REVIEW ARTICLE

Review of Obesity Paradox

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Introduction: Obesity is a risk factor for many health conditions and complications but may be regarded as a prognostic factor in other conditions. This has been described as the "obesity paradox." The debate whether this paradox exists across all health conditions is a hot topic of research, which is why this review aims at systematically analyzing reviews on the obesity paradox to explore where it holds true and help guide further research and clinical implications.

Methods: PubMed was searched using the key term "obesity paradox" with a systematic review and meta-analysis filter with no restriction on the date.

Results: A total of 40 reviews were included. Most of the reviews included observational cohort studies focusing on various health conditions such as cancer, atrial fibrillation, stroke, heart failure, acute coronary events, dialysis, chronic diseases, surgery, etc. The obesity paradox appeared to exist in all reviewed health conditions except for solid tumors, where there was no obesity paradox regarding mortality or treatment toxicities. The obesity paradox relationship, however, was not homogeneous across the health systems, and the relationships were described as linear, U-shaped, or J-shaped (the latter two being the most common).

Conclusions: The relationship between obesity and health outcomes is not straightforward as obesity is sometimes a risk factor for worse outcomes and other times associated with improved mortality. Hence, there is a need for randomized controlled trials to validate why and in which diseases the obesity paradox exists and understand its pathophysiology. Meanwhile, patients with obesity remain a challenge in the clinical context and need special attention to address their obesity and control their risk factors.

Keywords: obesity paradox, obese, obesity, overweight; mortality

INTRODUCTION

Obesity is considered a risk factor for many health conditions and complications, yet it is a prognostic factor in other conditions. This has been described in the literature as the "obesity paradox". Obesity was correlated with improvement in mortality outcomes in

sepsis compared to patients with a lower Body Mass Index (BMI) [1-4]. This decrease in overall mortality has also been validated in other healthcare conditions, such as in pulmonary arterial hypertension [5], Chronic Obstructive Pulmonary Disease (COPD) [6], and burn patients [7]. Although obesity is linked to a higher incidence of atrial fibrillation, patients with obesity hospitalized for atrial fibrillation had lower in-hospital mortality and lower odds of acute stroke events than patients who are non-obese [8]. Patients who are obese with diabetic foot ulcers were less likely to have amputation rates, yet morbid obesity was a risk factor for increased rates of sepsis [9]. Patients with obesity or morbid obesity admitted for intracerebral hemorrhage were associated with lower in-hospital mortality yet are at increased risk for tracheostomy or gastrostomy [10]. Other conditions were not affected by obesity. For example, obesity was not linked to worse outcomes, including disease recurrence, inpatient and long-term mortality among older patients admitted for acute pancreatitis [11]. In patients receiving extracorporeal life support, obesity did not influence mortality but was associated with a shorter stay [12]. The literature is vast and reports a broad and varied spectrum of the effect of obesity on different conditions. With this debate about whether the obesity paradox exists across different health conditions, this review will systematically analyze the published reviews about the obesity paradox. The objective of this review of reviews is to explore whether the obesity paradox exists across different health conditions regarding mortality and other health outcomes. This review will set the stage to understand better the obesity paradox and guide further research and clinical implications.

METHODOLOGY

PubMed was searched using the key term "obesity paradox" with a systematic review and meta-analysis filter with no restriction on the date. We found that almost all the articles were dated back to 2012. This search was limited to articles since 2012. A total of 46 articles were retrieved and read in-depth by both Dr. Jumana Antoun (JA) and Dr. Roxane Assaf (RA). Six articles were excluded as they were either irrelevant or duplicates. This review includes a total of 40 articles. An excel sheet was prepared to extract the data from the articles that included the following items: year of publication, healthcare disease or condition, nature of the review, number and type of studies included in the review, the total number of participants in the review, level of bias in the included studies in the review and description of the health outcomes.

RESULTS

A total of 40 reviews were included (Table 1). Most of the reviews focused on cardiovascular diseases and included observational cohort studies. Yet, the reviews covered various health systems: cancer (4 reviews), atrial fibrillation (4 reviews), stroke (3 reviews), heart failure (7 reviews), acute coronary events (2 reviews), dialysis (3 reviews), chronic diseases (3 reviews), surgery (4 reviews) and others.

The obesity paradox existed almost in all reviews except for solid tumors, where there was no obesity paradox regarding mortality or treatment toxicities. Nevertheless, the obesity paradox relationship was not homogeneous across the health systems since the reviews have either measured the relationship between mortality and BMI as a continuous variable or between mortality and obesity groups. The relationships found in the reviews were linear, U-shaped, or J-shaped. In most of the U-shaped and J-shaped relationships between

BMI and mortality, the nadir for the least mortality was found in overweight; however, the nadir was for the obesity group in very few reviews.

While overweight and obesity were associated with better survival and less mortality, patients with obesity had higher wound infections, increased risk for kidney disease, longer duration on ventilation, increased cardiac surgery complications, increased risk for heart failure, and higher risk for lower limb ischemia. On the other hand, patients with obesity or overweight may have favorable health outcomes other than mortality, such as better efficacy of Direct Oral Anticoagulants (DOAC), lower risk of bleeding in patients with atrial fibrillation, and less Forced Expiratory Volume (FEV) decline in patients with COPD.

