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Covid-19 and obesity

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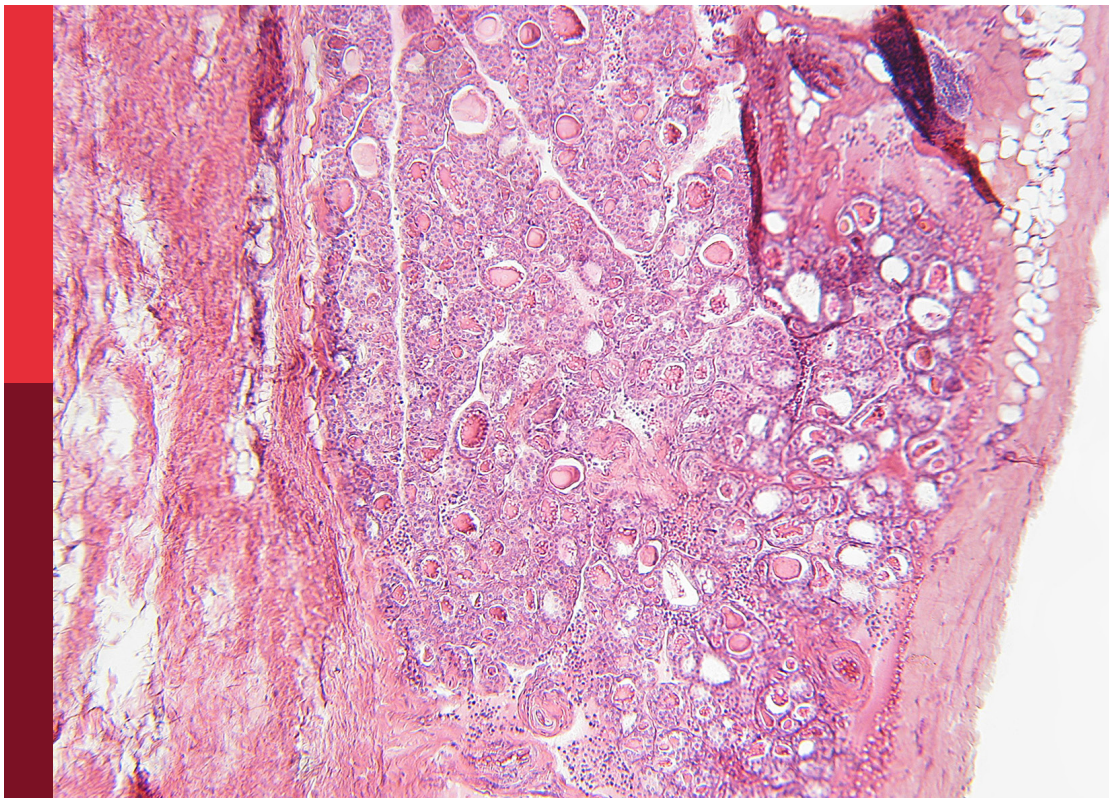

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Covid-19 and obesity

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Editorial: Covid-19 and obesity

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Editorial on the Research Topic
Covid-19 and obesity

The COVID-19 pandemic is reaching its third year and at the time of writing, approximately 641,900,000 people have been infected and over 6,622,000 deaths have been registered.

Importantly, approximately 50% of deaths related to COVID-19 have been in people with co-existing vascular and metabolic disorders (1). Among these, in addition to advancing age, a significant contributor to poorer outcomes is the coexistence of the SARS-CoV-2 infection with obesity.

Thanks to the development of vaccines and improved therapeutic approaches, daily global deaths have been markedly reduced. However, further pandemic spikes may be expected as virus mutation occurs, as shown by the rapid spread of the more recent SARS-CoV-2 variants, the waning of vaccine effectiveness, vaccination hesitancy and impaired immune responses. From this perspective, it remains crucial to continue to identify and understand the susceptibility of at-risk populations.

The present Research Topic, including eight review articles (three systematic reviews and metanalyses), five original papers, one brief research report and one opinion article, revisits some of the most important aspects of COVID-19 in people living with obesity, and summarizes the main insights into the field, collected during the early and more aggressive phases of the pandemic.

By analysing data relating to the hospitalizations of 176,137 patients throughout Germany, with a confirmed COVID-19 infection in 2020, Keller et al. found that patients with obesity were at increased risk of major adverse cardio- and cerebrovascular events, acute respiratory distress syndrome (ARDS), venous thromboembolism, intensive care unit (ICU) admission, mechanical ventilation and extracorporeal membrane oxygenation.

Considering the data of over 1,000 individuals from the UK Biobank, Morys and Dagher investigated whether metabolic health, defined by waist circumference, dyslipidaemia, hypertension, type 2 diabetes and systemic inflammation, on average 11 years prior to 2020, were related to increased rates of SARS-CoV-2 infection and

mortality during the first phase of the COVID-19 outbreak. After controlling for confounding variables (i.e., socioeconomic status, age, sex and ethnicity), poor metabolic health resulted in a higher COVID-19 mortality but did not affect the risk of SARS-CoV-2 test positivity. Although all of these co-existing chronic conditions have been proven to be significant predictors of adverse outcomes in COVID-19 patients (2), Yu et al. provided evidence from the ORCHID study that obesity was independently linked to prolonged hospital stays in 116 COVID-19 patients without comorbidities.

Although many studies confirmed the positive association between the severity of COVID-19 and BMI (3, 4), a more in-depth approach has recently been taken to understanding the interactions between obesity and poor outcomes, following a SARS-CoV-2 infection. In particular, the importance of adipose distribution has been pointed out, with visceral adiposity being shown to be more predictive of a poorer outcome than subcutaneous fat. As a consequence, questions have been raised regarding the assessment of obesity *via* BMI, which can overlook the role of fat distribution and sarcopenia, potentially further increasing the risk of critical illness, especially among the elderly (Azzolino and Cesari). To disentangle the independent causal relationships of body fat mass and fat-free mass in relation to COVID-19 severity, Yoshiji et al. conducted a Mendelian randomization study using single nucleotide polymorphisms associated with body fat mass and fat-free mass in individuals of European ancestry from the UK Biobank, and analysed their effects on severe COVID-19 from the COVID-19 Host Genetics Initiative. In this analysis, only body fat mass was independently associated with severe COVID-19, indicating that the causal relationship between COVID-19 severity and obesity is likely to be mediated by adiposity.

The contribution of obesity to the severity of COVID-19 may be explained in multiple ways (5, 6).

Increasing evidence indicates that obesity could result in altered lung physiology, including reduced lung volumes, ventilation–perfusion abnormalities and respiratory muscle inefficiency, as well as management difficulties in critical care settings. Bhattacharya et al. also considered the many lessons learnt from the 2009 H1N1 influenza A pandemic, and discussed how increased inflammation and activation of the renin-angiotensin-aldosterone system (RAAS) may be factors contributing to COVID-19 severity, resulting in a further deterioration of the cardiovascular and lung functions of individuals with obesity. In addition, those with obesity present a hypercoagulability state that may potentiate COVID-19 coagulopathy, implicated in severe COVID-19 cases. Such a pro-thrombotic state is also promoted by the dysregulated immune responses observed in obesity and, in particular, orchestrated by inflammation, hypoxia and endothelial hyper-activation, as detailed by Gammone and D'Orazio.

This impaired antiviral immunity renders subjects with obesity more susceptible to the SARS-CoV-2 infection and disease progression (7), which are also likely to be due to higher levels of ACE2, the main receptor to SARS-CoV-2 entry into the host cell. Indeed, ACE2 has also been identified in adipocytes, enabling adipose tissue to serve as a functional viral reservoir especially in conditions of adiposity excess (Pasquarelli-do-Nascimento et al.). Thus, an accumulation of cardiac and perivascular adipose tissue may potentially act as a viral reservoir in heart proximities, locally mediating the detrimental effects of obesity. In obesity, even the reduced levels of Angiotensin (1–7), a vasoactive peptide generated by the enzymatic activity of ACE2 (directly from AngI and indirectly, *via* the activity of ACE, from AngII) with vasodilatory and cardioprotective effects, may contribute to the cardiac and haemodynamic complications of COVID-19 (Pasquarelli-do-Nascimento et al.). Finally, the so-called fat embolism syndrome was suggested as another mechanism expanding the major risk of severe disease in patients with obesity (8).

Despite the clear association between obesity and disease severity, many studies, such as those included in the metanalyses of Zhao et al. and Helvaci et al. Failed to confirm a significant impact of obesity on mortality (Peres et al.). Conversely, the metanalysis of Singh et al. which included 167 studies and over three million patients, identified a clear association between obesity and increased COVID-19 mortality. The meta-regression analysis indicated that half of the heterogeneity in mortality data could be explained by age, gender, diabetes, hypertension, pulmonary and cardiovascular diseases possibly accounting for these inconsistencies, together with differences in study populations, healthcare systems and threshold values for BMI.

Fortunately, a significant proportion of morbidity and mortality has been avoided by putting into action prevention strategies for patients with COVID-19 at risk of severe disease, including neutralizing monoclonal antibodies targeting SARS-CoV-2, novel oral antiviral agents and, above all, vaccines with high efficacy and levels of safety.

However, data from previous vaccine trials have shown defective immune responses to vaccinations against different viruses in people with obesity, therefore, attention has been raised regarding the reduced vaccine-induced immunity in such patients. Data from the phase III SARS-CoV-2 vaccine trials on Pfizer, Moderna and Johnson & Johnson formulations indicated a similar efficacy in individuals with and without obesity. However, these outcomes were not statistically validated, and subsequent clinical trials have reported decreased antibody titers and weakened immune responses following the SARS-CoV-2 vaccination linked to obesity; therefore, the effectiveness and durability of these vaccines in individuals with obesity are still matters of debate (Nasr et al.)

