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Demystifying the Obesity Paradox in Acute Conditions and Injuries

Bowei Su* and Sebastien Fuchs
Western University of Health Sciences, USA

Abstract

Efficient lipid storage has been crucial to survival for much of human history; however, in the modern era, this trait has evolved into a rising obesity pandemic of great concern, with rates tripling since 1975. Obesity is a well-established pro-inflammatory process leading to diabetes, hypertension, heart disease, cancer, and other long-term sequelae. The detrimental effects of obesity are prevalent throughout literature. On the other hand, the question of any possible benefits yields less of a consensus. There has been growing evidence across multiple fields describing a phenomenon called the "Obesity Paradox", which describes a possible mortality benefit with being overweight/obese in the setting of acute and chronic illness. We compiled studies investigating this phenomenon in relation to leading American causes of death, including heart disease, blunt trauma, cancer, and lung injury which are covered in this current snapshot. We examine common clinical and methodological themes between studies, and limitations of the implications inherent in study design and the body mass index metric. This review is meant to be a bird's-eye overview of the ongoing debate surrounding this in several fields to facilitate discussion and propose directionality for future research to further elucidate the nuances of the complex relationships with obesity.

Introduction

The process of efficient storage of energy-rich molecules from the diet for later use has been a crucial component to survival for much of human evolution. However, in the modern era of nutritional surplus and overconsumption, this process has instead led to a growing obesity pandemic. Worldwide obesity rates have almost tripled since 1975, and as of 2016, 39% of adults were overweight and 13% were obese [1]. Extensive research has established obesity as a pro-inflammatory process, making it a major risk factor towards developing chronic conditions such as heart disease, atherosclerosis, stroke, diabetes, osteoarthritis, and several cancers including colon, kidney, gallbladder, liver, breast, ovarian, endometrial, and prostate [1]. These sequelae are amongst the leading causes of death in the US, accounting for over 1.47 million deaths in 2017 [2].

The detrimental effects of obesity are well-described in literature, and associated stigma is prevalent in the present day. However, there has been recently emerging evidence describing a possible mortality benefit in patients with certain pathologies. One of the earliest instances of this phenomenon was seen in 1999 with chronic kidney disease patients [3], and the term "Obesity Paradox" was coined by Gruberg et al., [4] in 2002 when they found surprisingly lower complication rates with percutaneous coronary interventions (PCI) in overweight and obese patients compared to normal and underweight groups. The validity of this phenomenon remains highly controversial, but several studies across multiple fields pointing to a U or inverse J-shaped curve between mortality and BMI following an acute injury or illness. We briefly survey the paradox in the broader setting of post-acute illness, including blunt trauma, stroke, cancer, and intensive care unit (ICU) conditions such as sepsis and lung injury which are amongst the leading causes of death in America [2]. An abundance of obesity paradox literature parallels these same conditions available for discussion and evaluation. Conflicting observations are presented, and the mechanisms behind this relationship remain speculative. Recurrent themes amongst hypotheses can be separated into clinical and methodological explanations. The physiological aspect posits an energy reserve, where obesity is speculated to confer a higher metabolic reserve necessary for recovery post-exposure to an insult. Other hypotheses describe paradoxical protective effects in terms of toxicological exposure, inflammation, and tumor development that appear with obesity. The methodological aspect attributes findings to low-quality evidence [5] and confounding bias [6] amongst other study design considerations that will be covered.

The scope of this review is not to be systematic, but to propose a discussion regarding the obesity paradox based upon evidence-backed publications. A full meta-analysis of the phenomenon as a whole is challenging due to the limitations and heterogeneity of currently available data; instead, we provide an eagle-eye overview of the most promising fields in support of further in-depth investigation of the obesity paradox. We examine thematic trends in our review and contrast them to study limitations in order to put the implications in perspective. As a secondary discussion, we examine the validity and limitations of body mass index (BMI) as the common underlying metric.

Methods

We searched the PubMed database with the keywords "obesity", "paradox", "trauma", "mortality", "BMI", "cancer", "sepsis", "lung injury", "stroke", "COVID", "atherosclerosis", and "myocardial infarct" from inception to 2020 and selected relevant papers discussing the relationship between mortality and BMI in the setting of these stressors, and the mechanisms behind them. We then compiled and contrasted findings with the intent to provide a broader understanding of the current landscape and indicated remaining points of contention to be investigated in future research.

