Obesity Facts

Review Article

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Obesity Paradox in Lung Diseases: What Explains It?

Surui Yao[a] Lei Zeng[a] Fengyuan Wang[b] Kejie Chen[a]

[a]School of Public Health, Chengdu Medical College, Chengdu, PR China; [b]College of Animal and Veterinary Sciences, Southwest Minzu University, Chengdu, PR China

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Abstract
Background: Obesity is a globally increasing health problem that impacts multiple organ systems and a potentially modifiable risk factor for many diseases. Obesity has a significant impact on lung function and is strongly linked to the pathophysiology that contributes to lung diseases. On the other hand, reports have emerged that obesity is associated with a better prognosis than for normal weight individuals in some lung diseases, including pneumonia, acute lung injury/acute respiratory distress syndrome, chronic obstructive pulmonary disease, and lung cancer. The lesser mortality and better prognosis in patients with obesity is known as obesity paradox. While obesity paradox is both recognized and disputed in epidemiological studies, recent research has suggested possible mechanisms. ***Summary:*** In this review, we attempted to explain and summarize these factors and mechanisms, including immune response, pulmonary fibrosis, lung function, microbiota, fat and muscle reserves, which are significantly altered by obesity and may contribute to the obesity paradox in lung diseases. We also discuss contrary literature that attributes the "obesity paradox" to confounding. ***Key Messages:*** The review will illustrate the possible role of obesity in the prognosis or course of lung diseases, leading to a better understanding of the obesity paradox and provide hints for further basic and clinical research in lung diseases.

Introduction

Due to excessive intake of food and/or lack of physical exercises, obesity has become a leading preventable disease worldwide. The latest data of the World Health Organization (WHO) show that there are nearly 2 billion overweight adults (≥18 years) and more than 650 million obese adults [1]. A body mass index (BMI) describes a weight of adult in four categories: underweight (BMI <18.5 kg/m^2), normal weight (BMI 18.5–<25 kg/m^2), overweight (BMI ≥25 kg/m^2), and obesity (BMI ≥30 kg/m^2). Obesity has been linked to an increased risk of numerous diseases (like diabetes, hypercholesterolemia, and hypertension) and is harmful to human health. Obesity has a pronounced effect on lung mechanics and is closely associated with obstructive sleep apnea [2] and chronic inflammation of respiratory tracts [3].

In 1982, Degoulet and colleagues [4] found that the mortality of obese patients on dialysis was significantly decreased in comparison to the patients of normal weight. Afterward, many researchers found that, with percutaneous coronary intervention, the mortality of obese patients suffering from heart failure or coronary heart disease was markedly lower than that of the patients with normal weight

karger@karger.com
www.karger.com/ofa

Correspondence to:
Kejie Chen, ckj930@126.com

[5–7]. In 2002, the obesity paradox was proposed to describe the situation that obesity had protective effects on the patients, including decreased mortality and better prognosis. Once it was put forward, obesity paradox has been found to exist in various diseases. Although obesity paradox is found mostly in the cardiac diseases, obesity paradox of certain lung diseases, including pneumonia, acute lung injury (ALI)/acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD), and lung cancers, has also been reported. In the present review, we provide an overview of the current understanding of the obesity paradox in lung diseases.

Obesity Paradox in Lung Diseases

Pneumonia

Pneumonia, secondary to viruses, bacteria, and fungus, is a lung inflammation that mostly affects the alveoli, and primarily divided into two categories: hospital-acquired pneumonia and community-acquired pneumonia (CAP). According to two independent studies, there is a significant inverse trend between BMI and pneumonia mortality [8, 9]. Nie et al. [10] and Hespanhol et al. [11] found that the risk of pneumonia mortality decreased in obese people in comparison with normal weight population. Similarly, de Miguel-Diez et al. [12] found that the risk of in-hospital mortality decreased in the obese and morbidly obese patients with CAP in comparison to the non-obese patients. Several research studies reported that, among patients with pneumonia, obese individuals had a considerably lower 30-day mortality than normal weight counterparts [13–17], indicating that obesity protects against death from CAP. This occurred despite the fact that there was no difference in illness severity on arrival or immediate need for mechanical ventilation or inotropic support between the obese and non-obese groups [15]. It is yet unknown whether obesity affects the long-term death rate of pneumonia patients. Braun et al. [18] found the all-cause 6-year mortality of the obese patients significantly decreased when compared with the normal weight patients. It has been reported that overweight/obese older patients hospitalized for pneumonia have better 1-year survival [19]. On the other hand, in other studies, the protection of obesity was not significant for 90-day and 180-day mortality of patients with pneumonia [20].