If the presence of obesity is detrimental to the COVID-19 outcome, on the other hand, the COVID-19 pandemic has made the treatment of obesity even more challenging. Indeed, the

lockdown conditions, which resulted in a decline in eating habits and psychological well-being, sleep disruption and mobility restrictions, as well as the deferral of bariatric surgery interventions have, in turn, worsened the obesity epidemic (9). Indeed, Yang et al. who examined the changes in obesity, physical activity and nutrient intake during the COVID-19 epidemic in 2020, using the Korean National Health and Nutritional Examination Survey (KNHANES) database, found that the obesity rate in Korea significantly increased by comparison with the expected obesity rate of 2019, especially among men, mainly due to a decrease in physical activity.

In this context, to counteract the detrimental effects of the pandemic on obesity prevalence, the effectiveness of self-managed weight loss through the use of smart body fat scales has been investigated by Huang et al. in over 100,000 Chinese adult users registered in 2020. The authors found that many participants with overweight/obesity achieved weight loss goals by smart body fat scales, and the effectiveness of weight and fat loss was greater among participants with obesity rather than those with overweight.

In conclusion, obesity is now well accepted as a substantial risk factor for poor outcomes following the SARS-CoV-2 infection, therefore, given the ongoing nature of the pandemic, constant attention and proactive clinical management are needed for patients with obesity in order to reduce morbidity and mortality from SARS-CoV-2. This also adds further motivation to the ongoing efforts to curb the prevalence of obesity, in addition to the many other recognised health benefits of maintaining an appropriate weight.

Author contributions

All authors listed have made a substantial, direct and intellectual contribution to the work, and have approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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REVIEW
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Hypercoagulopathy and Adipose Tissue Exacerbated Inflammation May Explain Higher Mortality in COVID-19 Patients With Obesity

Gabriel Pasquarelli-do-Nascimento[1], *Heloísa Antoniella Braz-de-Melo*[1], *Sara Socorro Faria*[1], *Igor de Oliveira Santos*[1], *Gary P. Kobinger*[2,3] *and Kelly Grace Magalhães*[1]*

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COVID-19, caused by SARS-CoV-2, is characterized by pneumonia, lymphopenia, exhausted lymphocytes and a cytokine storm. Several reports from around the world have identified obesity and severe obesity as one of the strongest risk factors for COVID-19 hospitalization and mechanical ventilation. Moreover, countries with greater obesity prevalence have a higher morbidity and mortality risk of developing serious outcomes from COVID-19. The understanding of how this increased susceptibility of the people with obesity to develop severe forms of the SARS-CoV-2 infection occurs is crucial for implementing appropriate public health and therapeutic strategies to avoid COVID-19 severe symptoms and complications in people living with obesity. We hypothesize here that increased ACE2 expression in adipose tissue displayed by people with obesity may increase SARS-CoV-2 infection and accessibility to this tissue. Individuals with obesity have increased white adipose tissue, which may act as a reservoir for a more extensive viral spread with increased shedding, immune activation and pro-inflammatory cytokine amplification. Here we discuss how obesity is related to a pro-inflammatory and metabolic dysregulation, increased SARS-CoV-2 host cell entry in adipose tissue and induction of hypercoagulopathy, leading people with obesity to develop severe forms of COVID-19 and also death. Taken together, it may be crucial to better explore the role of visceral adipose tissue in the inflammatory response to SARS-CoV-2 infection and investigate the potential therapeutic effect of using specific target anti-inflammatories (canakinumab or anakinra for IL-1β inhibition; anti-IL-6 antibodies for IL-6 inhibition), anticoagulant or anti-diabetic drugs in COVID-19 treatment of people with obesity. Defining the immunopathological changes in COVID-19 patients with obesity can provide prominent targets for drug discovery and clinical management improvement.

Keywords: adipose tissue, COVID-19, Obesity, SARS-CoV-2, hypercoagulopathy, ACE-2

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INTRODUCTION

On December 2019, a series of pneumonia cases without a recognized etiology was reported in Wuhan, a central China city (1). Rapidly spreading throughout the globe, Coronavirus disease (COVID-19) was recently discovered to be caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The Word Health Organization (WHO) declared SARS-CoV-2

an international public health emergency on January 2020 and pandemic on March 2020. On June 25, 2020, ∼9,527,124 COVID-19 cases were confirmed in the world and 484,972 deaths were considered to be caused by this disease. As a means of decelerating disease progression, health authorities advise their citizens to wear masks, wash hands (2) and increase in public and physical distancing (3).

COVID-19 symptoms may or may not include fever, fatigue, dry cough, dyspnoea, anosmia, dysgeusia, and diarrhea (4–6). Respiratory symptoms are believed to be caused by the occurrence of diffuse alveolar damage, tissue fibrosis, and chronic inflammatory infiltrates (7). Some of the COVID-19 patients can often also present with prominent changes in coagulation function (8). Common comorbidities observed in COVID-19 patients are hypertension, cardiovascular disease, type 2 diabetes (9), chronic obstructive pulmonary disease (10), and obesity (11).

Obesity is a major public health issue globally affecting a half a million people (12). As an inducer of cardiometabolic dysfunction, obesity is associated with increased risk for many diseases, such as Type 2 Diabetes (T2D) (13), dyslipidemia (14), hypertension (12), coronary disease (15), and coagulopathy (16). Chronic inflammation, defined as a low grade but persistent process, disrupting homeostasis and driving organ dysfunction (17). During obesity, chronic inflammation is not only associated with metabolic disturbances and decrease in heart health, but also impacts immune system function (18, 19). In this review we present evidence that indicates that people with obesity are more susceptible to develop severe forms of COVID-19 and higher mortality due to intrinsic alterations in blood coagulation parameters, inflammation, and immune response.

INCIDENCE OF COVID-19 IN PEOPLE WITH OBESITY

Obesity represents a risk factor for many chronic diseases, including hypertension, dyslipidemia, diabetes mellitus type 2 (T2DM), cardiovascular disease (20), and several types of cancer (21). As a consequence of excessive or abnormal fat tissue accumulation, overweight and obesity can alter innate and adaptive immune responses, making the immune system more prone to infections and less responsive to vaccinations, antivirals, and antimicrobial drugs (22). There is growing evidence that implicates obesity as one of the main risk factors for triggering severe forms of COVID-19 and poor outcomes (23).

Several studies have reported that obesity may affect the severity of COVID-19, with a direct correlation between increasing BMI and the proportion of patients with severe COVID-19 (24). It has been reported that comorbidities related to obesity are also correlated with increased COVID-19 mortality and morbidity, such as cardiovascular disease (22.7%), hypertension (39.7%), diabetes (19.7%), respiratory disease (7.9%), and cancers (1.5%) (25).

Several reports have shown a significant incidence of people with obesity presenting higher COVID-19 mortality and morbidity in different countries. According to WHO data, the United States of America ranks first in the world in terms of prevalence of obesity (36.2%), overweight (31.7%), as well as in the number of total deaths from COVID-19. Some American studies have indicated obesity as as important comorbidity deeply related to the development of severe forms of COVID-19 (26, 27). In a study developed in a large academic hospital in New York City investigating 3,615 individuals who tested positive for COVID-19, 775 (21%) had BMI values among 30–34 kg/m^2 and 595 patients (16% of the cohort) displayed BMI values higher than 35 kg/m^2 (28). Diabetes and obesity also increased the risk of COVID-19 infection in Mexico (29). In a French hospital that evaluated 124 patients admitted to intensive care by COVID-19, it was found that 28.2% of the cases had a BMI $>$ 35 kg/m^2 and required invasive mechanical ventilation (30). In Spain, from 48 critically ill COVID-19 patients admitted to ICU, 48% presented obesity and 44% arterial hypertension as most prevalent comorbidities (31). In Italy, the severity of COVID-19 and the tension in the health system related to the disease have been remarkable, with an estimated fatality rate of 7.2% (32). Recent Italian studies have highlighted the role of comorbidities in their COVID-19 cases, underlying obesity in the severity of this disease (33). Despite the low prevalence of obesity in China, the severely ill COVID-19 patients were older and had comorbidities, such as obesity and diabetes mellitus more often than non-severely ill individuals (34). In Republic of Korea, clinical data of COVID-19 early cases were collected and demonstrated that of the 28 hospitalized patients, 17.9% had one or more coexisting medical conditions being obesity the most common comorbidity (35).

Therefore, considering that obesity is one of the strongest risk factors for COVID-19 severity, it is important to better understand the correlation between obesity and COVID-19 and the mechanisms that could be involved in this process. In this way, it is crucial to analyze deeper this issue, focusing on the association among SARS-CoV-2 host cell entry, adipose tissue biology, and all the inflammatory, vascular and metabolic dysfunctions that may define COVID-19 progression.

SARS-CoV-2 HOST CELL ENTRY

Genomic analyses demonstrated that SARS-CoV-2 is 96% identical at the whole-genome level to a bat coronavirus SARS-CoV (36). It has been demonstrated that host cell entry of SARS-CoV-2 depends on the same receptor used by SARS-CoV to entry host cell, the Angiotensin-converting enzyme 2 (ACE2) (36, 37). ACE2 receptor was first described in 2000 (38, 39) and it was associated with multiple pathophysiological processes, including the pathogenesis of cardiovascular and renal diseases such as hypertension, myocardial infarction and heart failure (40), acute lung injury (ALI) (41), and acute respiratory distress syndrome (ARDS) (42, 43).

ACE2 gene contains 18 exons and 20 introns, maps to Xp22 chromosome and spans 40 kb of the genomic DNA (44). ACE2 protein is a type I transmembrane glycoprotein of 805 amino acids (∼120 kDa), containing a single extracellular catalytic domain whose sequence is 41.8% identical with the domain of angiotensin-converting enzyme (ACE) (43). ACE2 is part of

the renin-angiotensin-aldosterone system (RAAS), which is a peptidergic system that acts in the homeostatic regulation of the renal and cardiovascular systems, regulating extracellular fluid volume (40). Renin (an aspartyl proteinase secreted by kidney into the circulation) cleaves its starting substrate angiotensinogen to angiotensin I, which is hydrolyzed by ACE to angiotensin II. ACE2 cleaves angiotensin II to Angiotensin 1-7. Angiotensin II promotes inflammation, oxidative stress, vasoconstriction, salt and water reabsorption (45). Consequently, increased ACE2 activity can shift the balance to the Angiotensin 1-7 axis, leading to disease and inflammation protection. Moreover, ACE2 is a zinc metalloprotease multifunctional enzyme that can act on several vasoactive peptides (46), regulating important cardiovascular and renal functions. Therefore, ACE2 has an ambiguous role acting as both an important physiological receptor and a SARS-CoV-2 backdoor (47).