Non-obese	
Underweight	<18.5 kg/m^2
Normal	18.5-24.9 kg/m^2
Overweight	25-29.9 kg/m^2
Obese	
Class I Obesity	30-34.9 kg/m^2
Class II Obesity	35-39.9 kg/m^2
Class III Obesity (Morbidly Obese)	>40 kg/m^2

Table 1: BMI classifications as used by World Health Organization and National Institute of Health.

***Corresponding author:** Bowei Su, Western University of Health Sciences, USA, Tel: 4083682478; E-mail: bowei.su@westernu.edu

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We will be referring to BMI classifications as used by World Health Organization and National Institute of Health (Table 1).

Results

Clinical presentations

Trauma

Our initial investigation began with an inquiry of protective effects of excess fat mass in the setting of blunt trauma. Studies on the relationship between blunt trauma mortality and obesity have been revealing inconsistent findings. Retrospective cohort studies [7,8] detected no significant difference in blunt trauma mortality across all BMI subgroups. Additionally, increases in ventilator days, hospital and ICU length of stay (LOS) accompanied each increase in BMI category. LOS with morbidly obese patients were double that of normal weight patients. Dvorak et al., [9] instead found a U-shaped relationship between BMI and adjusted odds of mortality, with the bottom of the curve falling at 0.916 odds of mortality with the overweight BMI. Meanwhile, underweight, Class II obese, and morbidly obese patients appeared to have increased odds of mortality (1.378, 1.178, 1.515 respectively). The secondary analysis found a similar increase in ICU and hospital LOS with each BMI category increase over normal. This is likely due to a secondary finding of more than two-fold complication rates amongst obese patients, most commonly with infectious processes such as UTI and pneumonia [7]. In other words, the authors observed a decreasing mortality as BMI increased towards class I obesity followed by increasing mortality as BMI increased towards morbid obesity.

In contrast, other retrospective studies found an association between obesity and increasing mortality risk [10,11]. This is in agreement with a 2013 meta-analysis, where Liu et al., [5] pooled 18 relevant cohort studies (13 retrospective, 5 prospective) spanning from 1991-2012 including several studies mentioned above [5]. They found extended ICU stays and increased post-injury organ dysfunction rates consistent with previous literature, but also found an overall positive correlation between obesity and mortality risk. Interestingly, injury severity did not differ significantly between BMI groups during analysis and could not factor into the differing mortality rates [8,11].

Overall, the majority of studies covered seem to indicate a worse prognosis with higher BMI; obesity did not play a role in reducing injury severity and, in fact, lent to a higher risk of infectious complications.

Cardiovascular disease

Wang et al., [12] investigated post-acute myocardial infarction (AMI) mortality benefit of higher BMI within a pool of 20 prospective studies in 2015. They found that an increase BMI correlated with decreased mortality from all causes both in-hospital (11 studies) and post-discharge (15 studies). This post-discharge period was further separated into short (<6 months), medium (approximately 1 year), and long (>2 years) term follow up, and a mortality benefit persisted in all three categories. Although the study did not account for confounding factors due to study design heterogeneity, subgroup analyses of STEMIs patients only undergoing percutaneous coronary intervention (PCI) did not show this association. It seems that obese patients die less from cardiovascular causes, as substantiated by Brodsky et al., [13] studying atherosclerosis. The authors found that decedents in the BMI>40 kg/m^2 had a 40% reduction in atherosclerotic severity of the descending and abdominal aorta above the iliac bifurcation compared to decedents with BMI<40 kg/m^2. Some proposed explanations for this paradoxical finding include reduced aortic wall shear stress and different gene signatures with morbid obesity compared to the rest of the population, warranting further investigations [14,15].