In contrast, a study including 773 patients hospitalized with CAP indicated that there is no significant difference in mortality of obese patients with pneumonia compared to normal BMI patients with pneumonia [21], similar with the result of Wang et al. [22] using dual restricted propensity score matching model. Among COVID-19 patients, obesity is significantly associated with increased severity of pneumonia [23–26] and higher risk of mortality [27, 28], and morbid obesity (BMI ≥40 kg/m^2) is associated with the highest risk of in-hospital death or mechanical ventilation [29–31]. Table 1 demonstrates the details on the published research studies on the effect of obesity on pneumonia.

Acute Lung Injury/Acute Respiratory Distress Syndrome

Acute systemic inflammation quickly advances to acute respiratory failure with poor lung compliance often leading to ALI and its more severe ARDS. Clinical manifestations include pulmonary infiltrates, dyspnea, tachypnea, hypoxemia, and edema. The characterized syndromes of ALI/ARDS include acute onset of severe hypoxemia and bilateral pulmonary infiltrates without left atrial hypertension. According to the ratio of partial pressure of oxygen in arterial blood (PaO_2) to the inspired fraction of oxygen (FiO_2), the American/European Consensus Conference defines ALI as PaO_2/FiO_2 <300 mm Hg and ARDS as PaO_2/FiO_2 <200 mm Hg.

ALI/ARDS is a severe inflammatory lung syndrome that arises as a result of various significant medical disorders such as sepsis, pneumonia, trauma, and mechanical ventilation [33, 34]. The triggers activate acute systemic inflammation, inducing production of pro-inflammatory cytokines [35] and recruitment of neutrophils [36] that cause pulmonary impairment, leading to increased vascular permeability, damage to the alveolar epithelial barrier, and necrosis of alveolar cells. As a result, pulmonary edema and loss of surfactant cause hypoxemia, reduced lung compliance, dampened removal of alveolar fluid, inefficient air exchange, and pulmonary hypertension [34, 37, 38].

Although increasing BMI is correlated with risk of developing ALI/ARDS by cohort study and animal models [39], obese patients with ARDS have significantly lower mortality than the normal weight patients [40–44], and a similar difference of mortality in the ARDS patients receiving extracorporeal membrane oxygenation is also observed [45]. However, several studies report that the mortality is not significantly different between obese and non-obese ALI/ARDS patients [39, 46–50], even in the patients treated with extracorporeal membrane oxygenation [51, 52]. There are studies suggesting obesity increased all-cause mortality in the ARDS patients [53, 54], and the role of morbid obesity is still controversial [54, 55]. Table 2 demonstrates the details on the published research studies on the effect of obesity on ALI/ARDS.

Table 1. Summary studies on prognosis of obesity and pneumonia

Patients and country, *n*	BMI of obesity, kg/m^2	Event	Study design and time	OR/RR/HR (95% CI), *p* value	Reference
n = 1,375,482, multiple countries	≥30	Pneumonia mortality	Meta-analysis, up to Jun 2013	RR = 0.83 (0.77–0.91), <0.01	[10]
n = 519,750, Spain	ND	In-hospital mortality	Retrospective cohort study, 2016–2019	Men: OR = 0.59 (0.55–0.63); Women: OR = 0.71 (0.67–0.75)	[12]
n = 266, USA	≥30	30-day mortality	Retrospective cohort study, Jan 2000–Aug 2007	OR = 0.88 (0.81–0.96), <0.01	[13]
n = 907, Canada	≥30	In-hospital mortality	Prospective cohort study, 2000–2002	OR = 0.46 (0.22–0.97), 0.04	[14]
n = 1,079, UK	≥30	30-day mortality from CAP	Prospective observational study, Jan 2005–Nov 2007	HR = 0.53 (0.29–0.98)	[15]
n = 34,177, USA	30–<40; ≥40	30-day mortality	Retrospective cohort study, 2013–2014	HR = 0.41 (0.20–0.84); HR = 0.49 (0.25–0.96)	[17]
n = 763, Switzerland	≥30	All-cause 6-year mortality	Prospective cohort study, Oct 2006–Mar 2008	HR = 0.641 (0.46–0.89), 0.008	[18]
n = 4,182, USA	30–<35	1-year mortality	Prospective observational study, 1996–2012	HR = 0.74 (0.64–0.85), <0.05	[19]
n = 323, Denmark	≥30	90-day mortality; 180-day mortality	Prospective cohort study, Jan 2019–Apr 2022	HR = 0.9 (0.2–3.9), 0.86; HR = 0.8 (0.3–2.5), 0.72	[20]
n = 773, Switzerland	>30	30-day mortality	Randomized controlled trial, Dec 2009–Apr 2014	OR = 1.41, 0.58	[21]
n = 14,522, USA	≥30	In-hospital mortality	Retrospective observation study, 2013–2014	HR = 0.82 (0.63–1.07), >0.05	[22]
n = 399,461, multiple countries	30–<35	COVID-19 mortality	Meta-analysis, up to Sep 2020	OR = 1.48 (1.22–1.80), <0.001	[27]
n = 427,108, multiple countries	≥30	COVID-19 mortality	Meta-analysis, up to Oct 2021	RR = 1.09 (1.02–1.16), 0.006	[28]
n = 7,606, USA	≥40	COVID-19 in-hospital mortality; COVID-19 mechanical ventilation	Cohort study, up to Sep 2020	HR = 1.36 (1.01–1.84), <0.01; OR = 1.64 (1.23–2.21), <0.01	[29]
n = 2,112, USA	≥40	COVID-19 mortality	Retrospective cohort study, Mar 2020–Jun 2020	HR = 1.6 (1.1–2.1)	[30]
n = 773, Mexican state	≥40	COVID-19 mortality	Retrospective cohort study, March 2020–Nov 2020	OR = 3.54 (1.46–8.55), 0.005	[31]
n = 3,623, USA	30–<40	Hospital length of stay (>3 days)	Prospective observational study, Jan 2010–Jun 2012	Children: OR = 1.18 (0.81–1.71), 0.40; Adults: OR = 0.96 (0.77–1.20), 0.73	[32]
		ICU admission		Children: OR = 2.09 (1.36–3.22), <0.001; Adults: OR = 0.96 (0.73–1.25), 0.74	
		Invasive mechanical ventilation		Children: OR = 2.70 (1.31–5.57), 0.007; Adults: OR = 0.73 (0.45–1.18), 0.20	

