articles, 122 full-text articles were assessed eligible for this meta-analysis. After strictly considering the inclusion and exclusion criteria, 22 articles were finally selected for this systematic review and meta-analysis. PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

and a long-term follow-up of ≥ 1 year. Hitinder2002,¹² Luis2005,¹⁶ Zhi2012,²³ Heinz2007,¹⁹ and Miriam2015²⁸ had a follow-up period of 3 and 5 years, 3 years, 3 years, 17 months, and 12 years respectively.

Several outcomes have been reported in these studies. However, since our meta-analysis is concerned with the mortality rate, we have only used data reporting mortality.

Risk Factors Among the Different Groups of Patients

Age, hypertension, dyslipidemia, smoking, DM, and male gender act as risk factors for cardiovascular diseases. Overweight and obese patients are at higher risk of exposure to these cardiovascular risk factors.

The detailed risk factors reported in these patients have been shown in Table 3.

In this meta-analysis, obese patients were youngest with an average age of 59.3 years whereas the normal weight patients were the eldest with an average age of 65.5 years. Hypertension and dyslipidemia also mainly affected the obese patients with a mean percentage of 70.8 and 61.8 respectively whereas the mean percentages of these same 2 risk factors in the normal weight patients were 56.1 and 51.4 respectively. Of the obese and normal weight patients 33.2% were current smokers. The percentage of obese patients suffering from DM was also the highest with a mean value of 33.4. 65.7% of the normal weight patients, 77.3% of the overweight patients, and 69.1% of the

obese patients were males. If considered as a whole, younger age and a higher rate of certain cardiovascular risk factors were observed among the overweight and obese patients. However, there was no significant difference in the percentage of patients who smoke, among all the 3 groups. No significant differences in the risk factors between the overweight and the obese patients have been observed. The detailed risk factors and their corresponding percentages among the different groups of patients have been mentioned in Table 3.

Medications at Discharge and During the Follow-Up Period

Data from study Sandeep 2011,²² Won 2010,²⁵ Hidehiro 2013,²⁴ Ibrahim 2012,⁹ Pei 2015,³⁰ Yohei 2015,²⁹ Zhi 2012,²³ Heinz 2007¹⁹ and, Shubair 2006¹⁸ have been used to calculate the percentage of patients with their corresponding medications during the follow-up period and have been represented in Table 4. Studies that have not been included in this section have been ignored because they did not report the medications being prescribed at hospital discharge or during the follow-up period.

According to Table 4, 96.5% of normal weight patients, 96.9% of the overweight patients, and 96.6% of the obese patients used Aspirin. Medication use was higher among the overweight and highest among the obese patients. Overweight patients used more medications than normal weight patients whereas obese patients used more medications than overweight patients after PCI. Table 4 summarizes the percentage of patients on medications at discharge and during the follow-up period.

Main Results of the Meta-Analysis

The in-hospital mortality in these high BMI patients has been represented in Figure 2. There was evidence of a statistically significantly lower heterogeneity across the included studies. A low heterogeneity among the different subgroups has been observed during the in-hospital and long-term follow-up periods. According to this result, it can clearly be seen that the in-hospital mortality is significantly lower in overweight and obese groups (RR: 0.67; 95% CI: 0.63–0.72 and 0.60; 95% CI: 0.56–0.65, $P < 0.00001$) respectively as compared to the normal weight patients after PCI.

The 12 months follow-up for mortality in these high BMI groups has been represented in Figure 3. The result is in favor of the overweight and obese groups where the 1-year follow-up for mortality is significantly lower (RR: 0.62; 95% CI: 0.55–0.71 and 0.57; 95% CI: 0.52–0.63, $P < 0.00001$) respectively as compared to the normal weight patients after PCI.

The long-term (≥ 1 year) mortality in these high BMI patients has been represented in Figure 4. Data from the result shows that the long-term mortality in the overweight and obese patients are still significantly lower (RR: 0.70; 95% CI: 0.64–0.76, $P < 0.00001$ and RR: 0.80; 95% CI: 0.71–0.91, $P = 0.0006$) respectively.

DISCUSSION

We all know that high BMI patients have an increased risk of suffering from cardiovascular diseases.^{31–32} A large number of these patients are exposed to cardiovascular risk factors such as hypertension, DM, and hyperlipidemia as shown in this study too. Normally, these high BMI patients should have worse in-hospital and long-term adverse clinical outcomes after PCI. However, several studies have shown that overweight and obese