Previous reviews found that the obesity paradox has been paralleled in cardiovascular disease spanning coronary artery disease, chronic heart failure, unstable angina, and stroke [16-18]. A majority of studies found that obese and overweight patients suffering from stroke experienced better functional outcomes and lower mortality rates compared to underweight and normal-weight patients [6,19]. This was separated into studies that showed a linearly inverse relationship as opposed to a U-shaped relationship between obesity and post-stroke mortality after adjusting for several confounding variables (Table 2). Dehlendorff et al., [20] conducted follow up on patients a week and a month post-stroke, which yielded non-significant mortality risk differences between BMI groups. The authors did, however, find a positive association between BMI and mean age of stroke onset, with underweight patients averaging 76.2 years and obese patients averaging 67.1 years. Further studies assert several inverse associations of BMI and post-stroke outcomes: obese patients experienced lower risk of recurrent stroke, lower occurrence of hemorrhagic stroke transformation, and lower risk of unfavorable functional outcomes [6]. One argument against the existence of the obesity paradox in the stroke setting is the confounding variable of stroke severity, which was observed to be negatively associated with BMI. Statistical significance disappeared with adjustment for stroke severity [19,20]. Hubert et al., [21] observed worse cardiovascular outcomes with obesity in the Framingham heart study cohort that were not apparent until 8 to 14 years later, pointing out the possible limitations of short-term follow-up within studies.

Literature examining the obesity paradox within several cardiovascular diseases seem to indicate the existence of a negative association between obesity and mortality. However, this must be tempered with the presence of unaccounted confounding factors (such as stroke severity) and lack of long-term follow up that may distort the true relationship.

Cancer

Previous reviews on the existence of the obesity paradox within oncology show an interesting incongruence with expectations. Obesity is a known risk factor for several cancers, including post-menopausal breast, endometrial, ovarian, advanced prostate, colorectal, renal, pancreatic, liver, gallbladder cancers, and esophageal adenocarcinoma [22,23]. However, obesity paradox cases have been documented in the setting of lymphoma, leukemia, colorectal, endometrial, thyroid, renal, and lung cancers [22,23]. Of particular note is a 2014 meta-analysis conducted by Wu et al., [24] on colorectal cancer examining 29 studies (25 observational, 4 treatment cohorts). The authors found significant associations with obesity and worse overall survival, as well as overweight and better overall survival. This concurs with several studies in this review that found U-shaped curves [9,17,24-26], where patients in the overweight and class I obesity categories fell at the bottom of the mortality curve. Another notable observation from subgroup analysis is the consideration of tumor staging; overall survival with stage I-III colorectal cancer patients proved to be worse with obesity, whereas it conferred overall survival benefits with combined stage III/IV colorectal cancer patients (and no association with survival when III and IV were considered separately).

In contrast, a separate meta-analysis of 32 studies was unable to establish any relationships between obesity and colorectal cancer mortality [27]. In the setting of leukemia, further meta-analysis of 21 prospective cohorts found increased incidence and mortality of leukemia with obese but not overweight patients [28]. Regarding renal

Table 2: Characteristics of studies included in review.