Table 1: Summary of the reviews

No	System	Year	Type of review	No of studies (No of observational studies/ No of Randomized Control Trials)	Total no of patients	Bias/Quality of Studies	Mortality	Outcome 1	Outcome 2
Cardiovascular									
27 (13)	Acute Coronary Syndrome (ACS)	2014	Meta analysis	26 (0)	218,532	No publication bias	Patients with over-weight, obesity, and severe obesity had lower mortality compared with those with normal BMI—R=0.70 (95 % CI 0.64-0.76), RR 0.60, (95 % CI 0.53-0.68) and RR 0.70 (95 % CI 0.58-0.86), respectively)		
13 (14)	Stroke	2015	Meta analysis	17 (17/0)	381,921	Moderate or high quality	Non-linear associations of BMI with all-cause mortality ($P < 0.0001$) and mortality by stroke ($P = 0.05$) were observed. Among overweight and obese stroke patients, the risk of all-cause mortality increased, while the risk of mortality by stroke declined, with an increase in BMI.		

24 (15)	Percutaneous coronary intervention	2015	Meta-nalysis	22 (-)	242,377	Not mentioned	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). 1-year follow-up for mortality is significantly lower in overweight and obese groups (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. Long-term (more than one year) mortality in the overweight and obese patients is 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.		
26 (16)	Post percutaneous Coronary intervention	2015	Systematic review and meta-analysis	100 (-)	884,190	No publication bias	Mortality among the obese patients and the smokers showed an unexpected paradox after coronary intervention. RR of high BMI: 0.61 (in-hospital mortality), 0.67 (short term), 0.64 (long term mortality), p-value = 0.00001		

28 (17)	Post-acute myocardial infarction	2016	Meta-analysis	20 (20/0)	82,076	Good quality	Comparing a healthy weight group to a combined overweight and obese group, the pooled RRs were 0.72 (95% CI: 0.57–0.90) for in-hospital mortality, 0.39 (95% CI: 0.28–0.55) for short-term mortality, 0.66 (95% CI: 0.55–0.78) for medium-term mortality and 0.68 (95% CI: 0.57–0.81) for long-term mortality. Obesity is associated with neither an increased nor a decreased risk of death in patients after acute myocardial infarction (MI) compared with overweight patients		
30 (18)	Cardiac surgery	2016	Systematic review and meta-analysis	One large registry and 26 observational cohort	557,720	High quality	U-shaped association between mortality and body mass index classes was observed with lower mortality in overweight (adjusted odds ratio, 0.79; 95% confidence interval, 0.76–0.83) and obese class I and II (odds ratio, 0.81; 95% confidence interval, 0.76–0.86; and odds ratio, 0.83; 95% confidence interval, 0.74–0.94) patients relative to normal-weight patients.	A U-shaped relationship was observed for stroke and low cardiac output syndrome but not for renal replacement therapy or deep sternal wound infection.	

25 (19)	Percutaneous coronary intervention	2016	Systematic review and meta-analysis	12 (12/0)	91,582	No publication bias	Short-term (30 days) mortality in overweight and obese patients was significantly lower compared to the normal weight patients with RR: 0.72; 95 % CI: 0.56-0.92, p = 0.008 and RR: 0.47, 95 % CI: 0.34-0.65; p < 0.00001 respectively. The long-term (≥ one year) mortality was also significantly lower in the overweight and the obese groups with RR: 0.74, 95 % CI: 0.67-0.82; p < 0.00001 and RR: 0.63, 95 % CI: 0.55-0.72; p < 0.00001 respectively	An intensive medication use after the hospital discharge and during the follow-up period after PCI was observed in the subgroup of obese patients, followed by the overweight patients and the normal-weight patients respectively	
23 (20)	Coronary artery bypass grafting	2016	metanalysis	14 (-)	79,140 patients	No publication bias	Only overweight and not obesity was associated with lower short term (OR=0.85, 0.74-0.98, p=0,.03) midterm-long term mortality (OR=0.90 , 084-0.96, p=0.001).		

32 (21)	Vascular surgery	2017	Systematic review	8 (8/0)	92,525	Medium to high quality	Patients with obesity were associated with lower mortality (odds ratio [OR], 0.64; 95% confidence interval [CI], 0.541-0.757; P < .0001), cardiac morbidity (OR, 0.81; 95% CI, 0.708-0.938; P = .004), and respiratory morbidity (OR, 0.87; 95% CI, 0.802-0.941; P = .0006) after vascular surgery compared with patients of normal weight.	Patients with obesity were associated with a higher wound complication rate (OR, 2.39; 95% CI, 1.777-3.211; *P* < .0001) compared with normal patients.	
14 (22)	Stroke	2017	Systematic review	25	-	Not mentioned	Fewer mortality rates in stroke patients with higher BMI in 10/12 studies	Favorable effect on the recurrence of stroke, MI, or vascular death	Obesity paradox was not found in acute stroke patient treated with IVT (Intravenous Thrombolysis)
29 (23)	Transcatheter aortic valve implantation for aortic stenosis	2017	Systematic review and meta-analysis	16 (16/0)	14,882	Good quality	Paradox exists for thirty-day mortality OR 0.95[0.93,0.97, p<0.001	No effect on life-threatening bleeding, major vascular complications, acute kidney injury cerebrovascular events, or MI	
11 (24)	Lower limb ischemia (LLI)	2018	Systematic review	31 (30/1)	75,738	Not mentioned		Better results for endovascular and surgical treatment in patients with overweight and class I obesity	Greater prevalence in overweight and obese patients