SARS-CoV-2 bind to its host cell receptor is a critical initial step for this virus entry into target cells. SARS-CoV-2 use the homotrimeric spike glycoprotein S on the viral envelope to bind their cellular receptors, which facilitates viral attachment to the surface of target cells, inducing endocytosis of virion particle, catalyzing the fusion between viral and host cell membranes, and allowing the entry of the virus genome into the host cell cytoplasm. Each monomer of trimeric S protein is about 180 kDa, and contains two subunits, S1 and S2. S1 mediates viral attachment to host cell and S2 intermediates membrane fusion.

SARS-CoV-2 entry in host cell requires S protein priming by cellular proteases, such as the endosomal cysteine proteases cathepsin B and L (CatB/L) and the cellular and the serine protease TMPRSS2 (37). SARS-CoV-2 entry into susceptible cells is a complex process that requires the combined action of receptor-binding and proteolytic processing of the S protein to promote an efficient virus-cell fusion (48), followed by endosomal acidification (**Figure 1**). Contrasting SARS-CoV, cells infected with SARS-CoV-2 form typical syncytium, suggesting that SARS-CoV-2 may mainly use the plasma membrane fusion pathway to enter and replicate inside host cells (49). This plasma membrane fusion pathway is more efficient for most viruses since it may delay host cell antiviral immunity activation compared to the viral and endosomal membrane fusion pathway (50, 51).

Considering the recent findings showing that SARS-CoV-2 mainly uses TMPRSS2 for plasma membrane fusion, clinically proven inhibitors of the cellular serine protease TMPRSS2 might constitute an option for blocking SARS-CoV-2 host cell membrane entry. These results have important implications for our understanding of SARS-CoV-2 transmissibility and pathogenesis and reveal a target for therapeutic intervention.

Several studies have demonstrated how SARS-CoV-2 uses the human ACE2 as the main receptor to viral entry into host cell (36, 48, 52). Overexpression of human ACE2 led to more severe disease in a mouse model of SARS-CoV infection, indicating that viral entry into host cells is a key step for the establishment and progression of this disease (53). Moreover, Zhou and colleagues demonstrated that overexpressing human ACE2 in HeLa cells allowed increased SARS-CoV-2 infection and replication (36). ACE2-expressing cells may act as target cells and are susceptible to SARS-CoV-2 infection (54) and S protein-targeted neutralizing antibody may be prominent antiviral tools against SARS-CoV-2 infection. Several cellular types have been identified with high ACE2 expression including myocardial cells, type II alveolar cells, proximal tubule cells of the kidney, ileum and esophagus epithelial cells, and bladder urothelial cells (54), epithelial cells of oral mucosa (55), nasal epithelial cells (56), and interestingly, adipocytes (57).

SARS-CoV-2 AND ADIPOSE TISSUE

In patients with obesity, in which white adipose tissue (WAT) is exacerbated and brown adipose tissue (BAT) is decreased (58), RAAS is chronically activated and predisposes the individual to a plethora of dysfunctions, including heart and kidney pathologies. These alterations are associated not only with high blood pressure (59) but also related to insulin signaling in peripheral tissues (60), inflammatory status in pancreas and death profile of β cells (61). Increased oxidative stress is believed to be the root of the cytotoxic effects induced by Ang II and aldosterone during RAAS aberrant activation (62). The resulting insulin resistance acts as a driving force for the progression of cardiometabolic syndrome, commonly associated with obesity (63).

The counterbalance for this blood pressure-increasing action of RAAS is the alternative pathway, which consists in the agonism of the G-protein-coupled Mas receptor by Ang-(1-7). This compound is generated by the enzymatic activity of ACE2 in both AngI and AngII. Ang-(1-7) induces vasorelaxation and cardioprotection (64). ACE2/Mas axis induction associates with BAT activation and WAT browning, processes that are related to anti-obesity effects (65). Due to many alterations in the physiology during obesity, including RAAS dysfunction, BAT tend to present decreased size and activation, increasing the chance of comorbidities (58).

RAAS components, including ACE2, are expressed in adipocytes and are crucial for their glucose and lipid metabolism homeostasis (63). *In vivo* experiments in mice showed that high-fat diet (HFD)-induced obesity is associated with increased adipose tissue ACE2 expression (40). Thus, we hypothesize here that increased ACE2 expression in adipose tissue displayed by people with obesity may increase SARS-CoV-2 infection and accessibility to this tissue. Moreover, obesity causes hyperglycemia via insulin resistance whereas growing evidence demonstrates that SARS-CoV-2 may cause hyperglycemia as well by infecting and killing B-cells (66). In addition, some drugs often used for the treatment of patients with obesity complications (such as antihypertensives, statins, thiazolidinediones) can up-regulate ACE2, thus could potentially increase the viral up-take (67–70).

Obesity is characterized by dysfunction of immune system (19). During obesity, systemic inflammatory status is influenced by intense pro-inflammatory cytokines secretion (71), increasing the chance of cytokine storm occurrence (72). In addition, obesity associates with Type I Interferon (IFN) decreased secretion, key players in antiviral immune

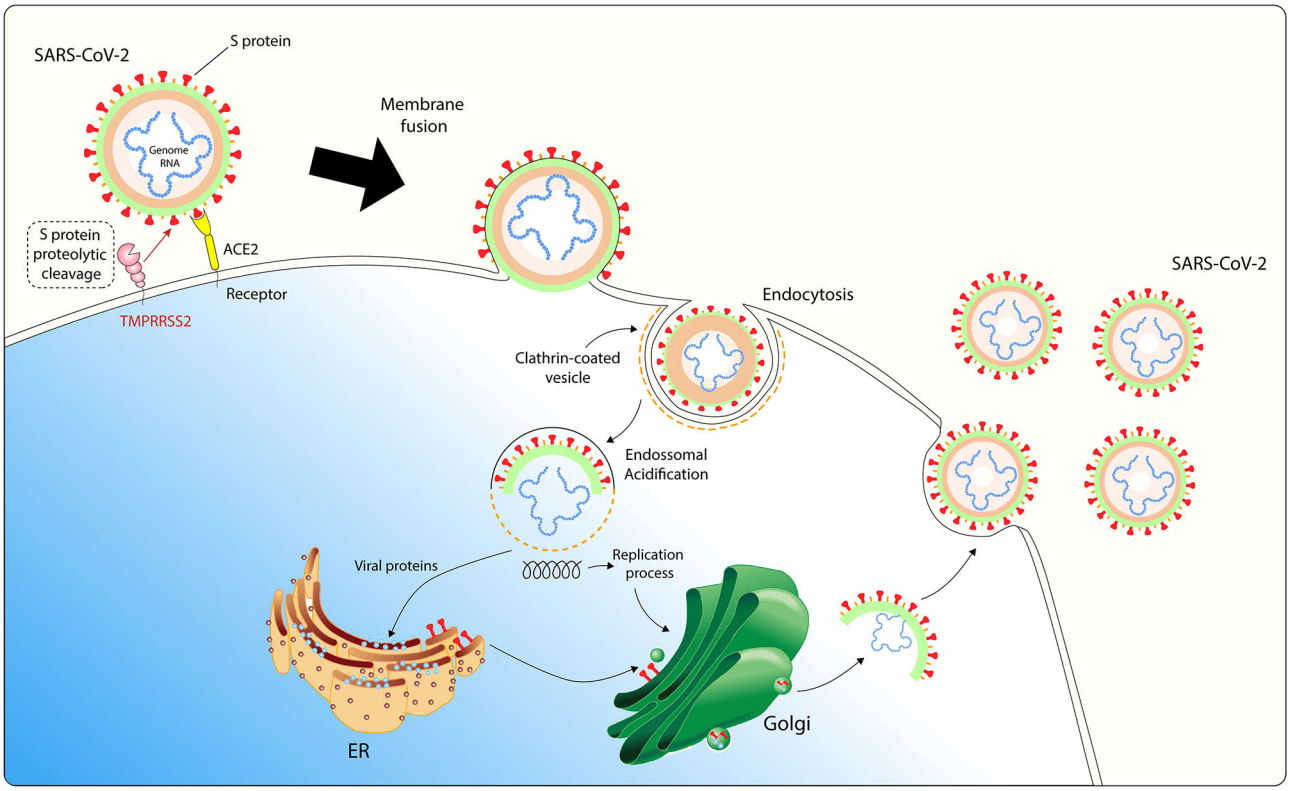

FIGURE 1 | SARS-CoV-2 host cell entry cell depends on the angiotensin-converting enzyme 2 (ACE2) and TMPRSS2. The virus uses the homotrimeric peak glycoprotein S present on viral envelope surface to physically interact with its cell receptor, which facilitates binding to the surface of target cells, enables endocytosis of the virion particle and entry of the viral genome into the host cell cytoplasm. This cell entry process requires priming of protein S by cellular proteases, such as the serine protease TMPRSS2. After endosomal acidification, viral proteins are synthesized in host ER for viral replication and virion particles shedding occurs through Golgi apparatus. ACE2 is expressed in adipocytes and adipose tissue may act as a reservoir for SARS-CoV-2.

response (73). Human studies showed that H1N1-infected patients with obesity stayed longer under ICU care (74), and investigations with Diet-induced obese (DIO) murine model informed that over nutrition impaired antiviral response against Influenza (75). Thus, individuals with obesity present immune system dysfunction that increase respiratory viral infection susceptibility (19).