	Study design	Cohort size	Adjusted covariables	Obesity association with mortality
Trauma				
Newell et al. [7]	Retrospective	1,543	Age, ISS, Revised Trauma Score	None
Brown et al. [8]	Retrospective	N/A	Age, sex, mechanism of injury, ISS, need for operation, HR, Systolic BP, GCS	None
Dvorak et al. [9]	Retrospective	4,15,807	Age, sex, ISS, blunt mechanism, penetrating mechanism, pulse, Systolic BP, GCS, Diabetes/COPD/cirrhosis/CHF diagnosis, smoking status	Negative (U-shaped)
Mock et al. [10]	Retrospective	27,263	Age, sex, seatbelt use, vehicle curb weight, seat position	Positive
Hoffmann et al. [11]	Retrospective	5,766	Revised Injury Severity Classification Score (Age, ISS, head injury, GCS, base excess, coagulation, signs of severe bleeding, cardiac arrest)	Positive
Liu et al. [5]	Meta-analysis	57,501	See Table 2 of study	Positive
Cardiovascular				
Gruberg et al. [4]	Retrospective	9,633	age, gender, diabetes, hypertension, previous PCI, smoking, saphenous vein graft intervention, left ventricular ejection fraction (LVEF)	Negative (linear)
Wang et al. [12]	Meta-analysis	85,254	None	Negative (linear)
Kapoor et al. [17]	Retrospective	1,236	age, history, medications, laboratory and echocardiographic parameters	Negative (U-shaped)
Romero-corral et al. [16]	Systematic Review	2,50,152	See included studies	Negative (J-shaped)
Buettner et al. [18]	Prospective	1,676	age, ST-segment depression, previous MI, elevated cardiac troponin T, elevated white blood count, platelet count, kidney function, left ventricular function, angiographic extent of coronary artery disease, C-reactive protein, and obesity	Negative (linear)
Forlivesi [6]	Narrative Review	N/A	Age, sex, stroke severity, vascular risk factors	Negative
Dehlendorff et al. [20]	Retrospective	71,617	age, sex, stroke severity (Scandinavian Stroke Scale score), stroke subtype, cardiovascular risk factors, civil status, and socioeconomic status	None
Oesch et al. [19]	Systematic Review	2,14,708	N/A	Negative (linear)
Cancer				
Wu et al. [24]	Meta-analysis	51,328	See Table 1 of study	Negative*
Ujvari et al. [23] (2019)	Narrative Review	N/A	N/A	
Lennon et al. [22]	Narrative Review	N/A	N/A	
Parkin et al. [27]	Systematic Review	See Tables 1, 2 of study	None	None
Castillo et al. [28]	Meta-analysis	~11 million	See Table 1 of study	None
Sanchez et al. [29]	Prospective	256	Tumor stage and grade	Negative (linear)
Sepsis				
Prescott et al. [31]	Prospective	1,404	Age, race, gender, marital status, wealth, acute organ dysfunction, ICU use, mechanical ventilation use, diabetes, other comorbidity, baseline cognitive status, functional limitation	Negative (linear)
Kalani et al. [40]	Narrative Review	N/A	N/A	Negative
Arabi et al. [34]	Retrospective	2,882	See Table 1 of study	None
Kuperman et al. [35]	Retrospective	792	age, gender, race, severity of illness, length of stay, comorbid conditions	None
Pepper et al. [33]	Retrospective	55,038	Demographic factors (age, sex, geographic location), admission year, hospital-level factors, illness severity, co-morbidities, site of infection, recent weight loss	Negative (linear)
Wacharasint et al. [32]	Retrospective	730	APACHE II score, gender, pre-existing diabetes, lung infection and fungal infection	Negative (linear)
Icu				
Akinnusi et al. [30]	Meta-analysis	62,045	N/A	None
Pickkers et al. [26]	Observational	1,54,308	Simplified Acute Physiology Score II, age, gender, admission type, neoplasm, AIDS, hematologic malignancy, immunologic insufficiency, mechanical ventilation, and calendar year	Negative (J-shaped)
Stapleton et al. [44]	Retrospective	1,409	gender, APACHE III score, comorbid diabetes, ALI risk factor, tidal volume group assignment	None
Zhi et al. [25]	Meta-analysis	91,87,248	N/A	Negative (U-shaped)
Covid				
Hussain et al. [36]	Meta-analysis	26,507	N/A	Positive
Pettit et al. [37]	Retrospective	238	age, race, gender, and other comorbidities (hypertension, diabetes, pulmonary disease, CV disease)	Positive
De siqueira et al. [38]	Systematic Review	7,671	N/A	Positive
Toxicologic				
Hong et al. [48]	Retrospective	635	age, gender, race ethnicity, smoking status and physical activity	Negative (linear)
*Negative relationship in association with overweight, positive association with obesity				

cell carcinoma, Sanchez et al., [29] observed a mortality benefit with obesity in a prospective cohort and notably investigated biomolecular mechanisms behind this paradox, discussed below.

Critical care/sepsis/lung injury

Obesity paradox has been discussed abundantly in the setting of critical care and intensive care unit (ICU) patients. A 2008 meta-analysis by Akinnusi et al., [24] examined obesity effects on ICU mortality, mechanical ventilation days, and ICU length of stay in 14 studies (7 prospective, 7 retrospective). They found no significant difference in ICU mortality rates across all weight groups but did see higher survival in obese compared to non-obese groups with hospital discharge [24]. There were also longer durations of mechanical ventilation (1.48 days) and ICU stay (1.08 days) with obese patients compared to non-obese. Subsequent subgroup analysis revealed no difference in ICU mortality between non-obese and morbidly obese patients; however patients with BMI 30-39.9 kg/m^2 had a lower mortality rate compared to non-obese [30]. In a larger-scale observational cohort of Dutch ICU patients with BMIs representative of the population, Pickkers et al., [26] found an inverse J-shaped relationship between BMI and in-hospital mortality rate, with minimal risk at BMI 42.6 kg/m^2 (morbidly obese, Class III) and increasing exponentially as BMI fell below 20 kg/m^2 (normal non-obese).