ND, not defined.

Chronic Obstructive Pulmonary Disease

COPD, one of the most common chronic respiratory diseases, is now the third most lethal and fifth most expensive disease in the world economy [56]. The primary distinguishing characteristics of COPD include chronic airflow restriction, emphysematous alveolar wall deterioration, increased persistent neutrophil infiltration, and recurrent infections [57]. Accumulating evidence suggested that the primary initiators of COPD are lung emphysema, oxidative stress, and airway inflammation [58].

In contrast to what is observed in a healthy population, the prognosis of the overweight/obese COPD patients was better than that of normal weight patients [59]. Individuals with BMI <25 kg/m^2 have the highest incidence of COPD acute exacerbations within 1 year [60], while COPD patients with BMI >25 kg/m^2 have considerably better survival than the patients with BMI <20 kg/m^2 [61]. In comparison to normal weight patients, the exacerbation frequency is significantly decreased in obese patients with COPD [62]. Moreover, obese patients suffering from COPD have lower mortality and live longer than non-obese patients [63–69]; BMI per 1 kg/m^2 unit increase is associated with 5% less chance of death [70].

However, there are also studies suggesting that the difference of in-hospital/all-cause mortality and exacerbation frequency between obese and normal weight patients with COPD is not significant [71–73]. The data of Jordan et al. and Brigham et al. [74, 75] suggested that the COPD mortality is increased in the individuals with BMI ≥40 kg/m^2, indicating that the obesity paradox of COPD appears to not exist in morbid obesity. Several additional reports show that obesity worsens outcomes of COPD patients, including quality of life, 6 min walk distance, and acute exacerbation of COPD [76–80], and adverse effect of obesity was enhanced when obesity was analyzed as dose-dependent responses [76]. Table 3 demonstrates the details on the published research studies on the effect of obesity on COPD.

Lung Cancer

It has been widely reported that obesity is positively associated with the risk of certain cancers [81]. However, of patients with lung cancer, obesity is related to better prognosis after surgery or treatment, while displaying decreased morbidities, suggesting that high BMI could be an independent predictor for better survival of patients with lung cancer (reviewed by Nitsche et al. [82] and Zhang et al. [83]).

Factors Involved with the Explanation of Obesity Paradox in Lung Diseases

Immune Responses/Inflammation

Obesity is associated with a chronic inflammatory state that changes the immune responses of body and functions of immune cells to contribute to the obesity paradox in lung diseases. Based on 1,409 participants in National Heart Lung and Blood Institute Acute Respiratory Distress Syndrome Network trials, compared with non-obese individuals with ALI, Stapleton et al. [48] found that obese patients with ALI have decreased levels of numerous pro-inflammatory cytokines, including IL-6 and IL-8. Recently, Yu et al. [84] also found that high-fat diet (HFD) protects mice from ARDS by mitigating the inflammatory responses (down-regulated expression of IL-6 or TNF-α in the lung tissue and bronchoalveolar lavage fluid [BALF]). The lower level of TNF-α in the BALF of HFD-induced obese mice was observed in the ALI caused by milder bacterial infection (10^9 CFUs of *E. coli*), rather than fatal infection (10^{10} CFUs of *E. coli*) [85, 86]. These data suggest that the effect of obesity on the immune response/inflammation could be by the severity of disease. The down-regulated production of pro-inflammatory cytokines in the obese individuals with ALI could be resulted from the suppressed STAT3/NF-κB inflammatory pathway [87] and NLRP3 inflammasome by obesity [88]. The increased expression of secretory leukocyte protease inhibitor by obesity could be another contributor in the attenuated inflammatory response of ALI [89].