It is currently known that adipocytes (76), which are the main cellular components of adipose tissue, and lung cells are targets for SARS-CoV-2 infection (77). Influenza A also presents shared tropism for lungs (78) and WAT (76). In an elegant study, Maier and colleagues showed that symptomatic adults with obesity shed influenza A virus more than 40% longer than non-obese adults. They suggested that WAT dysregulation, common in individuals with obesity, is related to prolonged viral shedding duration (76).

The alarming COVID-19 morbidity and mortality rates of individuals affected with heart pathologies may be related to epicardial adipose tissue (EAT). Classified as a visceral AT, EAT may act as a SARS-CoV-2 reservoir, prolonging viral shedding to cardiac tissue. In addition, EAT obtained from subjects with obesity tend to present higher levels of IL-6 and TNF-α (79), cytokines abundantly secreted in COVID-19 patients. Furthermore, the ACE2/Mas axis dysfunction, observed in individuals with obesity and in subjects affected by COVID-19, associates with EAT inflammation, probably due to Ang(1-7) level decrease, once this protein is associated with diminished proinflammatory macrophage polarization in EAT (80). Once metabolic syndrome, common in individuals affected by obesity, is associated with increased amounts of EAT (81), alterations in EAT amount and inflammatory status may be suggested to influence COVID-19 cardiac morbidity in individuals living with obesity. EAT measurement may play a crucial role in the management of COVID-19 progression in cardiac patients (82).

In a study investigating the influence of obesity in the prognosis of asthma patients, Elliot and others showed that individuals affected by obesity display WAT deposits in large airway walls. They found that BMI value impacts proportionally WAT deposits size, which favors both airway wall thickness increase and neutrophil infiltration within pulmonary tissue (83). Increase in lung wall thickness associates with difficulties in gas exchange (84), and immune cells infiltration is related to tissue damage and fibrosis (85). It is important to have in mind that the increased expression of ACE2 in WAT during obesity makes these intra-pulmonary deposits a susceptible point for SARS-CoV-2 infection within the lung tissue. In addition, the prolonged

viral shedding that may occur in WAT would facilitate for the occurrence of pulmonary damage and consequent respiratory failure in cases of obesity (76).

Also found in lungs, adipose-like cells called lipofibroblasts (LiFs) affect pulmonary function, since the transdifferentiation of these cells to myofibroblasts leads to pulmonary fibrosis (PF) (86). LiFs present lipid droplets (LDs) within their cytoplasm containing high levels of perilipin-2. Located in the alveolar interstitium, these cells reside in the proximity of ACE2-expressing type 2 alveolar epithelial cells (AEC2), to whom they provide surfactant molecules. AEC2 are considered to be the biggest pool of ACE2-expressing cells in the lungs and LiFs proximity may indicate higher chance of PF in the lungs of infected individuals with obesity (87). In addition, the possibility of LiFs to also express ACE2 should be assessed, once PF is a common feature among deceased COVID-19 patients.

Although WAT dysfunction is associated with high rates of COVID-19 morbidity and mortality in individuals with obesity, WAT can be a promising source of mesenchymal stem cells (MSCs). As described by Leng and others, intravenous administration of clinical-grade MSCs was capable of improving pulmonary functional activity into seven COVID-19 patients (88). Due to its accessibility and amount of stem cells, subcutaneous WAT (scWAT) is the main source of MSCs, the AT-derived stem cells (ASCs). Once ASCs display high secretory activity, they possess therapeutic potential for the treatment of pulmonary damage caused by COVID-19 (89).

Therefore, we suggest that individuals with obesity tend to be more susceptible to SARS-CoV-2 infection and COVID-19 progression. These patients show aberrant RAAS activation, high ACE2 levels, low Ang(1-7) amounts, decreased antiviral immunity, higher amounts of EAT and presence of lipid deposits in large airways, which potentially act as viral reservoirs in heart and lung proximities, and higher chances of LiF-myofibroblast transdifferentiation and consequent pulmonary fibrosis. These features help to explain the disturbing statistics related to susceptibility, morbidity, and mortality of individuals affected with obesity. Research under potential applicability of ASCs is crucial for alleviating the impact of SARS-CoV-2 infection on this risk group (**Figure 2**).

INFLAMMATORY ALTERATIONS IN OBESITY AND COVID-19

Exacerbated inflammation is associated with increased risk of severe disease and mortality in patients with COVID-19 (90). COVID-19 patients commonly present intense pro-inflammatory markers activation such as IL-1, IL-6, IL-17, IL-18, IFN, and C-reactive protein (90, 91) with deep lymphopenia and substantial mononuclear cell infiltration in the lungs, heart, lymph nodes, spleen, and kidney (92, 93). Considering that the mortality and morbidity observed in COVID-19 patients is associated with excessive inflammation, a better understanding of the immunological parameters seen in patients infected with SARS-CoV-2 and people with obesity is necessary to better correlate COVID-19 and obesity, improving the identification of therapeutic targets.

Inflammation is an essential factor for the protection against countless threats that affects the organism during a lifetime. Deficiencies on immune system activation arises several disorders, which can be deleterious depending on the immunosuppressive potential of the disease (94). On the other hand, the chronic or excessive activation of the immune system also contributes to homeostasis breakdown and play a key role on classic inflammatory diseases progression, such as obesity and other metabolic disorders (95, 96). Obesity has been characterized by low grade chronic inflammation. This process leads to exacerbated and prolonged activation of both innate and adaptive immune responses, bringing on tissue damage and metabolic and physiologic alterations.

WAT is the central organ that orchestrates obesity and is composed by different kind of adipocytes, immune and endothelium cells, among others. During obesity, pro-inflammatory cytokines are overexpressed concomitantly with adipocytes hypertrophy and hyperplasia (71). The uncontrolled increase in the number and content of adipocytes lead to hypoxic microenvironment that is associated to cellular necrosis, activating local immune response (97). In the WAT, immunological cells, such as macrophages, natural killers (NK), T and B lymphocytes are major sources of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which are central cytokines on driving inflammation linked to comorbidities establishment (98–100). In addition, macrophages are recruited by increased expression of monocyte chemoattractant protein-1 (MCP-1) and polarized to their pro-inflammatory profile due to the abundance of IL-6 and TNF-α (101–103). The huge macrophage infiltrate in the adipose tissue that accompanies obesity increases the source of inflammatory mediators, thus maintaining a chronic and persistent inflammation that affects systemic metabolism and immune response (99).

In obesity, inflammatory markers are found altered not only in the adipose tissue, but also in the serum, liver, skeletal muscle, lung, among other organs (71, 104, 105). As a result, the impact of immunomodulatory potential of obesity compromises systemically the response against homeostasis breakdown. Some comorbidities, such as insulin resistance, T2DM, hypertension, pulmonary illness, fatty-liver, and cardiovascular diseases are direct related to the chronic inflammation provided by obesity (106–108). In addition, these inflammatory modulations alter how the organism will face different pathogens infections, leading obesity to be considered a risk factor of a great number of them.

The intensive secretion of IL-6, TNF-α, and MCP-1 sustains the unbalanced inflammation on individuals with obesity. Together, these inflammatory mediators lead to several alterations on systemic responsiveness to nosocomial infections, increasing the incidence of generalized inflammation by the cytokine storm release (109, 110). Moreover, population with obesity also maintains a chronic inflammation on respiratory tract, presenting a higher susceptibility for acute lung injury caused by viral infections, such as H1N1 (110, 111). However, despite intensive inflammation has been considered factor that plays a major role in the higher mortality of population with