In terms of sepsis admissions, Prescott et al., [31] revealed a 1-year mortality benefit with obese patients in the prospective cohort. This paradox persisted with in-hospital and 90-day mortality rates, and with age group stratification between patients under and over 70 years old. This observation was supported by several other retrospective cohort studies [32,33]. However, the benefits conferred by obesity were reduced or abolished when better adjustments for co-morbidities and interventions were made [34,35].

Literature on acute lung injury includes a 2016 meta-analysis by Zhi et al., [25] examining the obesity paradox in acute respiratory distress syndrome (ARDS), which compiled 25 studies (9 prospective, 16 retrospective). The authors found a significant correlation between increased BMI, obesity and lower ARDS/acute lung injury mortality. The relationship also fell into the U-shaped curve, with obese patients (BMI 30-39.9 kg/m^2) at the lowest mortality rate and no association between morbid obesity and ARDS mortality. In subgroup analysis of studies with available data, the authors did not find any relationship between obesity and 28 day mortality; however, obesity was associated with lower 60 and 90-day mortality.

COVID-19

In light of the developing Novel Coronavirus Disease 2019 (COVID-19) pandemic at the time of writing, we briefly surveyed the impact of obesity on COVID-19 prognosis. Amongst emerging data is a meta-analysis conducted by Hussain et al., [36] exploring the association between COVID-19 mortality and several risk factors including age, sex, BMI, and presence of severe comorbidity and critical illness. Within 6 papers that incorporated BMI data, authors found a significant positive association with obesity and mortality with an obesity cutoff BMI of 25 kg/m^2. These results were in consensus with a separate retrospective cohort [37] and systematic review [38]. Aside from mortality risk, Yang et al., discovered in a separate meta-analysis that higher BMI was associated with more severe manifestations of COVID-19 and that obesity was associated with a 2.31 fold risk of disease exacerbation [38,39]. Current hypotheses propose the following contributing factors: pre-existent organ damage due to concurrent metabolic syndrome; obesity-induced hyper-inflammatory state leading to an overactive response and subsequent immune exhaustion; limited chest expansion impairing overall respiratory compensation; increased expression of Angiotensin Converting Enzyme 2 (ACE2), the receptor for SARS-CoV-2, in obese patients [36,39]. These preliminary studies are limited by a paucity of available data specific to obesity and COVID-19, as well as data heterogeneity due to differing obesity classifications between studies.

Within reviewed literature is a general agreement of an obesity conferred survival benefit within ICU admissions for acute lung injury and sepsis (with the exception of COVID-19), that persists between a range of 60 days up to a year of follow-up. Again, these observations are moderated in the face of possible confounding effects of co-morbidities and patient management.

Discussion

Clinical considerations

Energy reserve and timing

The most commonly proposed mechanisms within the reviewed literature is the theory of "Energy Reserve." A higher energy reserve present in obese patients allows them a greater "metabolic buffer" to weather the catabolic impact of an acute illness stressor and subsequent periods of malnutrition and malabsorption better than their lean counterparts [6,9,22,24,40]. This mechanism of evolutionary survival has been attributed to reduced mortality in the setting of modern-day stresses such as anti-cancer treatment and ICU stays. In the setting of cancer cachexia, this theory is evidenced in fat mass loss outpacing that of muscle, ultimately leading to worse outcomes. Cancer is associated with an energy homeostasis dysregulation mediated by pro-inflammatory cytokines where fatty acids in adipose tissue are depleted for futile thermogenesis [41]. Due to inconsistent timing of BMI data collection, it is unclear whether reverse causality plays a confounding role in this relationship, whereby cancer mediates subsequent weight loss through higher metabolic requirements and loss of appetite [22].

Interestingly, Wu et al., [24] explored the issue of BMI timing in a subgroup analysis and confirmed a positive association between overall survival and post-treatment overweight/obesity and peri-treatment overweight. This was absent with pre-diagnostic overweight/obesity and peri-treatment obesity [24]. This is line with other U-shaped relationships that highlight the survival benefit of an overweight BMI and seems to substantiate the advantage of carrying a nutritional surplus (although not to an excess) that is necessary to meet metabolic demands of acute illness recovery associated with a lower absorption rate and an often smaller appetite. This may have profound impacts on the foci of future post-operative, ICU, and post-treatment patient management, and further prospective studies analyzing BMI timing and overall survival post-acute illness are needed to confirm this hypothesis.