31 (25)	Post cardiac surgery	2018	Systematic review and meta-analysis	52 (30/22)	740,514	No publication bias	A reverse J-shaped association exists between in-hospital mortality rates after cardiac surgery and the different BMI groups with overweight and class I obese patients showing the lowest mortalities. Overweight and obese patients had similar or slightly lower in-hospital mortality rates after cardiac surgery compared with normal-weight individuals.	Postoperative complication rates increased with higher BMI levels.	
22 (26)	Coronary revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)	2018	Meta-analysis	65 (65/0)	865,774	Good quality, no publication bias	A U-shaped association was observed across BMI categories for all-cause mortality. Using normal weight as the reference, all-cause mortality was lowered in patients with overweight, obese, and severely obese.	The risk of major adverse coronary events (MACE) was lowest among patients with overweight.	Risks of myocardial infarction, cardiovascular-related mortality, stroke, and heart failure no significant association was observed among individuals with higher BMI as compared to patients with normal BMI.
15 (27)	Subarachnoid hemorrhage	2020	Systematic review	6 (6/0)	-	Low quality	Mixed results about paradox about short term mortality, long term mortality; Paradox positive for long term overall survival		

12 (28)	Stroke	2021	Systematic review and meta-analysis	33 (33/0)	84,660	Not mentioned	Obesity was associated with longer survival in ACUTE ischemic stroke patients than normal weight, the pooled HR of mortality was 0.75 (95% CI: 0.64-0.88) Obesity and overweight were associated with longer survival in MIXED-stroke patients (acute ischemic stroke combined with one or more other stroke subtypes) than normal-weight with pooled hazard ratios (HRs) of mortality were 0.77 (95% confidence interval [CI]: 0.71 to 0.83) for obesity, 0.76 (95% CI: 0.72-0.80) for overweight.		
Atrial Fibrillation									
7 (34)	Atrial Fibrillation	2017	Systematic review and meta-analysis	13 (8/5)	-	High quality	-	Both patients with overweight and obesity have a lower risk for stroke/systemic embolic event (odds ratio [OR], 0.75; 95% confidence interval [CI], 0.66–0.84 and OR, 0.62; 95% CI, 0.54–0.70, respectively)	For major bleeding, only patients with obesity were at lower risk compared with patients with normal weight (OR, 0.84; 95% CI, 0.72–0.98
8 (35)	Atrial Fibrillation (AF)	2017	Systematic review	61 (57/4)	1,307,563	Not mentioned	Lower all-cause mortality in AF patients with overweight compared to those of normal weight or who are underweight.		

9 (36)	Direct oral anticoagulants vs Warfarin in atrial fibrillation	2020	Systematic review and meta-analysis	9 (2/7)	-	Moderate to high quality	-	DOACs have better efficacy and safety profiles than warfarin in patients with normal weight and overweight and are not inferior to warfarin in obese patients.	
10 (37)	Anticoagulated patients with atrial fibrillation	2021	Systematic review and meta-analysis	9 (5/4)	-	No publication bias	Significantly lower risks of all-cause mortality (RR 0.73, 95%CI [0.64–0.83]; RR 0.61, 95%CI [0.52–0.71]; and RR 0.56, 95%CI [0.47–0.66], respectively) in anticoagulated AF patients who are overweight, obese, and morbidly obese compared to patients with normal BMI	Significantly lower risks of stroke or systemic embolism (RR 0.80, 95%CI [0.73–0.87]; RR 0.63, 95%CI [0.57–0.70]; and RR 0.42, 95%CI [0.31–0.57], respectively) in overweight, obese, and morbidly obese anticoagulated AF patients compared to normal BMI anticoagulated AF patients	Compared to anticoagulated AF patients with normal BMI, anticoagulated AF patients who are overweight and obese, had lower risks of (1)major bleeding (RR 0.86, 95%CI [0.76–0.99]; and RR 0.88, 95%CI [0.79–0.98], respectively) and (2) intracranial bleeding (RR 0.75, 95%CI [0.58–0.97]; and RR 0.57, 95%CI [0.40–0.80], respectively)
Heart Failure									
20 (38)	Heart failure	2014	Meta analysis	14 (14/0)	23,967	Not mentioned	Mortality in both HF subtypes was U-shaped, with a nadir at 30.0–34.9 kg m 2		