TABLE 1. Baseline Characteristics of Patients from the Included Studies

| Study/Year | Patients (n) | Age (Year) | Men (%) | HT (%) | Ds (%) | CS (%) | DM (%) |
|-----------------------------|-------------------|----------------|----------------|----------------|----------------|----------------|----------------|
| | N/Ov/Ob | N/Ov/Ob | N/Ov/Ob | N/Ov/Ob | N/Ov/Ob | N/Ov/Ob | N/Ov/Ob |
| Hitinder 2002 ¹² | 502/984/569 | NM* | 72.0/79.0/64.5 | 41.0/47.0/61.5 | NM | 29.0/21.0/20.5 | 11.0/15.0/32.0 |
| Luis 2002 ¹³ | 1923/4813/2897 | 68.0/64.0/61.0 | 59.7/74.4/65.1 | 55.6/63.1/72.3 | 63.1/71.3/73.6 | NM | 17.4/25.5/38.0 |
| Brian 2002 ⁶ | 1165/2546/2217 | 69.0/67.0/63.5 | 66.0/76.0/66.0 | 57.0/58.0/69.0 | 59.0/64.0/69.5 | 21.0/18.0/20.0 | 16.0/18.0/33.0 |
| Carlos 2004 ¹⁴ | 358/625/586 | 69.5/66.4/61.3 | 64.4/76.2/70.2 | 62.1/64.9/72.2 | NM | 25.5/23.2/23.3 | 17.7/19.2/35.2 |
| Robert 2004 ¹⁵ | 25010/41175/28326 | 65.1/62.3/58.5 | 65.5/73.8/59.2 | 56.1/60.2/70.6 | NM | 25.1/24.9/26.6 | 14.9/18.2/32.8 |
| Luis 2005 ¹⁶ | 168/307/124 | 61.0/61.0/60.0 | 70.8/83.7/69.3 | 37.5/45.0/53.2 | 51.8/58.6/63.0 | 37.0/24.4/24.2 | 8.9/19.5/30.0 |
| Eugenia 2005 ¹⁷ | 233/531/543 | 65.8/63.6/59.9 | 65.2/79.0/68.0 | 68.3/68.8/75.4 | 60.7/65.4/69.7 | 22.7/22.8/22.1 | 10.3/18.7/35.2 |
| Shubair 2006 ¹⁸ | 986/2017/1628 | 65.2/62.1/57.8 | 64.5/75.5/62.7 | 54.5/56.1/69.1 | 77.6/81.4/85.0 | 20.6/20.7/24.7 | 14.9/19.3/32.2 |
| Heinz 2007 ¹⁹ | 551/824/584 | 65.9/64.7/61.6 | 67.0/75.0/68.0 | 55.0/62.0/70.3 | 60.0/68.0/72.0 | 21.0/25.0/25.7 | 17.0/18.0/26.3 |
| Laxmi 2007 ²⁰ | 703/1039/583 | 63.0/60.0/57.0 | 67.0/79.0/73.0 | 39.0/45.0/57.0 | 33.0/38.0/43.0 | 47.0/43.0/41.0 | 11.0/15.0/23.0 |
| Masami 2008 ²¹ | 1759/866/114 | 67.0/63.0/57.0 | 75.0/79.0/70.0 | 55.0/59.0/69.0 | 32.0/44.0/50.0 | 47.0/50.0/53.0 | 29.0/36.0/39.0 |
| Terase 2010 ⁷ | 1189/2016/1426 | 67.4/64.7/61.4 | 73.2/79.0/68.8 | 58.6/61.9/74.1 | 68.5/71.7/75.6 | 23.4/19.9/23.2 | 15.9/22.3/33.6 |
| Sandeep 2011 ²² | 11780/19391/18158 | 66.0/60.0/56.3 | 61.9/75.3/69.6 | 56.9/58.5/69.7 | 43.4/49.7/55.4 | 45/43.1/42.1 | 14.8/19.5/35.3 |
| Ibrahim 2012 ⁹ | 1436/2839/1531 | 66.1/65.5/63.7 | 69.8/78.5/72.1 | 75.4/84.2/91.2 | 75.9/81.0/83.5 | 26.3/21.4/20.4 | 21.5/29.2/46.9 |
| Zhi 2012 ²³ | 1592/3026/1465 | 60.9/58.8/56.8 | 62.7/64.7/66.4 | 58.0/60.8/70.9 | 30.3/30.9/38.1 | 44.4/42.4/40.2 | 34.6/33.5/38.4 |
| Hidehiro 2013 ²⁴ | 640/417/56 | 66.8/63.2/55.2 | 81.4/87.8/92.9 | 61.3/71.7/69.6 | 56.6/66.7/71.4 | 33.4/41.7/62.5 | 33.4/35.7/48.2 |
| Won 2013 ²⁵ | 1253/1959/483 | 64.7/59.4/56.5 | 70.9/79.5/76.4 | 39.9/47.2/54.2 | 7.0/10.4/12.7 | 60.3/64.2/66.2 | 22.5/23.5/28.7 |
| Park 2013 ²⁶ | 12093/9636/1113 | 64.0/60.5/59.0 | 70.0/69.5/58.0 | 48.3/61.0/71.0 | 37.3/44.5/51.0 | 32.0/29.5/29.0 | 27.0/30.5/38.0 |
| Fabienne 2014 ²⁷ | 2294/3123/1454 | 64.2/67.2/60.8 | 71.1/82.5/74.0 | 48.9/53.9/71.8 | 43.2/51.0/53.2 | 46.7/42.4/43.8 | 10.2/15.1/31.2 |
| Miriam 2015 ²⁸ | 1074/1927/1053 | 61.7/61.2/60.5 | 71.1/82.0/68.2 | 72.0/80.1/88.3 | 64.5/73.5/78.0 | 39.2/32.8/30.4 | 21.0/26.8/42.5 |
| Yohei 2015 ²⁹ | 5945/3100/635 | 69.4/65.4/59.2 | 79.3/83.5/78.7 | 70.9/80.0/84.9 | 63.9/72.9/78.4 | 33.3/38.7/44.7 | 40.0/46.4/58.6 |
| Pei 2015 ³⁰ | 489/447/81 | NM | 67.7/6.0/58.0 | 62.8/76.3/72.8 | 48.7/51/50.6 | 16.4/13.6/14.8 | 27.4/26.4/24.7 |

CS = current smoker, DM = diabetes mellitus, Ds = dyslipidemia, HT = hypertension, N = normal weight, NM = not mentioned, Ob = obese, Ov = overweight.