Anti-Inflammatory properties

Adipose tissue has been found to play an increasingly important endocrinologic role [19]. Although pro-inflammatory upregulation in obesity is well-described in literature (i.e. IL-1, IL-6, TNF-α), obesity also seems to modulate the immune response to exert a subsequent paradoxical anti-inflammatory effect in the setting of an acute stressor. The proposed pathways involved in the inflammatory pathway include:

Leptin – The adipocyte-produced hormone may have protective effects in the setting of infections through modulation of cytokine release, endothelial activation, and both innate and adaptive immunity.

Leptin is chronically elevated with obesity, and deficiency has been often associated with vulnerability to viral and bacterial infection as well as pro-inflammatory stimuli [9,30,40,42].

Adiponectin – This anti-atherogenic adipokine is shown to improve insulin sensitivity and reduce atherosclerotic severity, which helped suppress development of cardiovascular disease and metabolic derangements in murine models [43].

Pro-inflammatory Cytokines – Increased levels of IL-6, IL-8, Surface Protein-D (SP-D), von Willebrand Factor (vWF), and Plasminogen activator Inhibitor-1 (PAI-1) have been associated with increased odds of death [44]. Obese patients suffering stroke were observed with higher serum levels of pro-inflammatory cytokines during the acute phase; however, these levels decreased in the week following and were accompanied by an increase of anti-inflammatory cytokines (i.e. IL-10). Interestingly, this effect was not seen in non-obese patients [6]. In the setting of acute lung injury, Stapleton et al., [44] also found that increasing BMI was associated with lower levels of inflammatory cytokines, especially IL-6, IL-8, and SP-D. They did also find an increase in vWF (biomarker of endothelial damage) amongst obese patients, and this complex immunomodulatory interplay of obesity may have obscured detection of any initial relationships. Wacharasint et al., [32] found a similar decrease in IL-6 production and a lower rate of lung and fungal infections among overweight and obese patients, leading to lower 28-day mortality with sepsis.

Tissue Necrosis Factor-Alpha (TNF-α) – Adipocyte secretion of soluble TNF-α receptors may help nullify some of the downstream pro-inflammatory effects of TNF-α in sepsis and post-stroke patients [19,40].

Anti-oncogenic properties

Protective effects in the form of "concomitant resistance" against aggressive tumors as well as increased chemotherapy efficacy have been posited with obesity. Its pro-inflammatory property is a known catalyst for oncogenesis, but there is an apparent propensity for obese patients to develop tumors that are less aggressive with better prognosis as compared to those of normal weight [22]. One review accounted for this phenomenon by a direct correlation between tumor aggressiveness and accumulation of driver mutations. These accelerated benign neoplasms would then provide "concomitant resistance" against secondary tumor formation, as simultaneous angiogenic stimulation from two tumors would elicit a host angiogenic inhibitor response to limit further growth of the secondary tumor [23].

Obesity may also play a beneficial role in regard to chemotherapy pharmacokinetics. One study found that intra-abdominal fat volume served as a better predictor of doxorubicin pharmacokinetics and pharmacodynamics than body surface area, which may serve to more effectively dose doxorubicin and avoid toxicity [22]. Sanchez et al., [29] performed a biomolecular analysis of clear cell renal cell carcinoma patients wherein obese patients benefitted from lower mortality after sunitib therapy. Obesity increases adipocytic release of angiogenic factors, including leptin, which upregulates vascular endothelial growth factor (VEGF) and its receptor; although this would increase tumor growth, it would also increase drug exposure locally. Indeed, the authors found that higher angiogenic scores led to a better survival outcomes.

Toxicologically Protective Properties

Besides its well-known energy storage and endocrinological functions, adipose tissue also plays an under-appreciated toxicological role that ties back to the discussion on the obesity paradox. Pollutants are often processed by detoxification systems to increase water solubility and elimination as well as to decrease absorption. However, Persistent Organic Pollutants (POPs) are found in contaminated fatty animal products through food chain bioaccumulation and are resistant to detoxification and consequently accumulate and can induce chronic inflammatory pathways [45]. Adipose tissue acts as an effective sequestrant for these hydrophobic chemicals and prevents high exposure to other sensitive organs, especially the brain [46]. There are two conditions that lead to a release of these POPs from storage: insulin resistance and weight loss. Insulin suppresses lipolysis and subsequent POP release from adipocytes, whereas resistance (i.e. in diabetes) leads to a loss of this response. With weight loss, stored POPs will also redistribute back into remaining adipose as well as the bloodstream [47].