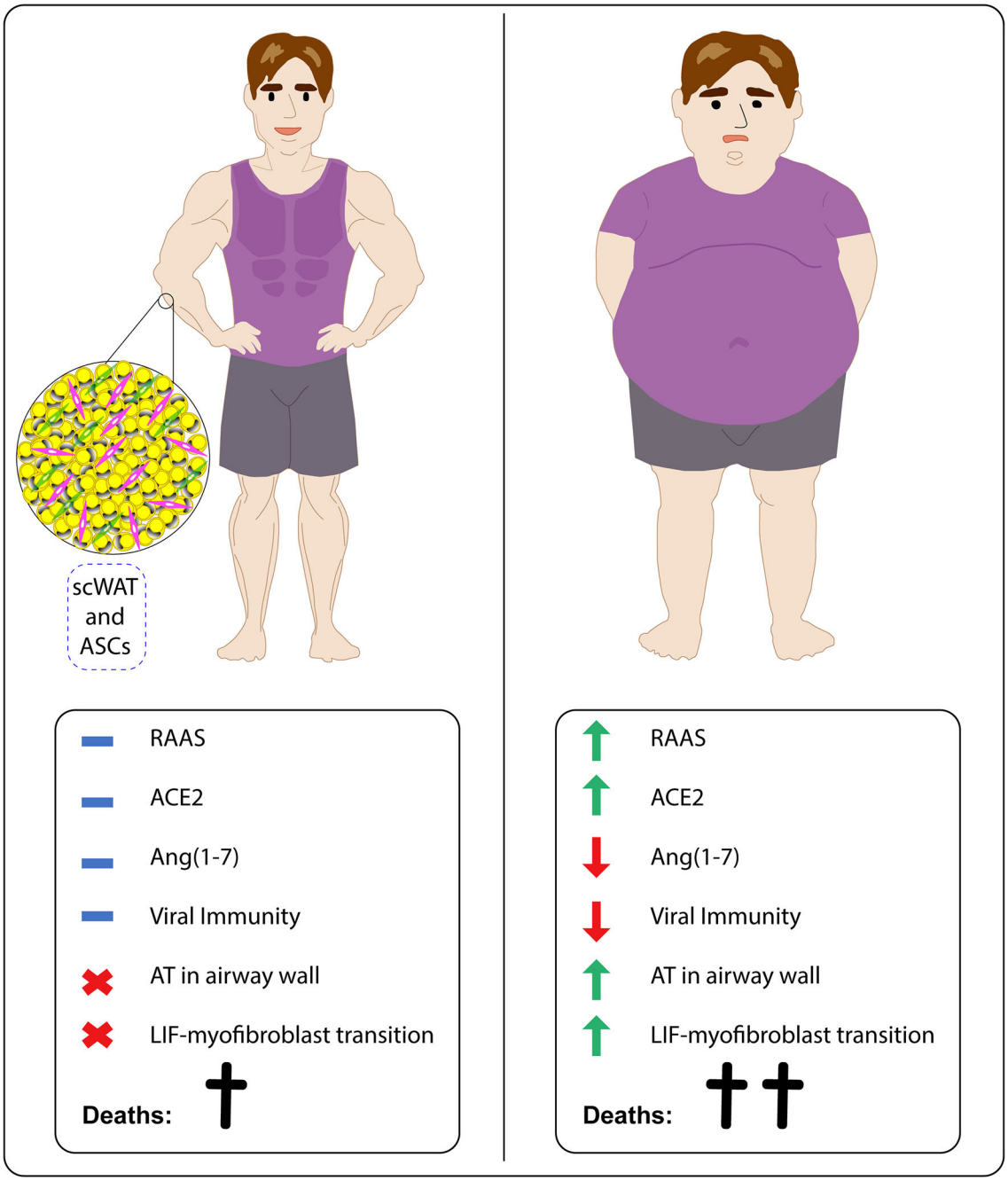

FIGURE 2 | Obesity increases SARS-CoV-2 infection vulnerability in affected individuals by interfering in RAAS activation, antiviral immunity, fat tissue accumulation, and differentiation status of pulmonary fibrosis related cells. While lean individuals tend to show adequate RAAS activation, including ACE2 and Ang(1-7) levels, effective antiviral immune responses and absence of both adipose tissue (AT) deposits in airways and LiF-myofibroblast transdifferentiation, subjects with obesity display aberrant RAAS activation, favoring high ACE2 expression and low Ang(1-7) availability, decrease of immune responses against viruses and presence of both AT deposits in airways and LiF-myofibroblast transdifferentiation. ScWAT-derived stem cells (ASCs) could be applied in COVID-19 treatment.

obesity on several viral illnesses (110), there are other alterations on immunological system that contribute to this scenario. Currently, it has been shown a downregulation of a central pathway during immune system activation against viral infection, being also a factor responsible for the greater involvement observed during obesity (73).

Studies have shown impairment of IFN secretion on individuals with obesity, besides other pro-inflammatory

cytokines are being overly produced (73, 112). IFN is the most important cytokine for combating viral infections and reducing this signalization pathway makes the organism more susceptible to the severity of viral disease (113, 114). Moreover, influenza vaccination seems to have a worse performance on obese or overweighed population, demonstrating that the efficacy of adaptive immune response is also decreased (115, 116). During influenza vaccination in humans, type I IFN signalization has been shown to be modulated throughout dendritic cells activation, which is central for long-term CD8+ T cells immunity (117). In addition, the use of type I and III IFN as vaccine adjuvants have demonstrated benefits for adaptive immune response development *in vivo* (118). The leptin overproduction found in individuals with obesity leads to an aberrant type I interferon secretion, thus impacting how the organism will handle vaccination-induced immunity (112). Currently, it is not possible to affirm if SARS-CoV-2 vaccine response will be less effective on individuals with obesity. However, the available data regarding the immune response of obese or overweighted individuals *in vivo* demonstrate that hiporresponsiveness to a COVID-19 vaccine could be a concern (119–121).

Thereby, it is clear that therapeutic targets may not be focused on turning off the pan activation of the immune system, but through the induction of the appropriate mediators for better combating the infectious agent. Moreover, the maintenance of controlled levels of inflammatory mediators is essential for homeostasis establishment and tissue recovery. Therefore, therapeutic targets aiming inflammatory response may be proposed to improve treatment of COVID-19 patients with obesity, once this group is at higher risk for developing severe viral illness considering their intrinsic alterations in inflammatory profile.

COAGULATION ALTERATIONS IN OBESITY AND COVID-19

Alterations in blood coagulation parameters have been increasingly implicated in COVID-19 severity, mortality, and morbidity (122–124). Several recent studies have shown that COVID-19 is commonly complicated with coagulopathy and disseminated intravascular coagulation (DIC) or associated with hypercoagulability together with a severe inflammatory state (125), leading to higher mortality (1, 8, 126). COVID-19 patients with acute respiratory failure present a severe hypercoagulability rather than consumptive coagulopathy (127). A significant portion of the patients hospitalized with COVID-19 usually present a pattern of coagulopathy characterized by elevations in D-dimer levels (8) and fibrin/fibrinogen degradation products, while abnormalities in prothrombin time, partial thromboplastin time, and platelet counts are relatively uncommon in initial presentations (123). Indeed, the DIC seen in the COVID-19 infection is clinically evidenced with high concentrations of D-dimer, being a poor prognostic characteristic (128) and higher risk of mortality (9). COVID-19 patients show a fulminant activation of coagulation and consumption of coagulation factors, with severe thrombocytopenia (low platelet count) (129). Likewise, obesity is highly related to a hypercoagulopathy status.

Excess body weight and especially abdominal fat accumulation can increase cardiovascular diseases morbidity and mortality, directly and indirectly. Direct effects are mediated by the structural and functional adaptations of the cardiovascular system to accommodate excess body weight, as well as by adipokine effects on inflammation and vascular homeostasis, leading to a pro-inflammatory and pro-thrombotic state. Indirect mechanisms occur concomitantly to other factors, such as insulin resistance, T2DM, visceral adiposity, hypertension, and dyslipidemia (130, 131).

Apart from metabolic and hemodynamic changes, central adiposity is also characterized by a systemic oxidative stress process, leading to the loss of the antithrombotic properties of endothelium (132). This mechanism partially supports the obesity as a pro-thrombotic clinical condition, presenting increased platelet activation and decreased fibrinolysis (133). Stimulation of vascular endothelium, platelets, and other circulating vascular cells by exacerbated production of proinflammatory cytokines by people with obesity promotes the upregulation of procoagulant factors and adhesion molecules, downregulation of anticoagulant regulatory proteins, increased thrombin generation, and enhanced platelet activation (134).

Adipose tissue could play a crucial role in the induction of a procoagulant state in obesity. Obesity is associated with overproduction of procoagulant microparticles (MP) and increased Tissue factor (TF), a primary initiator of the blood coagulation cascade through its Factor VII receptor activity, leading to hypercoagulopathy (135, 136). Moreover, release of adipokines/inflammatory factors by adipose tissue, such as TNF-α, IL-8, and IL-6, can lead to the release of ville Willebrand factor (vWF) from the endothelium and elevate platelet activation and aggregation, inducing coagulation factors production and changes in the vessel wall, thus contributing to the thrombosis event (137). Platelets store cytokines and growth factors and the entire subcellular apparatus for protein synthesis involved in the coagulation cascade, IL-1β, plasminogen activator inhibitor-1 (PAI-1) and TF (138). The inflammatory effects of cytokines also result in endothelial injury (139) and the substantial increase in the production of pro-inflammatory cytokines results in a cytokine storm, leading to an elevated risk of vascular hyperpermeability, organ failure, and death (140). Moreover, the platelets of individuals with obesity exhibit a series of abnormalities contributing to the status of hypercoagulability observed in these people (141). In this way, an inherent exacerbated inflammation state and a tendency to develop hypercoagulation together are the main causes for people with obesity present higher mortality rates due to COVID-19 (**Figure 3**).

It has also been shown that pro-trombotic factors are positively related to central fat. People with obesity have higher plasma concentrations of all pro-thrombotic factors (factor VII, fibrinogen, and vonWillebrand factor), as compared to non-obese individuals (142). Similarly, plasma concentrations of PAI-1, a physiological inhibitor of plasminogen activators (urokinase and tissue types) synthesized by adipose tissue, is highly elevated