* In the trial Hitinder 2002,¹² 41%, 35%, and 28.5% of the normal weight, overweight, and obese patients respectively were > 65 years old.

patients have a lower in-hospital and long-term mortality rate as compared to normal weight patients after cardiac intervention.⁶⁻⁷

Similarly, results from our meta-analysis showed that the in-hospital and long-term (≥ 1 year) mortality in overweight and obese patients were significantly lower than that compared to the normal weight patients. The mortality in normal weight patients after PCI was significantly higher compared to that of the other 2 categories of patients confirming that the "obesity paradox" does exist after PCI.

Certain studies have mentioned that obesity paradox could be associated with several biases. For example, if the disease was diagnosed earlier, it could have been confused with prolonged or increased survival of the patient. This could give rise to a lead time bias. On the contrary, a lower pretest probability has been commonly observed among the lean or underweight individuals, and consequently, these people tend to have a more advanced disease, which could finally lead to a worse prognosis in these low BMI patients. Also, a publication bias which occurs when more positive studies are likely to be published compared to negative studies, and a confounding bias may also potentially exist.³³ However, several recent meta-analyses have really shown the existence of an obesity paradox which could be associated to other reasons.

The suggested reasons mentioned in other studies, behind this "obesity paradox," are still not so clear. Many hypotheses have been considered for this unexpected result. First of all, younger age could be one of the main factors contributing to this phenomenon. Even our study has shown that younger age was most obvious in the obese group followed by the overweight

group.^{20,34} Younger patients have a stronger body function and still have the power to tolerate and fight serious health conditions and compensate to correct any abnormal condition affecting the body. As shown in our result, the obese patients had a mean age of 59.3 years while in normal weight patients, the mean age was 65.5 years. The recovering capability of older patients from cardiac complications, and their body's ability to compensate during disease condition is weak. Accompanied by co-morbidities, which render their immune system weaker could also be among the reasons for the in-hospital and long-term (≥ 1 year) mortality risks to be lower among these younger overweight and obese patients. Life-long and intensive medication use from an early age and for a longer period of time could be another reason responsible for this "obesity paradox."^{7,35-38} As shown in our results, overweight and obese patients used more medications as compared to normal weight patients.

These patients are at a higher risk of cardiovascular diseases, and most of them are diabetics, or suffer from hypertension and dyslipidemia in their early 40s. They are treated for these conditions at an earlier age and they use several medications daily to control their high blood pressure and hyperglycemia. Sometimes, medications such as statin and aspirin are given to them as a measure of prevention and they are advised very often about regular exercise and healthy habits to keep them fit. Very few normal weight patients go through similar conditions and hence they even have less chance of being taught about these important health tips as compared to high BMI individuals.⁷ Being younger, obese patients may have received more aggressive or attentive care compared to underweight or

TABLE 2. The Inclusion and Exclusion Criteria, Total Participants, and Follow-Up Period of Each Study Included in Our Meta-Analysis