The obesity paradox may be explained by the role of POPs as a confounding risk factor for metabolic derangement leading to chronic inflammatory activation. The efficient storage of POPs in adipose tissue may be a key player independent of obesity—in fact, one reviewed study found that diabetes type 2 was not correlated with obesity when serum POP levels were low [45]. Hong et al., [48] showed that within a control group of low serum POP levels, fat mass was positively correlated with mortality. However, the obesity paradox became apparent in the high serum POP level group, where the highest quintile of fat mass had mortality rates one-fifth that of the lowest quintile. The study was carried out in a population of elderly patients in order to amplify the effects of POPs, as the degradation-resistant compound accumulate over time and the body's elimination mechanisms slow down with age. Consequently, weight loss benefits may decrease with age in terms of toxicological protection from POPs. POPs and obesity share a complex and non-linear relationship that must be further investigated, particularly its role as a potential obesogenic. Regardless, it is important to factor in POPs as a potential toxicological confounding variable in studies on the obesity paradox but unfortunately it is often omitted from consideration.

Methodological considerations

Study design/biases

Although we endeavored to include high-quality evidence (Level I) within each area of this review, the majority of literature covered (including studies examined within meta-analyses) are retrospective cohort studies (Table 2). Limitations such as selection/inclusion bias follow this mid-tier evidence (Level III) and could not be fully accounted for [5,19,30].

The broad nature of the investigation meant that much of the reviewed literature inevitably contained data heterogeneity. This was true especially amongst meta-analyses, which made extracting true relationships more difficult. Inherent differences in study design included prospective vs. retrospective cohorts, self-reported vs. measured BMI values, different categorizations of obesity, adjustment of different confounding variables, sample sizes, and participant clinical variability [12,25,30]. Wu et al., [24] found that although these factors did not alter associations significantly, BMI timing remained an important source of heterogeneity to be controlled for and should be explored in future studies. Other meta-analyses even excluded certain or all confounding variables from analysis due to the limited number of included studies that adjusted for key variables [12,25].

Due to discussion focused on the possible existence of a newly described phenomenon, one could reasonably suspect publication

bias to be at play. Many of the reviewed meta-analyses conducted funnel plot visual analyses, and Akinnusi et al., [30] did find an under-publication of negative results. However, these meta-analyses also carried out formal statistical evaluation with Begg's rank correlation and detected no bias [5,12,24,25].

The possibility of geographical bias was also proposed, as most of the included studies originated from North American and Europe and limited interpretation beyond Caucasian populations [5,49]. Within subgroup analysis, Wu et al., [24] found that similar or better colorectal cancer survival with overweight and obesity only applied to non-North American regions. Again, the true nature of this relationship is obscured by the presence of heterogenous BMI data collection, small sample sizes, and unaccounted confounders that could play a role. In relation to geographical bias, these unadjusted variables may include cross-cultural dietary differences as well as social risk factors that contribute to the mortality difference between the obese and non-obese. This will be important to tease out in future investigations of the phenomenon.

Another factor for consideration is the notion of treatment bias, where obese patients are in essence receiving higher acuity care due and vigilance in dealing with a higher risk population. Oesch et al., [19] believed that more intensive anticoagulation, statin, and antihypertensive treatments post-stroke with obese patients may have overinflated the survival and functional endpoints. Several studies suggested that more aggressive treatment from the medical provider countered heightened risk of complications, i.e. early intubation in anticipation of difficult airways and lowering threshold of ICU admission. Prescott et al., [31] countered this idea of different thresholds of admission by designing the study to include the patient population according to diagnosis and not by ICU admission, and still reached conclusions in agreement with the obesity paradox. They went further so as to investigate plausible effects of a "healthcare utilization bias", wherein higher healthcare spending and resource utilization would falsely strengthen the association between obesity and a mortality benefit. They found that obese patients indeed used significantly more resources in the year following discharge due to their higher survival rates. However, average daily usage amounts and rate of acquiring functional limitations was equivalent to non-obese patients. One review even discussed the possibility of obese patients diagnosed with sepsis benefitting from an under-treatment bias. Fluid over-resuscitation has been seen to be detrimental in a septic patient and receiving similar fluid volumes to non-obese patients was shown to have similar outcomes as opposed to true weight-based dosing. Similar findings were reported in lower than expected weight based dosing of vasopressors and antibiotics [40]. Future investigations in these treatment biases should be prospectively evaluated to more clearly elucidate their influence on obesity and mortality.