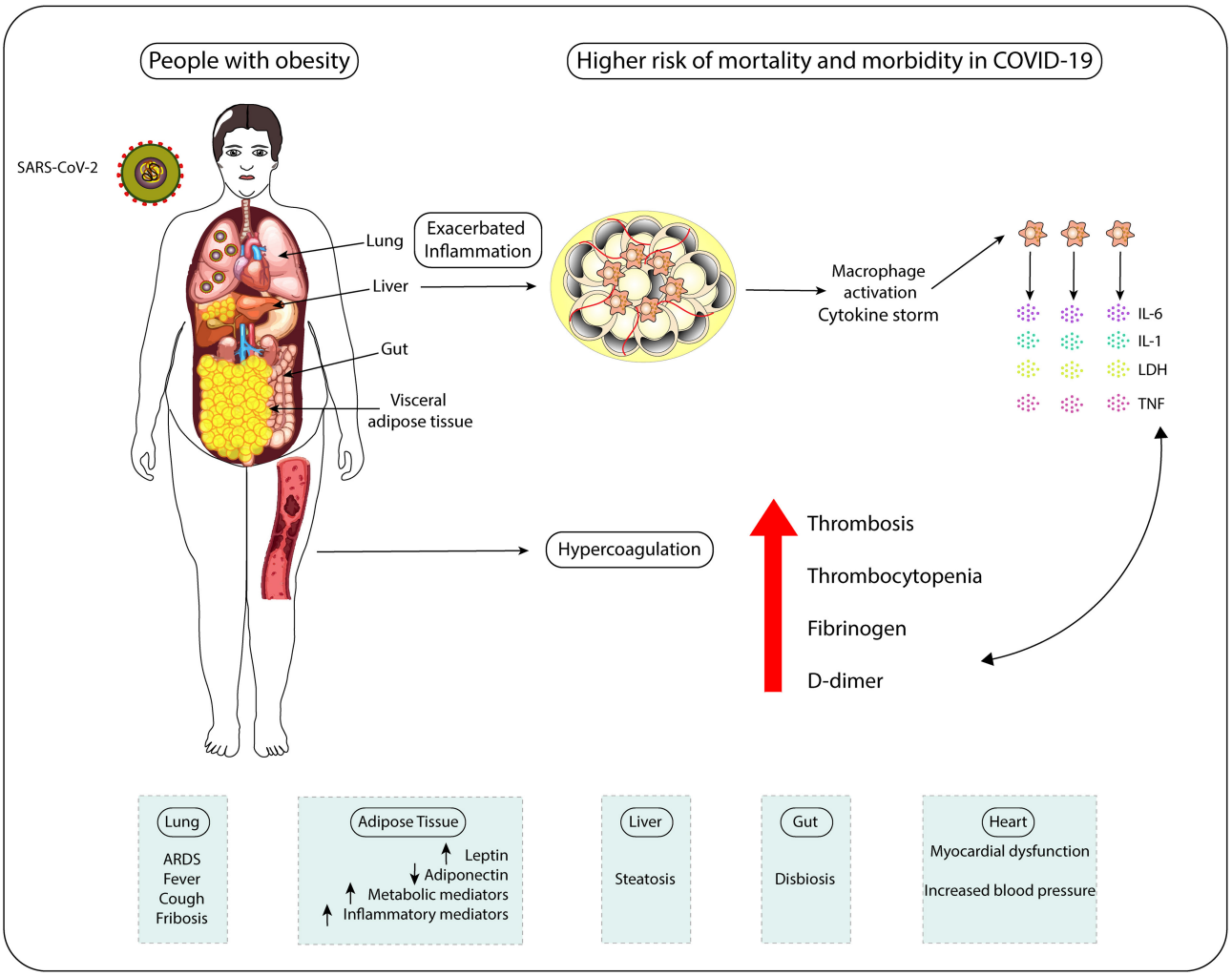

FIGURE 3 | People with obesity display higher risk of mortality and morbidity in COVID-19 due to exacerbated inflammatory status and hypercoagulation tendency. Individuals with obesity show systemic chronic inflammation, which favors macrophage activation, cytokine storm occurrence (aberrant secretion of pro-inflammatory cytokines IL-6, IL-1, and TNF) and cytotoxicity (LDH release). This inflamed status associates with the increased clotting risk (hypercoagulation) presented by these patients. All these features make subjects with obesity more prone to develop pathological alterations in the physiology of lungs, AT, liver, heart, and intestines, which negatively influences gut microbiome composition. The impact of obesity-associated chronic inflammation on systems' physiology, including on antiviral immune responses, and the increased levels of coagulation-inducing mediators (fibrinogen and D-dimer) in COVID-19 patients help to explain the higher risks of these individuals to die of COVID-19 and to suffer with this infection compared to non-obese individuals.

in plasma of people with obesity (143–145), predisposing those individuals to thrombotic complications. All of these conditions contribute to the progression of the prothrombotic state found in obesity (**Figure 4**).

Genetic factors are also correlated with higher susceptibility to coagulation impairment among individuals (146). Similarly, growing evidence has also supported the role of genetic factors as influencers in COVID-19 respiratory failure. In this context, a report has shown an association between ABO blood system and COVID-19 symptoms variation among individuals (147). This genome meta-analysis is in accordance with previous reports, in which blood-type O individuals are less affected by respiratory complications than type A (148, 149). These data are interesting, once blood-type O individuals are also less susceptible for thromboembolism development compared to non-type O (A, B, or AB) (150, 151). Until this moment, there is no evidence that obesity can be modulated by blood type. However, blood coagulation and COVID-19 severity need special attention since they are both influenced by ABO system. Understanding the inherent factors that support coagulation dysfunctions observed in COVID-19 patients is important to the establishment of therapeutics against this disease.

The impact of obesity, often related with other comorbidities, has been highlighted in severe forms of COVID-19 (152). In

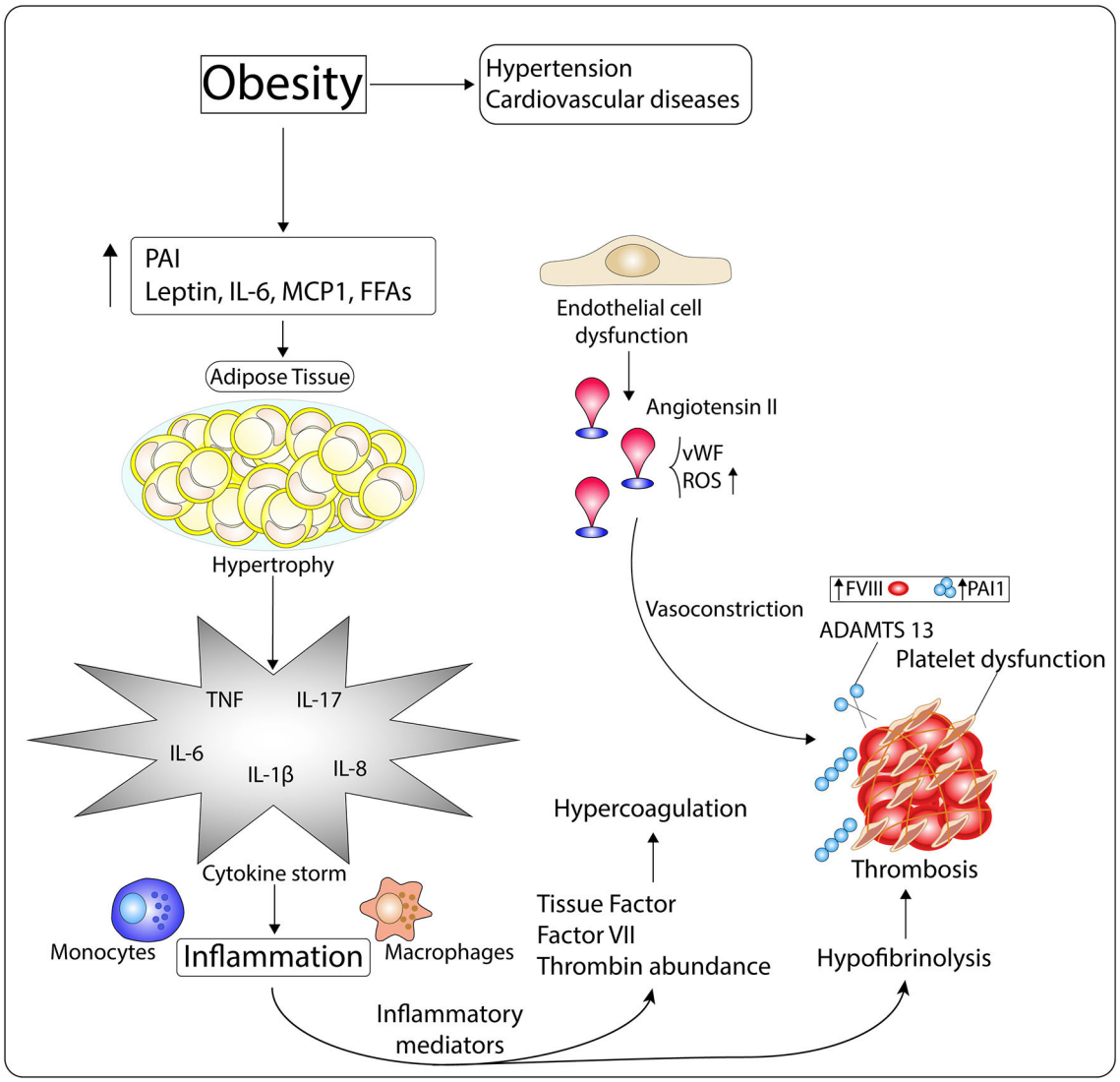

FIGURE 4 | Mechanisms of the hypercoagulopathy and exacerbated inflammation observed in people with obesity. Obesity, which is intimately related with the pathogenesis of hypertension and cardiovascular diseases (CVDs), is characterized by high levels of Plasminogen Activator inhibitor I (PAI), leptin, IL-6, MCP-1, and free fatty acids (FFAs). These molecules induce white adipocyte hypertrophy, which then enables the occurrence of inflammation through cytokine storm. Inflammatory mediators impact on the availability of tissue factor (TF), factor VII (FVII), and thrombin-inhibiting factors, disrupting procoagulant-anticoagulant balance, and leading to hypercoagulation. Moreover, inflammation dysregulates fibrinolytic homeostasis through platelet dysfunction, increased FVIII and PAI-1 levels, and diminished ADMTS 13 activity, which enhance the risk of thrombosis. In addition, endothelial cell dysfunction, common in the obese phenotype, associates with Angiotensin II (Ang II) elevated amounts, von Willebrand factor (vWF) release, and oxidative stress, which induce vasoconstriction and thrombus formation.

critically ill patients, coagulation alterations and inflammation are observed, with increased D-dimer and fibrinogen levels and, consequently, associated with a worse prognosis (126). The inflammation and hypoxemia related with a prothrombotic state are significant features of severe forms of COVID-19.

In conditions of obesity, coagulation disorders are emerging as an important issue in SARS-CoV-2 infection. Activation of leukocytes, endothelial cells, and platelets through the cytokine storm, positive regulation of TF and the subsequent generation of thrombin and fibrin formation can mediate the metabolic and cardiovascular complications associated to obesity (153). Together with coagulopathy, the thrombus formation in the microvascular environment contributes to tissue ischemia and organ dysfunction (154).

Under physiological conditions, shear stress increases the expression of ACE2, promoting the production of nitric oxide and reducing inflammation and proliferation in vascular endothelial cells. Endothelial cell activation/damage due to the coronavirus binding to the ACE2 receptor promoting acute

inflammation and hypercoagulation may be of importance to explain the thrombotic burden observed (155). Primarily, angiotensin II induces PAI-1 expression by endothelial cells via the AT1 receptor, giving to a PAI-1/tPA shortcomig and a hypercoagulable state (1). Additionally, angiotensin II stimulates PAI-1 release from adipocytes and may in part account for the increased severity observed in those individuals with high BMI (156).