| Studies | Number of Patients | Inclusion Criteria | Exclusion Criteria | Endpoints/Outcomes | Selected Endpoint for Our Study | Follow-Up Period |
|---------------|--------------------|---|---|---|---------------------------------|---------------------|
| Hitinder 2002 | 2055 | Patients with clinically severe angina or objective evidence of ischemia and angiographically documented multivessel disease suitable for PCI. | Patients with a history of coronary revascularization, single-vessel coronary artery disease, or primary congenital, valvular, or myocardial disease and those <17 years or >80 years. | Major in-hospital event (death, MI, stroke, or coma) and long-term mortality. | Mortality | >1 year |
| Luis 2002 | 9633 | Patients who underwent PCI between January 1994 and December 1999. | Patients not satisfying the inclusion criteria. | Major late clinical events including death, Q-wave MI, and revascularization procedures. | Mortality | In-hospital, 1 year |
| Brian 2002 | 5928 | Patients who underwent PCI between January 1, 1996, and June 30, 2000. If a patient had several qualifying procedures, only the initial procedure was included. | Patients who received coronary radiation therapy or underwent thrombectomy procedures and patients who denied the use of their records for research purposes. | Death, MI, and need for repeat revascularization | Mortality | In-hospital |
| Carlos 2004 | 1569 | Patients undergoing PCI from February 1999 through August 2000. | Patients not satisfying the inclusion criteria. | Mortality and repeat procedures | Mortality | At 1 year |
| Robert 2004 | 94,511 | Patients who underwent PCI and whose discharge dates were from January 1, 1994, to December 31, 1997. | Patients not satisfying the inclusion criteria. | Death was limited to in-hospital mortality. MI at 24 h, MACE. | Mortality | In-hospital |
| Luis 2005 | 599 | Patients with multivessel coronary artery disease between April 1997 and June 1998 as part of the ARTS trial. In brief, patients who had not had a previous revascularization—stable or unstable angina, silent ischemia. | Patients with left main disease, decreased left ventricular function (30%), overt heart failure, previous cerebrovascular accident, recent myocardial infarction (1 week), severe hepatic and renal dysfunction, or the need for major concomitant surgery. | Clinical outcomes such as MI, death, TLR, TVR. | Mortality | >1 year |
| Eugenia 2005 | 1307 | Patients with stable or unstable angina or inducible ischemia and who underwent percutaneous coronary interventions for a single de novo lesion in a native coronary artery. | Patients not satisfying the inclusion criteria. | Mortality, MI, TVR, TLR, and stent thrombosis at 1 year. | Mortality | At 1 year |
| Shubair 2006 | 4631 | Patients undergoing elective or urgent PCI at (Hamilton Health Sciences—General Site) between July 1997 and July 2002. | Patients who presented with cardiogenic shock. | MACE. Other adverse events including major bleeding, blood loss requiring transfusion, and femoral hematoma. | Mortality | In-hospital |
| Heinz 2007 | 1959 | UA/NSTEMI patients from January 1996 to December 1999—required typical chest pain at rest and early coronary angiography. | Patients with de novo angina pectoris on exertion or worsening angina during exertion only, patients with persistent ST-elevation, patients in whom angiography was not performed due to patient or extremely severe concomitant disease with severe dementia or advanced malignancy, and patients with no information regarding body weight or height. | The primary endpoint was defined as death from all causes. As secondary endpoints, we assessed nonfatal MI and the composite of death and nonfatal. | Mortality | >1 year |

TABLE 2. (Continued)

| Studies | Number of Patients | Inclusion Criteria | Exclusion Criteria | Endpoints/Outcomes | Selected Endpoint for Our Study | Follow-Up Period |
|---------------|--------------------|---|---|---|---------------------------------|---------------------|
| Laxmi 2007 | 2325 | Patients with AMI from the Primary Angioplasty in Acute Myocardial Infarction database who underwent PCI—included only those patients treated with emergency PCI in whom height and weight data were available for BMI calculation. | Patients previously treated with thrombolytic agents for the index AMI and those with cardiogenic shock, renal failure, and stroke within the previous 1 month, life expectancy <1 year from a noncardiac condition, or women with childbearing potential. | In-hospital death, MACE, TVR, pulmonary edema, reinfarction, long-term death. | Mortality | In-hospital, 1 year |
| Masami 2008 | 2739 | Patients who were admitted to 35 participating hospitals in Japan within 48 h after symptom onset between January 2001 and December 2003—patients with ST segment elevation AMI who underwent emergency PCI and had adequate clinical data. | Patients who did not satisfy the inclusion criteria. | In-hospital mortality | Mortality | In-hospital |
| Terase 2010 | 4631 | Patients undergoing PCI procedures between April 1, 2004, and September 30, 2007, enrolled in the Melbourne Intervention Group registry. | Patients who did not satisfy the inclusion criteria. | In-hospital outcomes included all-cause mortality, cardiac death, MI, MACE, congestive cardiac failure; arrhythmia Thirty-day and 12-month clinical outcomes included all-cause mortality, cardiac death, MI, TLR, TVR, and MACE. | Mortality | In-hospital, 1 year |
| Sandeep 2011 | 49,329 | Patients enrolled in the registry between January 1, 2007, and June 30, 2009, who were diagnosed with STEMI. | Patients who did not have BMI data available. | Primary outcome was all-cause mortality. Secondary outcomes included the rate and type of reperfusion, time to PCI, and rates of reinfarction, congestive heart failure (HF), cardiogenic shock, stroke, major bleeding. | Mortality | In-hospital |
| Ibrahim 2012 | 5806 | Patients undergoing PCI and stent implantation from DES.DE registry. | Patients who did not satisfy the inclusion criteria. | Occurrence of TVR and MACCE (defined as the composite of cardiac and noncardiac death, MI, and stroke). | Mortality | In-hospital, 1 year |
| Zhi 2012 | 6083 | Patients who underwent PCI with DES at Beijing Anzhen Hospital (Beijing, China), between January 2004 and December 2006. | Acute myocardial infarction with ST-segment elevation, cardiogenic shock, congenital or valvular heart disease, primary cardiomyopathy, age <17 or >80 years, severe renal insufficiency with estimated glomerular filtration rate <30 mL/min per 1.73 m ² , prior coronary stent implantation or coronary artery bypass graft, thrombocytopenia, and ongoing bleeding or history of bleeding diathesis. | This follow-up study focused on clinical-driven repeat revascularization, including TLR and non-TLR and death. | Mortality | >1 year |
| Hidehiro 2013 | 1113 | All patients who underwent PCI between June 2004 and March 2011 (Shinken Database 2004–2010). | Those patients who had no available data for height and body weight. | Incidence of cardiovascular events and mortality. | Mortality | >1 year |