Moreover, obesity impairs neutrophil signaling response and reduces the recruitment of neutrophils during pneumonia and ALI [90–93], which is associated with diminished damage induced by neutrophils and improved pulmonary repair in pneumonia and ALI/ARDS. The inhibited filtration of neutrophil into the lung could be mediated by the decreased expressions of cytokines (e.g., IL-6 and monocyte chemotactic protein [MCP]-1) [91–93] and neutrophil CXCR2 [90] in the obese individuals. Leptin, one of the adipokines, promotes CD4$^+$ T cells to shift into Th1 phenotype [94], improves macrophage phagocytosis and bacterial clearance, and reduces bacteremia in *ob*/*ob* mice (leptin deficiency) [95, 96]. However, Maia and colleagues [93] showed that phagocytic capabilities of monocyte and macrophage in obese rat model of ALI significantly declined in comparison with lean counterparts, which could be contributed by increased circulating fatty acids that results from lipolysis

Table 2. Summary studies on prognosis of obesity and ALI/ARDS

Patients and country, *n*	BMI of obesity, kg/m^2	Event	Study design and time	OR/RR/HR (95% CI), *p* value	Reference
n = 1,795, Boston	≥30	ARDS mortality	Cohort study, Sep 1999–Aug 2007	OR = 0.89 (0.71–1.12)	[39]
n = 9,187,248, multiple countries	30–<40	28-day ALI/ARDS mortality; 60-day ALI/ARDS mortality; 90-day ALI/ARDS mortality	Meta-analysis, up to Apr 2016	OR = 0.92 (0.55–1.54), 0.76; OR = 0.84 (0.75–0.94), 0.002; OR = 0.38 (0.22–0.66), 0.0005	[40]
	≥40	ALI/ARDS mortality		OR = 0.87 (0.69–1.08), 0.21	
n = 2,378, USA	≥30	In-hospital mortality; ICU mortality; 1-year mortality	Retrospective cohort study, 2001–2012	OR = 0.72 (0.55–0.94), 0.0168; OR = 0.70 (0.53–0.93), 0.0140; HR = 0.80 (0.68–0.94), 0.0084	[41]
n = 9,149,030, USA	ND	In-hospital mortality	Retrospective cohort study, 1998–2007	OR = 0.31 (0.28–0.36), <0.0001	[42]
n = 202, China	≥30	ARDS mortality	Retrospective case-control study, Jan 2005–Dec 2015	OR = 0.91 (0.83–1.00), 0.039	[43]
n = 6,268, USA	≥30	ALI/ARDS mortality	Meta-analysis, up to Sep 2016	OR = 0.68 (0.57–0.80), <0.00001	[44]
n = 76, France	≥30	90-day mortality	Observational cohort study, Mar 2020–Nov 2020	OR = 0.775 (0.644–0.934), 0.007	[45]
n = 902, USA	≥30	28-day mortality	Retrospective cohort study, 1996–1999	OR = 01.111 (0.693, 1.782)	[47]
n = 613, USA	≥30	28-day ARDS mortality; 90-day ARDS mortality	Retrospective cohort study, Jan 2010–May 2017	HR = 1.21 (0.87–1.68); HR = 0.99 (0.73,1.33)	[49]
n = 1,285, multiple countries	≥30	In-hospital survival rate	Meta-analysis, up to Jan 2021	RR = 1.04 (0.86–1.25)	[52]
n = 418, USA	≥30	30-day all-cause mortality	Retrospective cohort study, 2001–2012	HR = 3.85 (1.73–8.57), 0.0019	[53]
		90-day all-cause mortality		HR = 3.01 (1.42–6.39), 0.0041	
		1-year all-cause mortality		HR = 2.84 (1.38–5.82), 0.0044	
n = 451, multiple countries	30–<40; ≥40	In-hospital death	Randomized controlled trial, 2007–2008	OR = 2.41 (1.05–5.54); OR = 1.89 (0.34–10.50)	[54]

ND, not defined.

induced by lipopolysaccharide [97]. These fatty acids bind to the macrophage Toll-like receptor (TLR)-4 and inactivate TLR-4, reduce the production of pro-inflammatory mediators, and attenuate pulmonary inflammation [98]. Although the mechanism on dysfunction of immune response by obesity is not completely clear in the lung diseases, the cargoes in the exosomes extracted from adipose tissue and adipose-derived stem cell have been reported to play a protective role in the lung diseases [84, 99].