16 (39)	Heart failure (HF)	2015	Systematic review and meta-analysis	6 (6/0)	22,807	Not mentioned	Risk for cardiovascular (CV) mortality was lowest in patients who are overweight (RR 0.79, 95% CI 0.70 to 0.90) Increasing degree of obesity failed to achieve a statistically significant effect on CV mortality (RR 0.82, 95% CI 0.64 to 1.05, and RR 0.71, 95% CI 0.50 to 1.01, for obese and severely obese, respectively)	Risk for CV hospitalization was lowest in patients with overweight (RR 0.92, 95% CI 0.86 to 0.97) Increasing degree of obesity failed to achieve a statistically significant effect on hospitalization (RR 0.99, 95% CI 0.92 to 1.07, and RR 1.28, 95% CI 0.88 to 1.87, for obese and severely obese, respectively).	
17 (40)	Heart failure	2016	Systematic review	10 (9/1)	-	Moderate to high quality	Better survival in persons with higher BMI, Waist Circumference (WC), or Triceps Skinfold thickness (TSF)		
19 (41)	Heart failure	2019	Systematic review	75 (72/3)	44,564 CHF incident cases among 2,560,753 participants	Not mentioned	Overweight and obesity are associated with the reduction of mortality in congestive h heart failure (CHF) by 24–59% and 15–65%, respectively.	Higher BMI increases the risk of CHF by 15– 70%, especially when associated with severe, long-lasting, and abdominal obesity.	Overweight and obesity do not affect the outcome of invasive CHF treatment.

21 (42)	Heart failure with preserved ejection fraction (HFpEF) and Heart failure with reduced ejection fraction (HFrEF)	2019	Meta-analysis	10 (10/0)	96,424	No publication bias	For patients with HFpEF, the summary hazard ratio (HR) for all-cause mortality was: 0.93 (95% CI 0.89–0.97) per 5 units increase in BMI (but the association was U-shaped with the nadir of risk at a BMI of 32–33 kg/m2). For patients with HFrEF, the summary HR for all-cause mortality was: 0.96 (95% CI 0.92–0.99) (The relationship was also U-shaped although 'flatter' than for HFpEF, with the nadir at a BMI of 33 kg/m2		
18 (43)	Heart failure	2020	Systematic review and metanalysis	20 (-)	-	Good quality	A U-shaped relationship curve was observed between CV mortality and BMI; the overweight cohort experiencing the least CV mortality	J curve relationship between BMI and risk of heart failure max risk in morbid obese 1.73 [1.3 to 2.31 p<0.001]	
Cancer									
4 (29)	Renal cell carcinoma	2016	Meta-analysis	8 (8/0)	10,512	The quality of the articles ranged from high, moderate to low quality	The association of BMI with cancer-specific survival (CSS) and overall survival (OS) was non-linear (P<0.0001, P=0.004, respectively). Each unit increase in BMI over 25 was associated with decreased OS.		

5 (30)	Lung cancer	2017	Meta analysis	15	15,191,571	Good quality	A nonlinear association between BMI and the risk of lung cancer mortality was found. Participants with higher BMI have a lower risk of lung cancer death than slim people. Combined relative risks per 5kg/m2 in BMI for risk of lung cancer mortality is 0.94 (95% confidence interval] 0.92–0.96), and a nonlinear association was found (P nonlinearity<.0 001).		
6 (31)	Lung cancer surgery	2017	Systematic review and metanalysis	25 (25/0)	78,143	Good quality	Significantly lower mortality rate in patients with obesity (OR: 0.78; 95% CI: 0.63–0.98; P = 0.031)	No significant benefit of increased BMI on in-hospital morbidity when BMI was measured as continuous; but there was a decrease in overall morbidity among obese patients OR=0.84 (0.73-0.98, p=0.025)	
2 (32)	Solid tumors	2021	Systematic review	18 (18/0)	7273		No association between BMI and survival outcomes	No impact of BMI on the incidence of treatment-related toxicities in melanoma, NSCLC, and solid tumors.	

3 (33)	Kidney cancer	2021	Systematic review and meta-analysis	34 (-)	50,717	The methodological quality of the studies was good in most of the studies, but 2 were poor and 2 were fair.	Compared to patients with normal BMI, patients who are overweight and obese were associated with improved (1) cancer-specific survival (HR 0.85, 95% CI 0.79–0.93). (2) progression-free survival (HR 0.68, 95% CI 0.59–0.78) and (3) overall survival (HR 0.66, 95% CI 0.55–0.79)		
Renal/Hypertension									
39 (44)	Hemodialysis	2012	Meta analysis	4 (4/0)	81423	Low quality	Elevated BMI (BMI >25, OR 0.67, 95% CI 0.65–0.68) had lower all-cause mortality. In a risk-adjusted sensitivity analysis, elevated BMI levels (adjusted hazard ratio 0.94, 95% CI 0.92–0.96) remained protective against mortality		
38 (45)	non-dialysis-dependent chronic kidney disease	2015	Systematic review and meta-analysis	14 (14/0)	484,906	Medium to high quality	In stage 3-5 chronic kidney disease (CKD), overweight or obese class I was associated with a lower risk of death; however, obesity classes II and III were not associated with risk of death.	Reanalysis of the largest available study showed that a higher BMI was associated with an incrementally higher risk of kidney disease progression; however, this association was attenuated in our pooled results.	