TABLE 2. (Continued)

| Studies | Number of Patients | Inclusion Criteria | Exclusion Criteria | Endpoints/Outcomes | Selected Endpoint for Our Study | Follow-Up Period |
|---------------|--------------------|--|--|---|---------------------------------|---------------------|
| Won 2013 | 3695 | STEMI patients who arrived at hospital within 12 h after the onset of chest pain and underwent primary PCI. | Patients who did not satisfy the inclusion criteria. | In-hospital mortality, MACEs, including in-hospital mortality, revascularization. | Mortality | In-hospital, 1 year |
| Park 2013 | 22,842 | Databases from 11 independent, prospective clinical studies (8 randomized clinical trials and 3 registries) were pooled to provide a patient-level data analysis. | Patients with cardiogenic shock, terminal illness, or malignancy at baseline. | Major cardiovascular events and death from any cause. | Mortality | >1 year |
| Fabienne 2014 | 6871 | Patients enrolled between January 1, 2005, and July 9, 2012, with a discharge diagnosis of STEMI. | Patients with missing BMI data. | In-hospital mortality; cardiac and noncardiac causes of death. | Mortality | In-hospital |
| Miriam 2015 | 4054 | Patients consecutively registered between January 1, 2000, and December 31, 2008, who reached the hospital alive and whose survival time exceeded 28 days after AMI—patients with a nonfatal first ever AMI aged 28 to 74 years. | Patients with missing data on BMI, diabetes, and smoking were excluded as well as patients with incomplete data on any of the relevant covariates. Furthermore, patients who were underweight (BMI < 18.5 kg/m ²). | All-cause mortality as the outcome. | Mortality | >1 year |
| Yohei 2015 | 9680 | Patients who underwent PCI at 15 Japanese hospitals participating in the JCD-KICS registry from September 2008 to April 2013. | Patients with missing data on basic information, including sex, height, and/or body weight. | In-hospital mortality and other complications. Complications: severe coronary artery dissection or coronary perforation; MI after PCI; cardiac shock or heart failure; cerebral bleeding or stroke; and bleeding complications. | Mortality | In-hospital |
| Pei 2015 | 1017 | From June 1, 2006 to April 30, 2011, elderly patients (≥75 years old) who had PCI and stent implantation. | Patients with incomplete BMIs. | In-hospital major outcomes | Mortality | In-hospital, 1 year |

BMI = body mass index, MACCE = major adverse cardiovascular and cerebrovascular events, MACEs = major adverse cardiac effects, MI = myocardial infarction, PCI = percutaneous coronary intervention, STEMI = ST elevated myocardial infarction, TLR = target lesion revascularization, TVR = target vessel revascularization.

normal weight patients. However, older patients, with a majority in the normal BMI group, may not have fared as well with the treatments provided and unfortunately showing a higher rate of mortality in the normal BMI category compared

to the overweight and obese patients. Interestingly, studies have also shown that diabetic or nondiabetic overweight and obese patients on statin prior to acute coronary syndrome during their

TABLE 3. The Mean Values for the Risk Factors for Cardiovascular Diseases

| Risk Factors | Normal Weight | Overweight | Obese |
|--------------------|---------------|------------|-------|
| Age (years) | 65.5 | 63.0 | 59.3 |
| Hypertension (%) | 56.1 | 62.0 | 70.8 |
| Dyslipidemia (%) | 51.4 | 57.6 | 61.8 |
| Current smoker (%) | 33.2 | 30.5 | 33.2 |
| DM (%) | 19.8 | 32.1 | 33.4 |
| Men (%) | 65.7 | 77.3 | 69.1 |
| Women (%) | 34.3 | 22.7 | 30.9 |

DM = diabetes mellitus.

TABLE 4. The Medications at Discharge and During Follow-Up Used by the Patients Within the Different BMI Groups

| Discharged and Follow-Up Medications | Normal Weight Patients | Overweight Patients | Obese Patients |
|--------------------------------------|------------------------|---------------------|----------------|
| Aspirin (%) | 96.5 | 96.9 | 96.6 |
| Clopidogrel (%) | 82.4 | 83.1 | 83.2 |
| Statin (%) | 79.2 | 81.3 | 83.2 |
| ACEI/ARBs (%) | 70.2 | 72.1 | 75.2 |
| Beta blocker (%) | 72.8 | 75.0 | 75.4 |

ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, BMI = body mass index.