Table 3. Summary studies on prognosis of obesity and COPD

Patients and country, *n*	BMI of obesity, kg/m^2	Event	Study design and time	OR/RR/HR (95% CI), *p* value	Reference
n = 21,150, multiple countries	≥30	COPD mortality	Meta-analysis, up to Mar 2011	HR = 0.69 (0.54–0.89), 0.004	[63]
n = 263,940, Japan	≥30	In-hospital mortality	Retrospective study, Jul 2010–Mar 2013	OR = 0.67 (0.52–0.86), <0.002	[65]
n = 2,132, Denmark	≥30	COPD mortality	Prospective observational study, 1976–1978	RR = 0.34 (0.12–0.97), <0.001	[66]
n = 51,353, USA	≥30	COPD mortality	Retrospective study, 1999–2003	HR = 0.76 (0.70–0.82), <0.0001	[67]
n = 313,233, Spain	≥30	In-hospital mortality	Retrospective study, Jan 2006–Dec 2007	OR = 0.52 (0.49–0.55), <0.001	[69]
n = 968, Slovenia	>29.05	All-cause mortality	Retrospective study, Feb 2002–Jun 2007	HR = 0.95 (0.93–0.97)	[70]
n = 187,647, USA	≥30	In-hospital mortality	Retrospective cohort study, 2012–2013	OR = 0.86 (0.75–1.00), 0.06	[71]
n = 17,116, multiple countries	≥30	All-cause mortality	Randomized controlled trial, 2005–2014	HR = 0.84 (0.70–1.01), 0.0686	[72]
n = 33,994, USA	30–<35	Respiratory mortality	Retrospective cohort study, 1988–1994	HR = 0.31, <0.05	[74]
	35–<40			HR = 0.53	
	≥40			HR = 1.81	
n = 16,485, multiple countries	30–<35	Respiratory mortality; moderate/severe COPD exacerbation; severe COPD exacerbation	Randomized controlled trial, Jan 2011–Jun 2015	HR = 0.77 (0.46–1.30); HR = 1.02 (0.93–1.11); HR = 1.02 (0.87–1.21)	[75]
	35–<40			HR = 0.80 (0.37–1.72); HR = 1.14 (1.01–1.28); HR = 1.14 (0.90–1.43)	
	≥40			HR = 1.31 (0.54–3.16); HR = 1.05 (0.89–1.23); HR = 1.07 (0.77–1.49)	
n = 3,631, USA	30–<35	Modified medical research council score ≥2; moderate acute exacerbation COPD	Prospective cohort study, Jan 2008–Apr 2011	OR = 1.22 (1.00–1.50), 0.052; OR = 1.24 (0.97–1.59), 0.082	[76]
	35–<40			OR = 1.66 (1.21–2.27), 0.001; OR = 1.08 (0.76–1.54), 0.669	
	≥40			OR = 2.95 (1.86–4.69), <0.001; OR = 0.83 (0.52–1.33), 0.433	
n = 364, USA	≥30	Modified medical research council score ≥2; exacerbation COPD	Cross-sectional study, Nov 2004–Dec 2007	OR = 4.91 (1.80–13.39), 0.002; OR = 0.60 (0.32–1.12), 0.108	[80]

Fibrosis

Apart from the regulation of immune response, leptin is involved in the pathophysiology of the fibroproliferative stage of ARDS. Transforming growth factor-β1 (TGF-β1) is potent to enhance fibrotic response and involved in fibroproliferative ARDS [100, 101]. Leptin significantly increased TGF-β1 expression in TGF-β1-treated human lung fibroblasts [102]. In vivo, the *ob*/*ob* mice exerted decreased pulmonary lesions and better survival in the context of ALI/ARDS [103]. In the patients with ALI/ARDS, the level of BALF leptin in non-obese patients was 6-fold higher than obese patients [102], suggesting that the inhibited expression of pulmonary leptin by obesity could be a contributor to the obesity paradox in ALI/ARDS.

Furthermore, obese individuals with type II diabetes are less likely to develop ALI/ARDS and have a reduced mortality after ALI/ARDS [33, 104, 105], which could be resulting from leptin resistance, a common feature of obese patients with type II diabetes [106, 107]. Compared with WT mice of ALI/ARDS, the *db/db* mice (leptin resistance) with ALI/ARDS manifested reduced pulmonary damage and improved survival [103], which could be due to the up-regulated level of peroxisome proliferator-activated receptor (PPAR)-γ, an inhibitor of the TGF-β1 [108] and pulmonary fibrosis [109]. Jain et al. [102] found that *db/db* mice show resistance to the increase of TGF-β1 and pulmonary fibrosis caused by intratracheal instillation of bleomycin. Maia et al. [93] also found that, compared with non-obese counterparts, obese rats with ALI have decreased levels of collagen fiber but not deposition of collagen fibers and TGF-β expression. Therefore, the depression of TGF-β1-mediated pulmonary fibrosis by obesity could partially account for the obesity paradox in ALI/ARDS.