40 (46)	Peritoneal Dialysis	2016	Systematic review and meta-analysis	13 (13/0)	213,403	High quality	Underweight was associated with higher 1-year mortality but had no significant association with 2- and 3- to 5-year mortalities. Overweight or obesity was associated with lower 1-year mortality, but it had no significant association with 2-, and 3- to 5-year mortalities		
33 (47)	Hypertension	2018	Systematic review	14 (14/0)	489,222	Medium to high quality	5-unit increment in BMI was associated with an 8% reduction in the risk of all-cause mortality (Pooled RR: 0.92, 95% CI: 0.87, 0.97, P = 0.003; I2 = 95.7%, n = 13), and marginally and inversely associated with the risk of cardiovascular mortality (Pooled RR: 0.95, 95% CI: 0.88, 1.02, P = 0.15; I 2 = 90.3%, n = 5). A reverse J-shaped association between BMI and risk of all-cause and cardiovascular mortality, with a nadir at BMI of ~27.5–30 kg/m2.		
Others									

1 (48)	Fitness and Physical Activity	2015	Systematic review	15 (15/0)	261472	Selection and methodologic bias	Increasing BMI had a non-positive association with all-cause mortality, with the persistence of the obesity paradox despite adjustment for physical activity or cardiorespiratory fitness.		
34 (49)	Type 2 Diabetes Mellitus (DM)	2017	Meta-analysis	18 (18/0)	537,966 (Sixteen cohort studies on all-cause mortality (n = 445,125) and two studies on cardiovascular mortality (n = 92,841)	No publication bias	A non-linear U-shaped association was observed between BMI and all-cause mortality among patients with type 2 diabetes with a BMI nadir of 28–30 kg/m2. The risk of cardiovascular mortality exhibited a gradual non-linear increase for BMI > 31 kg/m2, with a BMI nadir of 29–31 kg/m2 .		

35 (50)	Mechanically ventilated adults in an intensive care unit (ICU)	2018	Systematic review and meta-analysis	23 (14/9)	199,421	Good quality	Higher BMI is associated with lower mortality and longer duration on mechanical ventilation In comparison to non-obese patients, obese patients had lower ICU mortality (odds ratio (OR) 0.88, 95% CI 0.0.84–0.92, I2 = 0%), hospital mortality (OR 0.83, 95% CI 0.74–0.93, I2 = 52%), short-term mortality (OR 0.81, 95% CI 0.74–0.88, I2 = 0%) as well as long-term mortality (OR 0.69, 95% CI 0.60–0.79, I2 = 0%). All 4 mortality measures were higher in underweight subjects than in subjects with normal BMI.	Obese subjects had significantly longer duration on mechanical ventilation than non-obese group (mean difference (MD) 0.48, 95% CI 0.16–0.80, I2 = 37%),	Hospital length of stay (LOS) did not differ between obese and non-obese patients (MD 0.05, 95% CI -0.52 to 0.50, I2 = 80%). Obese patients had longer ICU LOS than non-obese patients (Mean difference-MD 0.38, 95% CI 0.17–0.59, I2 = 70%).
36 (51)	COPD	2019	Systematic review and meta-analysis	5 (0/5)	33,021	Good quality	-	The rate of FEV1 decline decreased with increasing BMI.	
37 (3)	Sepsis	2020	Systematic review	9 (9/0)	1,895,323	Good quality	Lower sepsis mortality among obese patients in the first 30 days and 1 year		

DISCUSSION

This review of reviews regarding the obesity paradox has shown that obesity has a favorable effect on mortality almost in all reviews that cover a diverse set of health conditions, including stroke, heart failure,

atrial fibrillation, post-cardiac revascularization, kidney failure, and others. The relationship between BMI and mortality was J-shaped or U-shaped. This highlights the fact that obesity is not a homogenous disease state. Overweight and class I obesity seem to have the best prognosis. Most of the studies use BMI as a measure of obesity; this is what led some to argue that a better term would be "BMI paradox" rather than "obesity paradox" (52). Many of the patients studied in the literature were elderly where BMI may not be the best estimate of obesity or fat content. In a prospective analysis of 23603 consecutive hospitalizations over two years, obese patients had a similar or lower risk of in-hospital all-cause mortality, non-schedule readmission in 14 days, and length of stay as compared to patients with a normal BMI (52). Yet, in the same study, high body fat based on BMI, age, and gender were associated with a higher risk of all-cause in-hospital mortality and readmission (52). Moreover, obesity may be accompanied by malnourishment. In one study, patients with morbid obesity and malnourishment were 11 times more likely to have pressure ulcers than patients with morbid obesity alone (53). Finally, age is an important contributor to this protective effect of BMI in specific outcomes. In an analysis of 22903 hospitalizations, the protective effect of BMI on death, length of stay, and adverse outcomes after discharge was not present in the youngest cohort but was significant in the older cohort only (54). Similarly, a subgroup analysis has shown that the strength and shape of the association between BMI and all-cause mortality in patients with hypertension might be influenced by age (47).