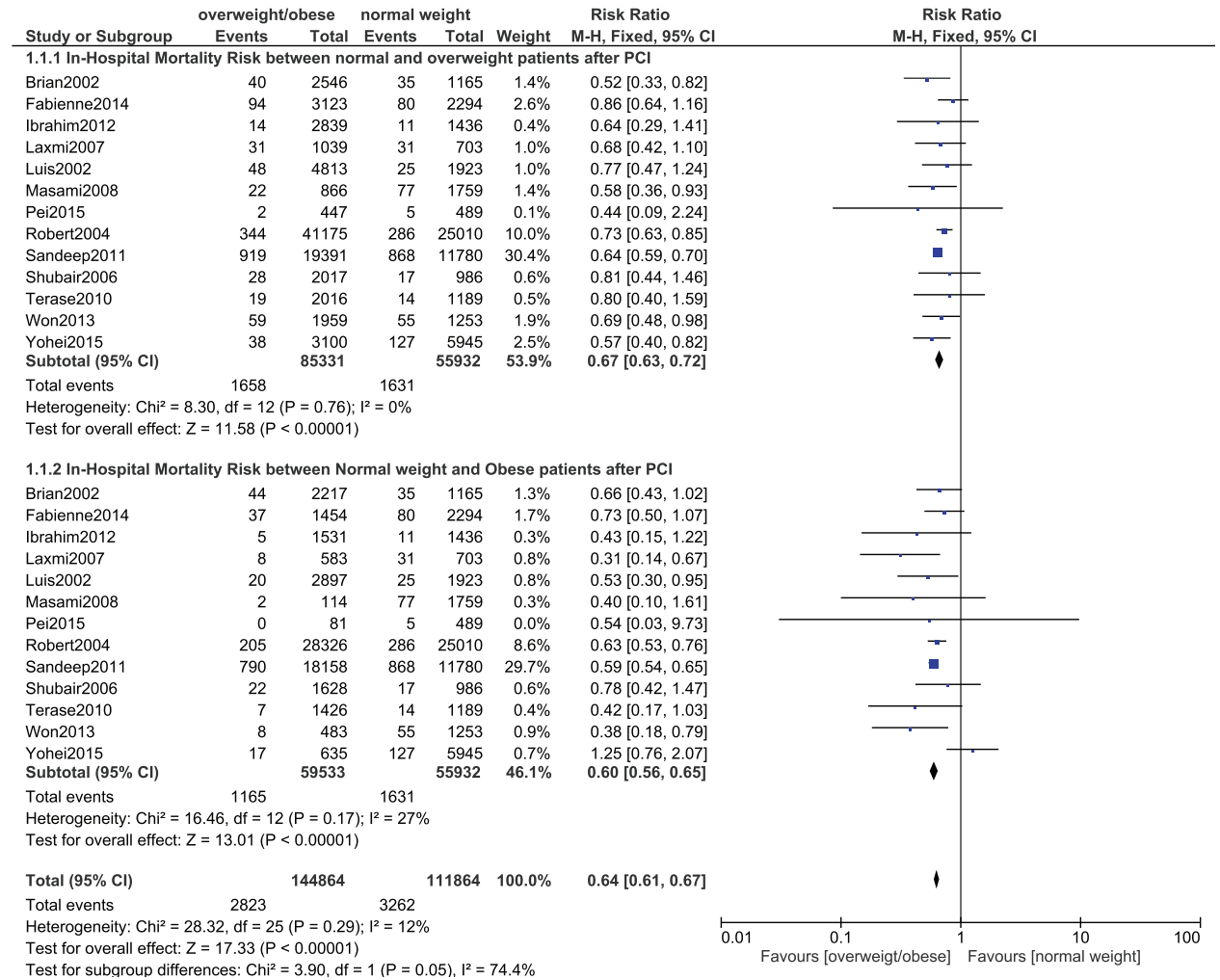


FIGURE 2. The in-hospital mortality risk among overweight and obese patients as compared to normal weight patients after percutaneous coronary intervention.

hospital stay and post discharged period, appeared to have a significant survival benefit.

Cessation of smoking, cardiac rehabilitation, and counseling about diet or healthy food consumption are more frequently enforced in overweight and obese patients than in normal weight patients.³² These could be among other reasons responsible for this “obesity paradox.”

Moreover, obese patients have a good storage for nutrients which is often required after surgery. This lack of nutrient could be another reason why the mortality rate is higher in normal weight patients after cardiac intervention. Furthermore, patients with a low BMI tend to be affected more by noncardiac mortality due to conditions such as cancer, smoking, chronic obstructive pulmonary disease, and insulin-dependent DM. These comorbidities have been suggested as a possible explanation for this “obesity paradox” too.

Size of the coronary blood vessels could also be considered as a reason to explain this “obesity paradox.” A study suggested that the size of the coronary arteries increases with increasing BMI. The study has observed a lower mortality rate among the overweight and obese patients because of their large coronary blood vessels. Underweight patients had the smallest

coronary arteries and the highest in-hospital and long-term mortality rates were observed among this category of patients.⁷

Platelets seem to play a major role in the pathophysiology of acute coronary syndromes, as well as the outcome after PCI with stent implantation. Adverse conditions such as stent thrombosis can occur due to platelet dysfunction. Sudden death can also be induced by stent thrombosis. Interestingly, other studies indicate that obese patients have a significantly lower platelet count when compared with normal weight patients.³⁹ So, this could also be a reason responsible for this lower in-hospital and long-term mortality risks among overweight and obese patients after cardiovascular interventions.