Recently, Qi et al. [110] found that the exosomal miRNAs from the adipose tissue are essential for the TGF-β1-mediated pulmonary fibrosis. The level of circulating exosomal miR-122-5p was significantly higher in obese ARDS mice than lean ARDS mice. Exosomal miR-122-5p derived from adipose inhibits endothelial-to-mesenchymal transition by down-regulating the TGF-1/TGF-R1/Smad2 pathway both in vivo and in vitro, protecting endothelial barrier and attenuating pathological lesions of lung. The data indicate that the exosomal cargoes, like miRNAs, could be indispensable parts in the obesity paradox of lung diseases and need further study.

Microbiota in the Lung and/or Intestine

The control of lung disorders, including ARDS, and the maintenance of healthy immune responses have both been linked to the lung and gut microbiota [111–116]. Alghetaa et al. [117] reported that staphylococcal enterotoxin B (SEB) caused ARDS of mice and increased the contents of pathogenic *Propionibacterium acnes species* and *Proteobacteria phylum* in the lungs. Resveratrol mitigated ARDS and mortality of mice exposed to SEB, accompanied with increased levels of probiotic *Tenericutes phylum*, *Actinobacteria phylum*, and *Lactobacillus reuteri species* in the colon and lung. Moreover, after *L. reuteri* treatment, 20% SEB-exposed mice survived for more than 30 days [117]. The data indicated that the modification of the microbiota in the gut and/or lung plays a significant part in ARDS. Importantly, several studies revealed a favorable correlation between the BMI and the content of *L. reuteri* in the body [118–121]. Therefore, it can be inferred that individuals with obesity may improve the prognosis of ARDS because of the higher level of *L. reuteri*, but its role and mechanism in the obesity paradox of ARDS are unclear.

Lung Function

Both in people without COPD and in those with the disease, the roles of obesity on pulmonary physiology have been thoroughly studied [122]. Several authors argued whether the BMI is positively associated with the lung function of COPD patients [64, 66, 123, 124]. Of the individuals with BMI 20–40 kg/m^2, the BMI is positively associated with the forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio, and forced expiratory flow at 25–75% ($FEF_{25–75}$)/FVC ratio [124]. Abston et al. and Oey et al. [124, 125] reported that the risk of COPD exacerbation, hospitalization, and mortality of patients with larger $FEF_{25–75}$/FVC ratios was reduced in the follow-up. It has been reported that, moreover, the COPD patients with higher BMIs had lower estimated rate of FEV_1 decline [126], indicating that obesity delays the decline of lung function of COPD patients.

The main factor influencing the maximum expiratory airflow of the lung is the elastic recoil, which is related to the rebound of the lungs after having been stretched by inhalation. It has been reported that obesity increased elastic recoil of the lung in several studies [122, 127, 128], which could be involved in the obesity paradox of COPD via increasing FEV_1/FVC or $FEF_{25–75}$/FVC ratio.

Beyond that, it has been demonstrated that the BMI is negatively correlated with emphysema [124, 129], and the severity of emphysema in the COPD patients is associated with lower body weights [130]. Significantly, BMI

dramatically rises after lung volume reduction surgery for emphysema, which is correlated with improvements in health status [125]. Emphysema severity affects mortality from all causes and from COPD [131, 132]; therefore, the protection of obesity against COPD is more related to low-grade emphysema through altering lung function than to the excess weight.

Another study, moreover, showed that obese COPD patients had higher symptom-limited peak oxygen uptake during incremental cycling exercise (V_{O2}, given as a percentage of the anticipated normal value corrected for ideal body weight) than COPD patients of normal weight [128]. V_{O2} is a powerful predictor of mortality and a measure of cardiorespiratory fitness, thus it is tempting to assume that an increase in V_{O2} may contribute to the better outcomes observed in obese COPD patients [133].

Fat and Muscle Reserve

Clinically, of patients with cancer, fat loss is commonly observed and has been closely associated with shorter survival independent of BMI [134]. An earlier investigation using a lung cancer mouse model showed that preventing the unchecked loss of adipose mass by decreasing adipose lipolysis might increase survival [135]. The BMI is positively related to not only fat mass but also muscle mass [136]. It has been reported that individuals who are obese are better equipped to handle acute exacerbations because of higher reserve brought on by more muscle mass [137]. After controlling for muscle mass, the influence of obesity on mortality is reduced [138]. Marquis et al. and Wouter et al. [139, 140] found that, by computed tomography scan, the measurement of the cross-sectional area of the mid-thigh muscle was negatively correlated with the mortality of COPD patients. It has been demonstrated in the literature that the reduction of muscle mass is associated with the exacerbation of COPD [141, 142], and the COPD patients who are resistant to muscle loss have improved survival [68]. In the patients with small-cell lung cancer or non-small cell lung cancer, sarcopenia, characterized by atrophy and weakness of skeleton muscle and identified by cross-sectional computed tomography image, has been confirmed as independent prognostic factor [143, 144]. According to a retrospective research including 636 patients undergoing surgical excision for lung adenocarcinoma, however, there is not a relationship between the mass of skeletal muscle and the effect of BMI on overall survival [145].