What does the obesity paradox mean in our clinical practice? Do we stop advising patients to lose weight when they are obese and have disease complications? Is the observed improved mortality among patients with obesity related to a more intensive treatment of their risk factors and conditions? One review has shown that intensive medication use was observed after hospital discharge and during the follow-up period after PCI in the subgroup of patients with obesity followed by overweight and patients with normal weight (19). Intentional weight loss by bariatric surgery was associated with improvement in cardiac function in patients with obesity (43). Finally, the non-linear relationship between obesity and mortality has shown that overweight and class 1 obesity may have more favorable outcomes than other obesity classes. Is this a call to avoid aggressive weight loss attempts in this group of patients? Is this the time to relook into BMI groups and redefine the normal? The lack of RCTs in the reviews and the non-homogeneous use of obesity groups and BMI in the data analysis will leave us with more questions than answers.

LIMITATIONS

The search was restricted to PubMed with limited keywords; nevertheless, the current review of reviews still included a good number of reviews (40 reviews). None of the reviews addressed the pathophysiology of the obesity paradox, although the authors of the reviews included possible explanations of the obesity paradox from statistical aberrations (example, BMI and age) to the role of inflammation and adipose tissue.

CONCLUSION

Obesity is related to better survival and lower mortality across diverse health conditions while increasing the risk for other health outcomes. There is a need for clinical randomized controlled trials to validate this benefit and understand the pathophysiology behind the obesity paradox. Meanwhile,

patients with obesity remain a challenge in the clinical context and need special attention to address their obesity and control their risk factors.

Notes

Potential conflicts of interest: The author reports no conflicts of interest in this work.

Abbreviations:

- ACS: Acute Coronary Syndrome
- AF: Atrial Fibrillation
- BMI: Body Mass Index
- CABG: Coronary Artery Bypass Grafting
- CHF: Congestive Heart Failure
- CI: Confidence Interval
- CKD: Chronic Kidney Disease
- COPD: Chronic Obstructive Pulmonary Disease
- CSS: Cancer-Specific Survival
- CV: Cardiovascular
- DOAC: Direct Oral Anticoagulants
- FEV: Forced Expiratory Volume
- HF: Heart Failure
- HFpEF: Heart Failure with Preserved Ejection Fraction
- HFrEF: Heart Failure with Reduced Ejection Fraction
- HR: Hazard Ratio
- ICU: Intensive Care Unit
- IVT: Intravenous Thrombolysis
- JA: Jumana Antoun, M.D.
- LLI: Lower Limb Ischemic
- LOS: Length of Stay
- MACE: Major adverse cardiovascular events
- MD: Mean Difference
- MI: Myocardial Infarction
- RA: Roxane Assaf, M.D.
- R2W4É80L-CT: Randomized Control Trial
- RR: Relative Risk
- OR: Odd's Ratio
- OS: Overall Survival
- PCI: Percutaneous Coronary Intervention
- TSF: Triceps Skinfold Thickness
- WC: Waist Circumference

References

1. Jagan N, Morrow LE, Walters RW, Plambeck RW, Wallen TJ, Patel TM, et al. Sepsis and the Obesity Paradox: Size Matters in More Than One Way. Crit Care Med. 2020;48(9):e776-e82.
2. Kalani C, Venigalla T, Bailey J, Udeani G, Surani S. Sepsis Patients in Critical Care Units with Obesity: Is Obesity Protective? Cureus. 2020;12(2):e6929.
3. Robinson J, Swift-Scanlan T, Salyer J. Obesity and 1-Year Mortality in Adults After Sepsis: A Systematic Review. Biol Res Nurs. 2020;22(1):103-13.
4. Robinson J, Swift-Scanlan T, Salyer J, Jones T. The Obesity Paradox in Sepsis: A Theoretical Framework. Biol Res Nurs. 2020;22(2):287-94.
5. Agarwal M, Agrawal S, Garg L, Lavie CJ. Relation Between Obesity and Survival in Patients Hospitalized for Pulmonary Arterial Hypertension (from a Nationwide Inpatient Sample Database 2003 to 2011). Am J Cardiol. 2017;120(3):489-93.
6. Ji Z, de Miguel-Diez J, Castro-Riera CR, Bellon-Cano JM, Gallo-Gonzalez V, Giron-Matute WI, et al. Differences in the Outcome of Patients with COPD according to Body Mass Index. J Clin Med. 2020;9(3).
7. Lester ELW, Dvorak JE, Maluso PJ, Bendjemil S, Messer T, Poulakidas S, et al. Obesity Paradox in the Burn Patient. J Burn Care Res. 2020;41(1):30-2.
8. Agarwal MA, Garg L, Shah M, Patel B, Jain N, Jain S, et al. Relation of Obesity to Outcomes of Hospitalizations for Atrial Fibrillation. Am J Cardiol. 2019;123(9):1448-52.
9. Harris CM, Abougergi MS, Wright S. Clinical outcomes among morbidly obese patients hospitalized with diabetic foot complications. Clin Obes. 2019;9(1):e12285.
10. Persaud SR, Lieber AC, Donath E, Stingone JA, Dangayach NS, Zhang X, et al. Obesity Paradox in Intracerebral Hemorrhage. Stroke. 2019;50(4):999-1002.
11. Biberci Keskin E, Buyukaydin B, Soysal P, Kiremitci S, Yabaci A, Senturk H. The impact of obesity on acute pancreatitis outcomes in older patients. Eur Geriatr Med. 2020;11(3):427-32.
12. Christian-Miller N, Hadaya J, Nakhla M, Sanaiha Y, Madrigal J, Emami S, et al. The impact of obesity on outcomes in patients receiving extracorporeal life support. Artif Organs. 2020;44(11):1184-91.
13. Niedziela J, Hudzik B, Niedziela N, Gasior M, Gierlotka M, Wasilewski J, et al. The obesity paradox in acute coronary syndrome:

a meta-analysis. Eur J Epidemiol. 2014;29(11):801-12.
14. Bagheri M, Speakman JR, Shabbidar S, Kazemi F, Djafarian K. A dose-response meta-analysis of the impact of body mass index on stroke and all-cause mortality in stroke patients: a paradox within a paradox. Obes Rev. 2015;16(5):416-23.
15. 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(44):e1910.
16. Bundhun PK, Wu ZJ, Chen MH. Impact of Modifiable Cardiovascular Risk Factors on Mortality After Percutaneous Coronary Intervention: A Systematic Review and Meta-Analysis of 100 Studies. Medicine (Baltimore). 2015;94(50):e2313.
17. Wang L, Liu W, He X, Chen Y, Lu J, Liu K, et al. Association of overweight and obesity with patient mortality after acute myocardial infarction: a meta-analysis of prospective studies. Int J Obes (Lond). 2016;40(2):220-8.
18. Mariscalco G, Wozniak MJ, Dawson AG, Serraino GF, Porter R, Nath M, et al. Body Mass Index and Mortality Among Adults Undergoing Cardiac Surgery: A Nationwide Study With a Systematic Review and Meta-Analysis. Circulation. 2017;135(9):850-63.
19. Tan XF, Shi JX, Chen AM. Prolonged and intensive medication use are associated with the obesity paradox after percutaneous coronary intervention: a systematic review and meta-analysis of 12 studies. BMC Cardiovasc Disord. 2016;16:125.
20. Takagi H, Umemoto T, Group A. Overweight, but not obesity, paradox on mortality following coronary artery bypass grafting. J Cardiol. 2016;68(3):215-21.
21. Galyfos G, Geropapas GI, Kerasidis S, Sianou A, Sigala F, Filis K. The effect of body mass index on major outcomes after vascular surgery. J Vasc Surg. 2017;65(4):1193-207.
22. Oesch L, Tatlisumak T, Arnold M, Sarikaya H. Obesity paradox in stroke - Myth or reality? A systematic review. PLoS One. 2017;12(3):e0171334.
23. Lv W, Li S, Liao Y, Zhao Z, Che G, Chen M, et al. The 'obesity paradox' does exist in patients undergoing transcatheter aortic valve implantation for aortic stenosis: a systematic review and meta-analysis. Interact Cardiovasc Thorac Surg. 2017;25(4):633-42.
24. Spychalska-Zwolinska M, Zwolinski T, Anaszewicz M, Budzynski J. The influence of patients' nutritional status on the prevalence, course and treatment outcomes of lower limb ischemia: an overview of current evidence. Int Angiol. 2018;37(2):100-11.
25. Borracci RA, Ingino CA, Miranda JM. Association of body mass index with short-term outcomes after cardiac surgery: retrospective study and meta-analysis. Medicina (B Aires). 2018;78(3):171-9.
26. Ma WQ, Sun XJ, Wang Y, Han XQ, Zhu Y, Liu NF. Does body mass index truly affect mortality and cardiovascular outcomes in patients after coronary revascularization with percutaneous coronary intervention or coronary artery bypass graft? A systematic review and network meta-analysis. Obes Rev. 2018;19(9):1236-47.
27. Rautalin I, Kaprio J, Korja M. Obesity paradox in subarachnoid hemorrhage: a systematic review. Neurosurg Rev. 2020;43(6):1555-63.
28. Zhang P, Yan XL, Qu Y, Guo ZN, Yang Y. Association between abnormal body weight and stroke outcome: A meta-analysis and systematic review. Eur J Neurol. 2021.
29. Bagheri M, Speakman JR, Shemirani F, Djafarian K. Renal cell carcinoma survival and body mass index: a dose-response meta-analysis reveals another potential paradox within a paradox. Int J Obes (Lond). 2016;40(12):1817-22.
30. Shen N, Fu P, Cui B, Bu CY, Bi JW. Associations between body mass index and the risk of mortality from lung cancer: A dose-response PRISMA-compliant meta-analysis of prospective cohort studies. Medicine (Baltimore). 2017;96(34):e7721.
31. Li S, Wang Z, Huang J, Fan J, Du H, Liu L, et al. Systematic review of prognostic roles of body mass index for patients undergoing lung cancer surgery: does the 'obesity paradox' really exist? Eur J Cardiothorac Surg. 2017;51(5):817-28.
32. Indini A, Rijavec E, Ghidini M, Tomasello G, Cattaneo M, Barbin F, et al. Impact of BMI