Clinically, the most prominent coagulation marker is elevation of D-dimer levels that has been consistently reported in many studies, representing a prognostic indicator for severity and mortality of disease (157). The high D-dimer indicates that other inflammatory markers including ferritin, IL-6, troponin I and lactate dehydrogenase (LDH) are accompanied by a secondary hypercoagulable condition (9, 158). It also has been suggested that the sustained inflammation due presence of continuous consumptive coagulopathy may contribute to the thrombocytopenia (159).

Therefore, it is highly recommended that COVID-19 patients with obesity are early and rapidly tested for coagulation screening, including the measurement of D-dimer and fibrinogen levels, following thromboembolic prophylaxis for critically ill hospitalized patients. Moreover, anti-coagulation drugs, such as heparin, may be especially important for treatment of COVID-19 patients with obesity, potentially leading to lower mortality rates in this high susceptible group of individuals.

OBESITY AND THERAPEUTICS AGAINST COVID-19

Obesity-related conditions increase the risk of disease severity caused by the SARS-CoV-2 (160, 161). Daily use of several medications is necessary for controlling such conditions and an important influence of them on the body's responsiveness to infections are being extensively discussed worldwide (162–165). Studies regarding this interaction create potential therapeutic targets aiming to soft or protect against the intense symptoms. In the absence of a COVID-19 vaccine, the study of available promising drugs is essential for combating the COVID-19, to reduce the high mortality rate observed on people with obesity.

As previously discussed, the chronic inflammation presented in the lung during obesity leads to a cytokine storm by overexpressing pro-inflammatory mediators, such as IL-6 and TNF-α (166). This is one of the mechanisms through which host unbalanced inflammation worsens the prognosis of individuals with obesity affected by COVID-19 (90, 167). Thereby, anti-inflammatory drugs could have an important role on protecting specially people with obesity against COVID-19 multi-organs damage, once inflammation is an inherent characteristic of obesity and COVID-19 aggravation. However, this has to be carefully analyzed, once reducing pan inflammatory response can also prolong the time required for effective virus clearance (167).

Effective class of anti-inflammatory drugs against COVID-19 is a concern. It has been suggested an increasing risk for developing severe COVID-19 by the use of non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. The chronic use of NSAIDs is associated to increased cardiovascular and pulmonary outcomes (168, 169), complications which are also found in COVID-19. Considering this, a synergism can in fact occur, but no evidence regarding this interaction to SARS-CoV-2 is available yet (170). Corticosteroids anti-inflammatory drugs lead to a high suppression of innate immune system and delay of viral clearance (171). Harmful responses have already been found after corticosteroids medication for different respiratory virus infection, such as influenza, SARS-CoV and MERS-CoV (165, 172). Nevertheless, the use of this class of drugs seems to have no positive interference on COVID-19 cases (173, 174). However, a preliminary *in vitro* study showed SARS-CoV-2 replication suppression by the use of a corticosteroid (175). Moreover, a correlation between lower gene expression of ACE2 and TMPRSS2 with inhaled corticosteroids medication in asthma patients has already been demonstrated (176). The current scenario of available data indicates that consistent evidences about benefits or harms of corticosteroids use on COVID-19 still need deep investigation for accurate conclusions. In the absence of both positive and negative conclusion about this question, clinicians are avoiding to prescribe this class of pan anti-inflammatory drug for COVID-19 cases, since controversial reports make the conclusion about their real impact still unknown.

Considering the above mentioned points, reports have suggested that specific cytokine blocking could be more efficient for protection against COVID-19 than systemic anti-inflammatory drugs (165, 177). In this context, the use of monoclonal antibodies makes it possible to selectively inhibit key agents that drive to hyperinflammation during COVID-19. Preliminary evidence suggests that IL-6 blockade could be helpful on curbing the cytokine storm, being a highly promising treatment for severe COVID-19 (178). Nevertheless, the clinical trials that could provide trustable answer about this question are still in progress (179, 180). In addition, studies regarding TNF-α therapy in COVID-19 are scarce and need urgent attention of the scientific community, given the importance of this cytokine on inflammatory diseases (181). As already been reported, SARS-CoV increases this TNF-α production, leading to tissue damage (182). Moreover, the treatment with anti-TNF antibodies reduces the severity of lung disease for both influenza and respiratory syncytial virus (183), indicating that it could be efficient on COVID-19 cases.

Besides blocking such pro-inflammatory cytokines, the improvement of antiviral responses is also an interesting point to be considered. As earlier discussed, increasing evidence suggests obesity-associated impairment of IFN secretion, enhancing the susceptibility of this group for viral severe illnesses (73, 112). Reports have shown that IFN-β treatment reduces SARS-CoV RNA replication *in vitro* (184, 185). Indeed, type 1 IFNs are being pointed as potential effective therapeutic for COVID-19 and seems to be even more effective for SARS-CoV-2 compared to other coronaviruses (186). Moreover, given the impact of this cytokine for adaptive immune system activation, it might be suggested IFN also as a vaccine adjuvant for enhancing effective anti-viral protective response for especially individuals with obesity.

Obesity-induced chronic inflammation leads to alterations of hemodynamic properties and increasing risk for coagulopathies

establishment. Moreover, the activation of coagulation pathway also triggers inflammation (167). Some recent case reports brought thromboembolism as a COVID-19 complication (187–189). Considering the interplay between coagulopathies and inflammation, the combination of anti-inflammatories and anticoagulants drugs could be key for avoiding systemic complications in COVID-19 patients with obesity. Heparin and its low-molecular derivate are examples of frequently used anti-coagulant drugs for tromboprophylaxis due to their inherent potential of preventing blood clot occurrence (190). Currently, heparin is also known for its anti-inflammatory properties, expanding its potential for the treatment of coagulopathies (191). Heparin is already recommended as prophylactic agent against thromboembolism for COVID-19 cases and preliminary data suggests a better prognosis after the treatment (192, 193); it is important to emphasize that heparin anti-inflammatory properties in addition to its anticoagulant function may explain its great potential compared to single target anticoagulant drugs (191). In addition, a report has shown that heparin also binds to the spike protein and partially inhibits SARS-CoV-2 invasion *in vitro*, thus presenting anti-viral potential (194). Besides, other anticoagulant drugs can also act on immune response, such as antithrombins and anti-factor Xa. Study the effectiveness of these drugs can be an important step for ameliorating complications that specially overweighed individuals are suffering by COVID-19 (167).

Chronic inflammation provided by obesity also intermediates the establishment of metabolic disorders. Diabetes and hypertension are considered a risk factor for developing SARS-CoV-2 severe illness, both in the presence and absence of obesity (160). The high mortality rate that affects these groups brought questions regarding the impact of daily medication on the viral infectiveness capacity. The use of angiotensin-converting enzyme inhibitors (ACEi) and angiotensin-receptor blockers (ARBs) seems to improve ACE2 expression on pulmonary cells (195). Increasing the number of the viral entry receptor could lead to higher severity of the disease. However, the available data about these modulations of humans' RAAS is too limited for conclusions (196). Until now, the impact of discontinuing this medication on individuals with diabetes or hypertension conditions can be much worse, due to protection of vital organs provided by them (197, 198). In addition, there is recent evidence that, in fact, those drugs could protect against COVID-19, once the virus leads to a reduction of ACE2; increasing the amount of this receptor could interfere on the viral pathway somehow (198). Moreover, ACE2 plays an important role on reducing inflammation, what could ameliorate complications of COVID-19 (199). A report has shown a reduction of IL-6 secretion and an improvement of antiviral immune response, decreasing the viral load (163). Regarding other medicines used for diabetes, such as metformin, no interaction was found with ACE2 expression, indicating that its intake should not be a concern (200). Analyzing the available data about anti-hypertensive and anti-diabetic drugs, it is clear that the harms related to their interaction with COVID-19 are not evidenced enough compared to the known risks of stopping the treatment. Thereby, the use of those medications may not be discouraged, once these untreated comorbidities highly increase the mortality risks for COVID-19, so as the risks of developing secondary health problems.

CONCLUSION

A better understanding of the link between obesity and severe complications following COVID-19 infection is vital for implementing appropriate public health and therapeutic strategies to avoid COVID-19 severe symptoms and complications in people living with obesity. Adipose tissue from people with obesity show high expression of ACE2 receptor and can function as SARS-CoV-2 reservoir. Moreover, obesity can cause hyperglycemia via insulin resistance. SARS-CoV-2 may also cause hyperglycemia as well by infecting and killing pancreatic B-cells, leading to a worsen metabolic dysfunction of people with obesity and a poor prognostic of COVID-19. People with obesity present a pro-inflammatory and metabolic dysregulation that may favor the occurrence of the cytokine storm, implicated in COVID-19 pathophysiology of severe cases. Pulmonary lipofibroblasts can transdifferentiate into myofibroblasts aggravating the development of pulmonary fibrosis and consequently, contributing to the clinical severity of COVID-19, with development of a severe acute respiratory syndrome. Taken together, it may be crucial to better explore the role of visceral adipose tissue in the inflammatory response to SARS-CoV-2 infection and investigate the potential therapeutic effect of using specific anti-inflammatories (canakinumab or anakinra for IL-1β inhibition), anticoagulant (heparin), or anti-diabetic drugs in COVID-19 treatment since patients with obesity may benefit to a greater extent from a treatment that modulates these parameters.

AUTHOR CONTRIBUTIONS

GP-N, HB-M, SF, GK, and KM wrote different sections of the manuscript. KM revised, wrote, and prepared the manuscript. IS prepared the figures.