Due to increased fat and/or muscle reserve, obese patients may have a stronger nutritional and metabolic reserve [146], which might better withstand the catabolic effects during COPD [147, 148] and wasting condition of lung cancer [149]. Moreover, adipose tissue may potentially operate as a possible reservoir diluting the harmful compounds in the body, which might attenuate the stress of chemotherapy and partially explain the better outcomes of patients with lung cancer after chemotherapy [150–152].

Discrepancy of Obesity Paradox in Lung Diseases

There are a number of research studies reporting that the obesity paradox exists in various lung diseases by animal model and population, but some studies showed the opposite effect of obesity in the lung diseases. Here, based on the characteristics of population in different studies, we put forward potential factors contributing to the discrepancy of obesity paradox in the lung diseases.

Age

The differences between children and adults may contribute to the different effect of obesity on pneumonia. The studies discussing the relationship between obesity and pneumonia focused on the adults [8, 9, 13–15, 18, 19, 153], specially aged ≥55 years, in which obesity protects adults against pneumonia. Bramley et al. [32] focused on the young and found that obese or overweight adults (≥18 years) exhibited better prognosis from CAP, including shorter in-hospital length, less ICU admission, and invasive ventilation, but overweight/obese children and adolescents (2–17 years) had worse prognosis compared with normal weight counterparts. According to the study of Liu et al. [53], in which the obese patients were younger than the normal weight patients, the obesity was not associated with reduced all-cause mortality of ARDS patients. Moreover, there are some evidences to suggest that "increasing age may be related to the obesity paradox." Baik et al. [154] found that obesity was associated with a higher risk of pneumonia among females, while the study conducted by Kornum et al. [155] showed lower risk of pneumonia in the obese females. Compared with the research by Kornum et al. [155], there were more younger females (aged 27–44 years) in the study of Baik et al. [154], demonstrating that the protective effects of obesity could be more significant in the old than that in the young. Although the immature lung and immune system of children and adolescents may contribute the differences, it needs further research works to explore whether certain hormonal levels different between children and adults are also involved in the relationship between age and the obesity paradox in pneumonia.

Gender

Differences in biological processes, such as adipokines, hormonal levels, and fat distribution, differ by gender and may impact the pathophysiology of lung diseases [155, 156]. The role of gender in the obesity paradox of lung diseases is still inconsistent. Several independent studies showed that obesity protected both men and women from pneumonia and CAP [9, 12, 156, 157], whereas the studies conducted by Kornum et al. [155] and Phung et al. [158] showed the obesity-reduced risk of pneumonia among women, not men, which is also observed in the patients with lung cancer [159]. In COPD patients, significant correlation between obesity and COPD was only found in males [160], which could be involved with less rapid decline of FEV_1 in male patients with higher BMI [161]. Conversely, Maria et al. [162], through an analysis stratified by gender, found the association between obesity and obstructive lung disease was only significant in women, not in men. The data from different studies showed that the gender could play different role in various lung diseases, in which the effect of estrogen on the immune response and lung function needs attention [163, 164]. Further studies are warranted to illustrate the relationship between gender and obesity paradox in the lung diseases, as well as the mechanisms.

Smoking

Smoking increases the likelihood of developing lung diseases, including COPD and lung cancer, and potent effects on the physiological processes of lung, resulting in the confounding data from different studies. Based on 1,723 COPD patients (ever- or never-smoker), Wu et al. [165] found that, compared with the normal weight patients, the decreased hazard of death in the overweight/obese COPD patients was observed among ever-smokers but not never-smokers. However, of the study including 15 million never-smokers (more than 10,000 lung cancer cases), an inverse linear trend between BMI and risk of lung cancer was fitted in a random-effects meta-regression model, and obese subjects are associated with lower risk of lung cancer in never-smokers [159].