on Survival Outcomes of Immunotherapy in Solid Tumors: A Systematic Review. Int J Mol Sci. 2021;22(5).
33. Kim LH, Doan P, He Y, Lau HM, Pleass H, Patel MI. A Systematic Review and Meta-Analysis of the Significance of Body Mass Index on Kidney Cancer Outcomes. J Urol. 2021;205(2):346-55.
34. Proietti M, Guiducci E, Cheli P, Lip GY. Is There an Obesity Paradox for Outcomes in Atrial Fibrillation? A Systematic Review and Meta-Analysis of Non-Vitamin K Antagonist Oral Anticoagulant Trials. Stroke. 2017;48(4):857-66.
35. Anaszewicz M, Budzynski J. Clinical significance of nutritional status in patients with atrial fibrillation: An overview of current evidence. J Cardiol. 2017;69(5):719-30.
36. Zhou Y, Ma J, Zhu W. Efficacy and Safety of Direct Oral Anticoagulants Versus Warfarin in Patients with Atrial Fibrillation Across BMI Categories: A Systematic Review and Meta-Analysis. Am J Cardiovasc Drugs. 2020;20(1):51-60.
37. Grymonprez M, Capiau A, De Backer TL, Steurbaut S, Boussery K, Lahousse L. The impact of underweight and obesity on outcomes in anticoagulated patients with atrial fibrillation: A systematic review and meta-analysis on the obesity paradox. Clin Cardiol. 2021;44(5):599-608.
38. Padwal R, McAlister FA, McMurray JJ, Cowie MR, Rich M, Pocock S, et al. 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(8):1110-4.
39. Sharma A, Lavie CJ, Borer JS, Vallakati A, Goel S, Lopez-Jimenez F, et al. 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(10):1428-34.
40. Oga EA, Eseyin OR. The Obesity Paradox and Heart Failure: A Systematic Review of a Decade of Evidence. J Obes. 2016;2016:9040248.
41. Wawrzenczyk A, Anaszewicz M, Wawrzenczyk A, Budzynski J. Clinical significance of nutritional status in patients with chronic heart failure-a systematic review. Heart Fail Rev. 2019;24(5):671-700.
42. 4Zhang J, Begley A, Jackson R, Harrison M, Pellicori P, Clark AL, et al. Body mass index and all-cause mortality in heart failure patients with normal and reduced ventricular ejection fraction: a dose-response meta-analysis. Clin Res Cardiol. 2019;108(2):119-32.
43. Mahajan R, Stokes M, Elliott A, Munawar DA, Khokhar KB, Thiyagarajah A, et al. Complex interaction of obesity, intentional weight loss and heart failure: a systematic review and meta-analysis. Heart. 2020;106(1):58-68.
44. Jialin W, Yi Z, Weijie Y. Relationship between body mass index and mortality in hemodialysis patients: a meta-analysis. Nephron Clin Pract. 2012;121(3-4):c102-11.
45. Ahmadi SF, Zahmatkesh G, Ahmadi E, Streja E, Rhee CM, Gillen DL, et al. Association of Body Mass Index with Clinical Outcomes in Non-Dialysis-Dependent Chronic Kidney Disease: A Systematic Review and Meta-Analysis. Cardiorenal Med. 2015;6(1):37-49.
46. Ahmadi SF, Zahmatkesh G, Streja E, Mehrotra R, Rhee CM, Kovesdy CP, et al. Association of Body Mass Index With Mortality in Peritoneal Dialysis Patients: A Systematic Review and Meta-Analysis. Perit Dial Int. 2016;36(3):315-25.
47. Jayedi A, Shab-Bidar S. Nonlinear dose-response association between body mass index and risk of all-cause and cardiovascular mortality in patients with hypertension: A meta-analysis. Obes Res Clin Pract. 2018;12(1):16-28.
48. Yerrakalva D, Mullis R, Mant J. The associations of "fatness," "fitness," and physical activity with all-cause mortality in older adults: A systematic review. Obesity (Silver Spring). 2015;23(10):1944-56.
49. Kwon Y, Kim HJ, Park S, Park YG, Cho KH. Body Mass Index-Related Mortality in Patients with Type 2 Diabetes and Heterogeneity in Obesity Paradox Studies: A Dose-Response Meta-Analysis. PLoS One. 2017;12(1):e0168247.
50. Zhao Y, Li Z, Yang T, Wang M, Xi X. Is body mass index associated with outcomes of mechanically ventilated adult patients in intensive critical units? A systematic review

and meta-analysis. PLoS One. 2018;13(6):e0198669.
51. Sun Y, Milne S, Jaw JE, Yang CX, Xu F, Li X, et al. BMI is associated with FEV1 decline in chronic obstructive pulmonary disease: a meta-analysis of clinical trials. Respir Res. 2019;20(1):236.
52. Tojek K, Wustrau B, Czerniak B, Korzycka-Wilinska W, Winiarski P, Banaszkiewicz Z, et al. Body mass index as a biomarker for the evaluation of the "Obesity Paradox" among inpatients. Clin Nutr. 2019;38(1):412-21.
53. Ness SJ, Hickling DF, Bell JJ, Collins PF. The pressures of obesity: The relationship between obesity, malnutrition and pressure injuries in hospital inpatients. Clin Nutr. 2018;37(5):1569-74.
54. Woolley C, Thompson C, Hakendorf P, Horwood C. The Effect of Age upon the Interrelationship of BMI and Inpatient Health Outcomes. J Nutr Health Aging. 2019;23(6):558-63.