The study published by Hastie et al in 2010 also supports our results.⁴⁰ His study investigated the impact of body mass index on long-term all-cause mortality in patients following first-time elective PCI and it showed that increased BMI was associated with an improved 5-year survival rate. Another study published in 2009 by Oreopoulos et al showed that a paradoxical association between BMI and survival existed in patients with established CAD irrespective of treatment strategy and the author concluded that the reason behind this paradox could be that patients with obesity might be presenting earlier and

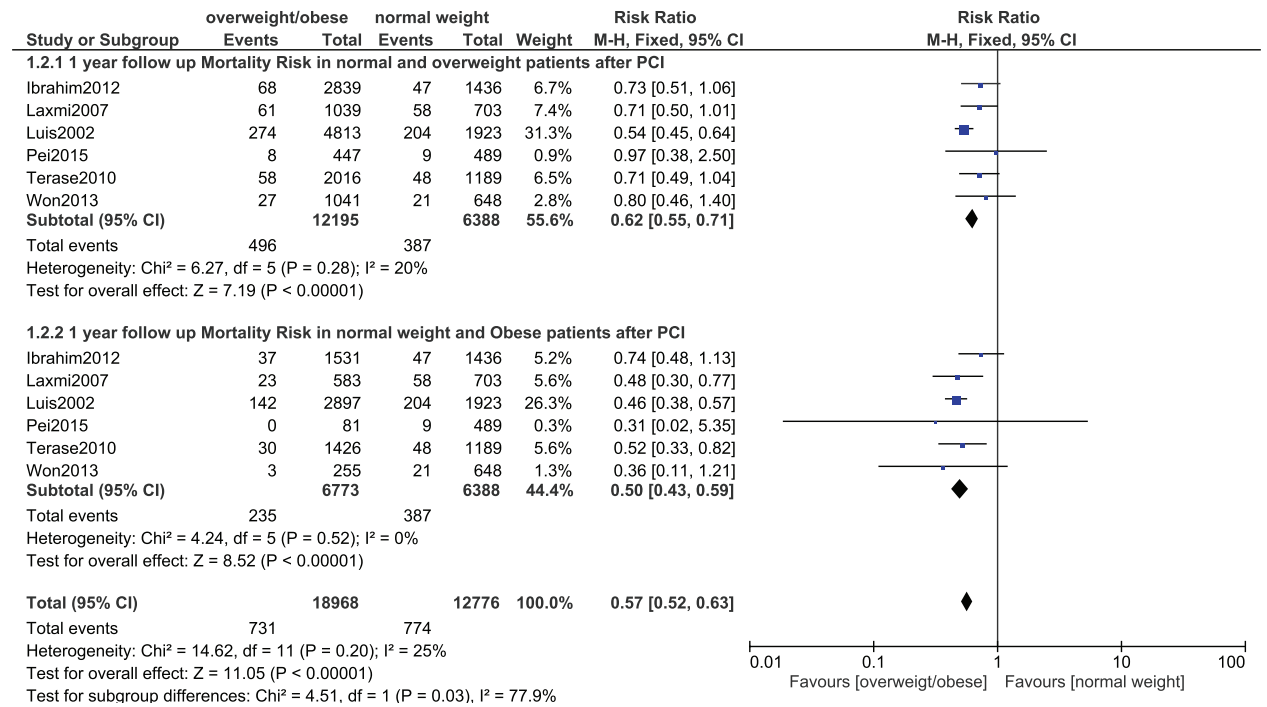


FIGURE 3. The 12 months follow-up for mortality risk among overweight and obese patients as compared to normal weight patients after percutaneous coronary intervention.