Body Shape

Although the BMI is widely used to define obesity, it does not analyze an individual body shape and distribution of adipose tissue. In addition to obesity or body size defined by BMI, abdominal obesity may be a potent confounder contributing to conflicting results in pneumonia and lung cancer. Of the patients with COVID-19-induced pneumonia, abdominal obesity, measured by waist circumference (WC) and waist-to-height ratio, positively correlated more closely with high chest X-ray (CXR) severity score than BMI and is an independent factor associated with high CXR severity scores [166]. Increased visceral adipose tissue is positively associated with severe forms of COVID-19 pneumonia [167, 168], higher need for ventilatory support [169], and intensive care [170–172], while subcutaneous adipose tissue is not significantly correlated with the severity of COVID-19 pneumonia [167, 168]. BMI is negatively related to the risk of lung cancer, while WC and waist-to-hip ratio (WtHR) are positively and linearly associated with the risk [173]. Visceral obesity promotes NSCLC progression [174], which is different from obesity paradox in lung cancer.

Introduced in 2011, A Body Shape Index (ABSI), an allometric power law based on WC, is approximately independent of height, weight, and BMI [175] and achieves better mortality risk stratification than alternative indices of abdominal obesity [176]. It has been reported that ABSI is negatively associated with pulmonary function, including FEV_1% of predicted value, FVC% of predicted value [177], FVC [178], vital capacity, and maximal voluntary ventilation [179]. ABSI is associated positively with the risk of lung cancer [173, 180], including adenocarcinoma, squamous cell carcinoma, and small cell carcinoma [181].

Moreover, different from the results of studies using BMI, WC/waist-to-height ratio/WtHR is positively associated with the risk of all-cause mortality [182, 183], sepsis-related mortality [184], mortality of heart failure in women [185], and stroke [186]. These data indicate that body shape could be a potent confounder for the explanation of difference among studies. However, Yajima et al. [187] reported that, in patients undergoing hemodialysis, visceral fat area or subcutaneous fat area level is negatively associated with risks for all-cause mortality. Consequently, the role and mechanism of body shape or distribution of adipose tissue in the obesity paradox of lung diseases is worthy to further study.

Comorbidity

Obesity is often associated with hypertension, diabetes, metabolic syndrome, and chronic kidney disease, and the literatures on obesity in patients with lung diseases and comorbidity are limited. Among COVID-19 patients, comorbidity is positively associated with risk of death [188] and HRs for case fatality rate [189], and the obese patients with comorbidities have higher mortality in comparison with non-obese patients with comorbidities [190, 191].

It has been reported that obesity significantly increases ORs for mortality in COVID-19 patients with hypertension or diabetes mellitus (DM) [192], and the OR reaches the peak in patients with hypertension, DM, and obesity [192, 193]. Several independent research works show that obesity confers increased risk of adverse outcomes, including ICU admission, invasive mechanical ventilation, and in-hospital death, to COVID-19 patients with DM [194–196]. Holman et al. [197] found that obesity only increases risk of COVID-19-related death in patients with DM type I, which is opposite to the report of Cariou et al. [198]. Differently, Soeroto et al. [199] showed that DM type II and hypertension were inversely proportional with effect of obesity on related poor outcome. Longmore et al. [200] found that obesity fails to increase the risk of severe COVID-19 outcomes in the patients with DM. Moreover, of patients with heart failure hospitalized with COVID-19, morbid obesity significantly increases ORs of in-hospital mortality [201].

Conclusions

Obesity has been proven to be the risk factor of various diseases, like diabetes and hypertension, but obese patients with certain lung diseases, including pneumonia, ALI/ARDS, COPD and lung cancer, showed better prognosis known as the obesity paradox. The obesity paradox in lung diseases could be attributed by altered immune responses and lung function, thus increasing resistance to the development and exacerbation of lung diseases. Several knowledge gaps, however, continue to hinder our understanding of the complicated processes involved in the obesity paradox of lung illnesses. First, the mechanism or functional molecules contributing to the obesity paradox is worthy to be classified. Although the exosomes from mice fed with HFD-induced inhibited production of pro-inflammatory cytokines and protected mice from ARDS, the target and mechanism of functional molecules carried by the exosomes are incompletely elucidated. Second, BMI is widely used to define obesity in population in research on the lung diseases and obesity paradox, but it is still controversial whether BMI can reflect the full anthropometric status. The role of changed body composition in the obese population, such as fat/muscle mass, in the obesity paradox of lung diseases remains largely unclear. Third, studies may differ in characteristics of the population, such as age and gender, which could contribute to the discrepant results of different studies. Lastly, clinically, patients commonly present with comorbidities, like hypertension and DM, while there are limited information on the impaction of obesity in these situations, and it remains unclear whether the comorbidities could be a contributor to discrepancy of the obesity paradox in lung diseases. Further investigation from homogeneous population or detailed description of obesity or adipose tissue would provide more hints on the underlying mechanism of obesity paradox in lung disease. We hope that the current review will spark new interest in this topic and further obesity research.

Conflict of Interest Statement

The authors declare that they have no competing interests.

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Author Contributions

K.C. conceived the study; S.Y. and K.C. wrote the manuscript; L.Z. and F.W. reviewed the manuscript. All authors read and approved the final manuscript.

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