BMI metric/Documentation

A discussion of the validity of BMI lies in the crux of the obesity paradox. BMI is measured as weight in kilograms over the square of height in meters (kg/m^2) and is used as a rough barometer of nutritional status. It has widespread use due to its standardized definitions of weight categories and inherent simplicity but is blind towards lean (LM) and fat mass (FM) differentiation [9,40]. BMI had a specificity of 96% and sensitivity of 43% in obesity assessment in comparison to body fat percentage measurements [19]. Wildman et al., [50] demonstrated that over half of overweight individuals and 31.7% of obese individuals were metabolically healthy, whereas 23.5% of normal weight individuals were metabolically abnormal when elevated blood pressure, triglyceride, glucose levels, insulin resistance, systemic inflammation, and decreased HDL-C levels served as barometers for abnormality. This brings to light obesity phenotypes that are undifferentiated with the BMI metric. Carbone et al., [51] described three: the athlete (low FM, high LM), non-sarcopenic obese (high FM, high LM), and sarcopenic obese (high FM, low LM). The authors asserted that apparent heart failure mortality benefit with overweight/Class I obesity may be confounded by the unaccounted presence of athlete phenotype of obesity, with high cardiorespiratory fitness and lean mass critical to survival.

Another limitation of BMI is the exclusion of significant fractions of datapoints (i.e. 25% of study population in Mock et al.,) due to non-standardized BMI classification or lack of height/weight documentation [7,10,11]. Whether this missing data significantly alters outcomes is unknown, although authors had no suspicion that excluded points would be different from the remaining pool. Additionally, there were reports that one-fourth [24] to half [28] of included papers had self-reported height and weight data which could have led to some potential weight mis-classifications.

More reliable alternatives to BMI have been suggested; however, there is a scarcity of studies designed with these metrics to reach any definitive conclusions. Within available data, the presence of an obesity paradox disappeared when BMI was replaced with waist-to-hip ratio [19], waist circumference [24,40], and fat mass index [22]. Carbone et al., [51] further suggested that an improvement in cardiorespiratory fitness was an independent predictor of better prognosis regardless of BMI or fat mass in the setting of heart failure and chronic heart disease [51]. Until the use of alternative adiposity metrics are more widely adopted, we can only ensure that current BMI measurements are accurately measured and recorded in order to minimize its limitations.

Conclusion

This brief snapshot survey of the obesity paradox shows promise in regard to overweight and mild obesity helping with survival post-acute illness, possibly due to metabolic reserves, anti-inflammatory, and anti-oncogenic properties of obesity. At this point, it is important to reaffirm that public health should still be aimed at primary prevention of obesity, as it is an established major risk in the development of comorbidities such as diabetes, hypertension, and cancer. These findings are not to be conflated with a paradigm shift towards achieving obesity in the general public, but rather an additional consideration within the medical management of certain pathologies discussed within this manuscript.

The complex interactions between adiposity and other physiological processes and the broad scope covered by the paradox makes it exceedingly difficult to isolate true relationships. Some of the major concerns regarding these studies include sometimes suboptimal quality study designs, data heterogeneity, unaccounted confounders, and limitations of strict BMI records. BMI is a mediocre but practical index of a real-life metabolic issue and may be limiting further investigation into the true nature of the relationship between obesity and mortality. Rather than an "obesity paradox," we have several indications that BMI could be refined to be more accurate and clinically relevant. However, the unfortunate success and widespread use of BMI has allowed this oversimplified measure to be too deeply ingrained into academia to be simply discarded.

To address some of these issues, future studies would ideally be prospectively designed, targeting alternative body weight metrics such as waist-to-hip ratio or waist circumference (and encouraging its widespread use). Timing of these body composition data points

(pre/peri/post treatment) should be more closely tracked to maximize the usefulness of the measurements and better elucidate the possible value of obesity during and after acute illness. Additionally, it would be important to further elucidate the significance of POPs as a confounding factor within the obesity paradox. It is clear that obesity is detrimental to overall health, and should be combated in the population, but these observations suggest that it is important to factor obesity into the prognosis of specific pathologies. The possibility that obesity may not necessarily be a pejorative factor under certain settings is worth elucidating in future investigations that may have significant implications in directing future therapeutic management.

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