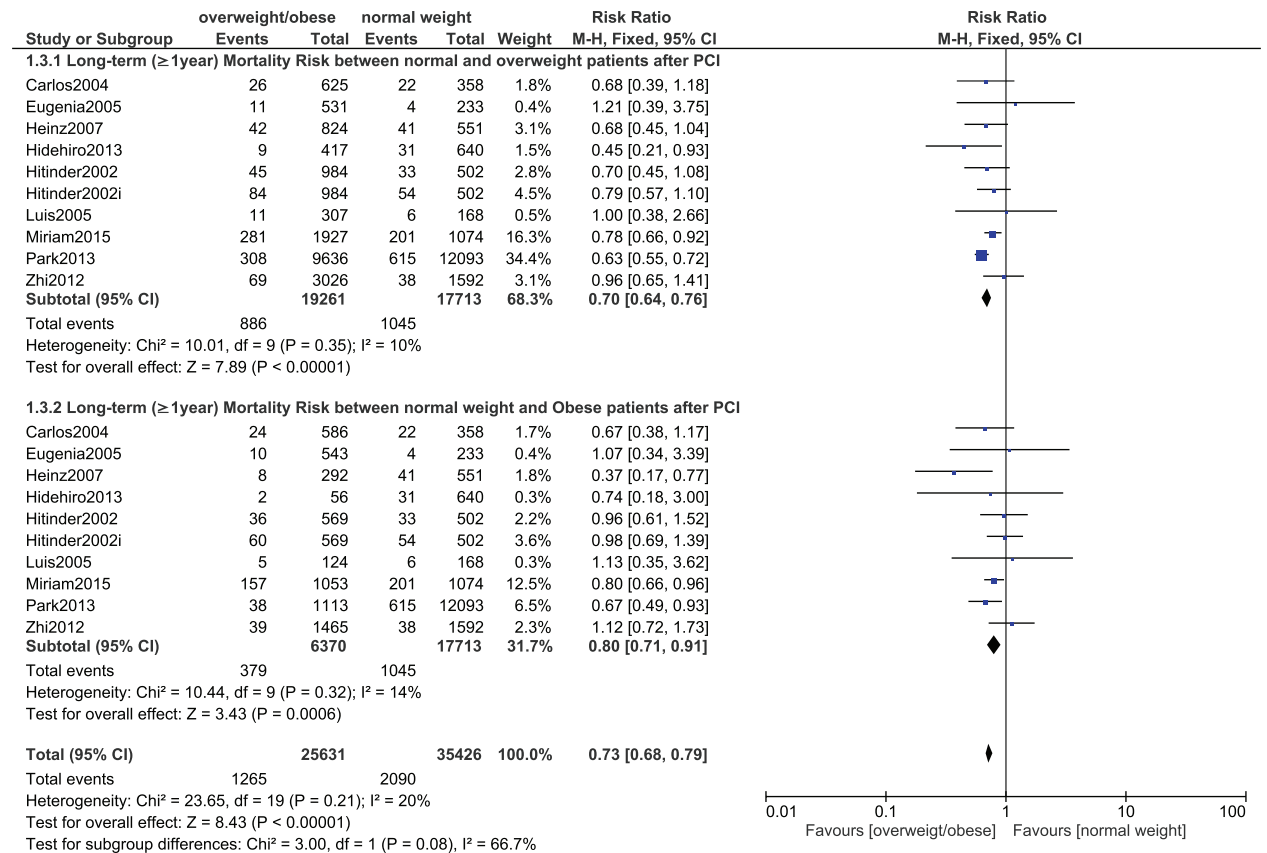


FIGURE 4. The long-term (≥1 year) mortality risk among overweight and obese patients as compared to normal weight patients after cardiovascular intervention.

receiving more aggressive treatments compared to those with normal BMI.⁴¹ The study published in 2013 by Hainer et al also supports the fact that this “obesity paradox” does exist.⁴² Furthermore, the meta-analysis by Sharma explaining the relationship of BMI with total mortality, after coronary revascularization (including PCI and CABG) showed a higher mortality rate among the underweight patients whereas a lower mortality rate was observed among the overweight patients.⁴³ Another recent meta-analysis including 1,300,794 patients from 89 studies also showed a significantly lower short- and long-term mortality among the overweight and obese patients, whereas the rate of mortality among the underweight patients were significantly higher.⁴⁴ The study by Lavie published in 2015 adds further support to this obesity paradox.⁴⁵ The study dealing with obesity and cardiovascular diseases published by Lavie in 2014 also supports our results and the author concluded that although obesity is among one of the risk factors for cardiovascular disorders, an obesity paradox does exist showing that overweight and obese patients with cardiovascular diseases have a better prognosis compared to the nonobese/nonoverweight ones.⁴⁶

Even though several studies show this obesity paradox to be present worldwide among obese patients from different ethnicities (observed in patients from Korea, Japan, America, and other European countries), the study conducted by He et al showed an absence of this paradox in Chinese patients above 75 years of age.³⁰ This phenomenon was also not observed in 2 cohorts from a northern Chinese population.^{47–48}

However, a few other studies from the Western regions also do not agree with this phenomenon. The study published by Akin et al in 2012 denies the existence of this “obesity paradox.”⁹ In his study, normal body weight patients and obese patients had similar rates of all-cause mortality; but in fact, his study dealt with the comparison of different types of coronary drug-eluting stents and their corresponding adverse clinical outcomes after PCI. Therefore, maybe that is why his results varied from our meta-analysis.

Oreopoulos et al meta-analysis published in 2008 compared the short- and long-term mortality in obese patients after cardiac interventions.⁸ His study included data from articles published almost 20 years ago, in the year 1996. His results supported the fact that the in-hospital and long-term mortality rates were similar or lower in obese patients compared to normal weight patients. Our result differs from his maybe because his study included not only post PCI patients but also post coronary artery bypass surgery patients.

Our meta-analysis is an updated version including studies published from the year 2000 to 2015 and consists mainly of post PCI patients. Consisting of the several obese groups, this current meta-analysis compares the mortality rate at different follow-up periods including (in-hospital, 1-year follow-up and ≥ 1 -year mortality among the different categories of patients) after PCI. The medication use and risk factors prominent among these different BMI groups have also been shown in our study. The lower in-hospital and 1-year follow-up as well as ≥ 1 -year mortality among the overweight and obese patients suggest that this “obesity paradox” still exists after PCI.

LIMITATIONS

Normally a patient with a BMI of $>30 \text{ kg/m}^2$ is considered as obese. However, in certain studies, patients with a BMI of $>27.5 \text{ kg/m}^2$ has been classified in the obese category. Similarly, the range for normal weight patients is supposed to be between 18.5 to $<25 \text{ kg/m}^2$ but in a few studies, a

weight of $<20 \text{ kg/m}^2$ was considered underweight or a BMI of $<25 \text{ kg/m}^2$ was considered as normal weight patients (a BMI of $<25 \text{ kg/m}^2$ could also include underweight patients).

CONCLUSION

This “obesity paradox” does exist after PCI. The mortality in overweight and obese patients is indeed lower compared to the normal weight patients. However, the exact reasons for this phenomenon need further exploration and research in the future.

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