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SYSTEMATIC REVIEW
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Body Mass Index and Prognosis of COVID-19 Infection. A Systematic Review

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A better understanding of the SARS-CoV-2 virus behavior and possible risk factors implicated in poor outcome has become an urgent need. We performed a systematic review in order to investigate a possible association between body weight and prognosis among patients diagnosed with COVID-19. We searched in Cochrane Library, EMBASE, MEDLINE, WHO-Global Literature on Coronavirus Disease, OpenGrey, and Medrxiv. We used the ROBINS-I tool or Cross-Sectional/Prevalence Study Quality tool from AHRQ, to evaluate the methodological quality of included studies. Nine studies (two prospective cohorts, four retrospective cohorts and three cross-sectional) were included and assessed the relationship between obesity and COVID-19 prognosis. Risk of bias of the included studies ranged from moderate to critical. Clinical and methodological heterogeneity among them precluded meta-analyses. Most of the included studies showed some degree of association to: (a) higher BMI and worse clinical presentation and (b) obesity and need of hospitalization. The results were inconsistent about the impact of obesity on mortality. Based on limited methodological quality studies, obesity seems to predict poor clinical evolution in patients with COVID-19. Further studies with appropriate prospective design are needed to reduce the uncertainty on this evidence.

Keywords: obesity, body mass index, SARS-CoV-2, COVID-19, risk factor

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INTRODUCTION

A better understanding of the SARS-CoV-2 virus behavior has become an urgent need as the pandemic caused continues to plague the world adding more and more victims. A series of reports have looked for risk factors in order to provide means of prevention and treatment to the population. The first Chinese publications made clear that age may impact prognosis (1–3), but with the advance of COVID-19 to western European and North American countries, some novel factors have emerged as determinants of risk and poor outcome. In contrast to China, there is a high prevalence of obesity in these countries (4) that may help explain, at least in part, the reason why obesity has just emerged as a marker of unfavorable clinical evolution.

The prevalence of obesity has rapidly increased over the years (5), especially among elderly (6). Obesity is a multifactorial disorder characterized by excessive fat accumulation and an increment of proinflammatory cytokines, which entails a constant state of immune deregulation (7). This chronic

deregulation may interfere with immune homeostasis and impair the effectiveness of the immune response. It is not without reason that obesity has been implicated in poor outcomes among many clinical conditions and high all-cause mortality (8).

However, although it accumulates rapidly, data on the role of obesity on COVID-19 risk and prognosis are still confusing and hard to interpret. Scrambling to learn more about the virus, doctors and scientists try to rapidly share their findings generating a large flood of publications that has put new strain on a scientific process accustomed to vetting and publishing new results much more slowly.

Herein, we perform a systematic review in order to evaluate if overweight and obesity may predict poor outcome in patients with COVID-19.

OBJECTIVES

To investigate a possible association between body weight and prognosis among patients diagnosed with COVID-19.

The clinical question is, as structured through the PECO acronym: (P, population): individuals with COVID-19; (E, exposure): overweight or obesity); (C, comparator): normal body weight; (O, outcomes): clinical, laboratory and image outcomes on COVID-19.

METHODS

Study Design and Setting

This was a systematic review carried out in the Universidade Federal de São Paulo (Unifesp) through a collaboration with the University of Campinas (Unicamp), Brazil. The study was conducted in accordance with the AMSTAR-2 (Assessing the Methodological quality of Systematic Reviews) (9). The protocol was prospectively registered at the PROSPERO database (registration number CDR42020182189, https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=182189). This reporting was written following the PRISMA statement (10).

Criteria for Including Studies

Types of Studies

We considered any study design using a comparative group as follows: controlled trials (randomized, quasi-randomized, or non-randomized) that conducted subgroup analyses according to body weight, cohort and case-control studies, and analytic cross-sectional studies with a control group.

Types of Participants

Adults or children with confirmed diagnosis of COVID-19, in accordance with World Health Organization criteria (11).

Types of Exposure

We considered any definition of overweight or obesity, as assumed by the authors of primary studies. However, only similar definitions were evaluated together into quantitative or qualitative synthesis.

Outcomes

We considered all clinical, laboratory and image outcomes as presented by the authors of primary studies. However, we prioritized the outcomes below:

Primary outcomes:

- All-cause mortality;
- Serious adverse events: assessed by the rate of participants who experienced at least one serious adverse event, as per defined as those that are life-threatening; which may lead to death, requirement of a treatment in an emergency room, hospitalization (initial or prolonged), disability or permanent damage, or congenital anomaly/birth defect (12).
- SARS-CoV-2 acute respiratory syndrome: assessed by the rate of participants who progressed to acute respiratory syndrome.
- Clinical status, assessed by the Ordinal Scale for Clinical Improvement—World Health Organization (scale from 0 to 7, the higher the score, the worse the clinical condition), as defined by the World Health Organization (WHO) (13).

Secondary outcomes:

- Mortality related to SARS-CoV-2 infection (COVID-19);
- Any adverse event: assessed by the rate of participants who experienced at least one adverse event.
- Time to clinical improvement, defined as a reduction of at least two points in the score of the Ordinal Scale for Clinical Improvement—World Health Organization (scale from 0 to 7, the higher the score, the worse the clinical condition), as defined by the World Health Organization (WHO) (13).
- Hospitalization in an intensive care unit;
- Need for invasive mechanical ventilation;
- Length of hospitalization.
- Length of hospitalization in intensive care unit;
- Length of invasive mechanical ventilation;
- Rate of negative PCR viral load (any specimen).

We assessed all dichotomous outcomes listed above at any time point. However, we only pooled similar time points together: short term (up to 1 month, inclusive) or long term (more than 1 month). When a study reported an outcome more than once in the same period, we considered the last measurement.

Search for Studies

A comprehensive search of the literature was carried out using an electronic search with no restriction regarding date, language or status of publication. Sensitive search strategies (**Supplementary File 1**) were developed for the following databases:

- Cochrane Library (via Wiley);
- EMBASE (via Elsevier);
- MEDLINE (via PubMed);
- World Health Organization—Global Literature on Coronavirus Disease (https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/).

A search for gray literature was conducted in the Opengrey database (https://opengrey.eu) and for preprint studies in

the Medrxiv (https://www.medrxiv.org/). Manual search was performed in the reference lists of the relevant studies.

Selection of Studies

The selection process was conducted in a two-stage process aided by the Rayyan platform (14). In the first phase, two review authors independently assessed all titles and abstracts retrieved by the search strategies. Studies marked as "potentially eligible" were then screened at the second phase, which consisted in the reading of the full text to confirm its eligibility. Any divergence was solved by a third reviewer. Studies excluded in the second phase were presented in the "excluded studies table" and the reasons for exclusion as well.

Data Extraction

The procedures for data extraction were performed by two independent reviewers and a pre-established data extraction form was used. Disagreements in this process were solved by a third reviewer.

Methodological Quality of Studies

The methodological quality of the included studies was evaluated by two independent reviewers by the use of validated tools for each study design, as following:

- Randomized controlled trial: Cochrane Risk of Bias Table (15);
- Non-randomized, quasi-randomized trial: ROBINS-I (16);
- Cohort or case-control: ROBINS-I (16). ROBINS-I was used as there are, as yet, no draft versions of ROBINS-E available. The domains "classification of interventions" and "deviations from intended interventions" were adapted to consider "exposures" instead of "interventions."
- Cross-sectional: Cross-Sectional/Prevalence Study Quality, Agency for Healthcare Research and Quality (17).

Unity of Analysis and Missing Data

The unit of analysis was the individual. Considering the context requiring a rapid answer, the authors from primary studies were not contacted for missing data.

Data Analysis and Presentation

Depending on data availability and homogeneity of studies, we planned to pool results from similar studies by random-effects meta-analyses (software Review Manager 5.3). Risk ratios (or odds ratios) and mean differences would be calculated for dichotomous and continuous data, respectively. A 95% confidence interval would be considered for the analyses. When meta-analysis was not possible the results were presented as qualitative synthesis (descriptive presentation).

Heterogeneity Assessment

Methodological and clinical diversity of included studies would be considered for conducting or not meta-analyses. The existence of statistical heterogeneity would be evaluated by Chi^2 test and its extension by the I^2 test ($I^2 \geq 50\%$ indicates high heterogeneity among studies).

Additional Analyses

We planned to conduct the following subgroup analyses: (a) presence of diabetes and/or hypertension and (b) age of participants (<65 vs. ≥ 65).

We planned to conduct the following subgroup analyses: (a) fixed effects vs. random effects model meta-analysis. When the results of fixed effect meta-analysis provide a different result, both would be reported; (b) excluding from analysis studies at high risk of bias; and (c) excluding from analysis unpublished studies or those available exclusively in a pre-print version and not peer reviewed.

Investigation of publication bias assessment was planned by visual inspection of funnel plots for meta-analysis with at least 10 studies.

However, due to heterogeneity between included studies it was not possible to conduct meta- analyses nor additional analyses.

RESULTS

Results From Search

The search retrieved 937 records. After excluding 88 duplicates, we screened the titles and abstracts of 849 references, excluded 836 that did not comprise inclusion criteria, and selected 13 for full text reading. We excluded four studies (detailed below). Therefore, the review included nine observational studies. The flow diagram of the process of study identification and selection is presented in **Figure 1**.

Results From Included Studies

This systematic review included nine studies: two prospective cohort studies (18, 19), four retrospective cohort studies (20–23), and three cross-sectional studies (24–26). **Table 1** presents the main characteristics of the included studies. **Table 2** summarizes the studies excluded after selection.

BMI was the only measure used as a criteria for classifying body weight, considered as a continuous or ordinal scale variable. The included studies had different study designs and considered different outcomes of interest.

Due to these clinical and methodological heterogeneity among included studies it was not appropriate to conduct meta-analyses.

Methodological Assessment of Studies

Risk of bias assessment of the included studies and reasons for judgement are presented in **Tables 3**, **4**. Overall, cohort studies were classified as critical to moderate risk of bias, and cross-sectional studies varied between 36 and 63% of agreement with bias domains.

DISCUSSION

We reviewed data from 17,568 patients with SARS-CoV-2 infection, included in nine studies. Most of these studies highlighted some level of association between obesity and disease severity, encompassing hospitalization rate, admission to ICU, invasive ventilation need and mortality. According to validated tools, these studies presented moderate to critical risk of bias, which limits the reliability in the results.

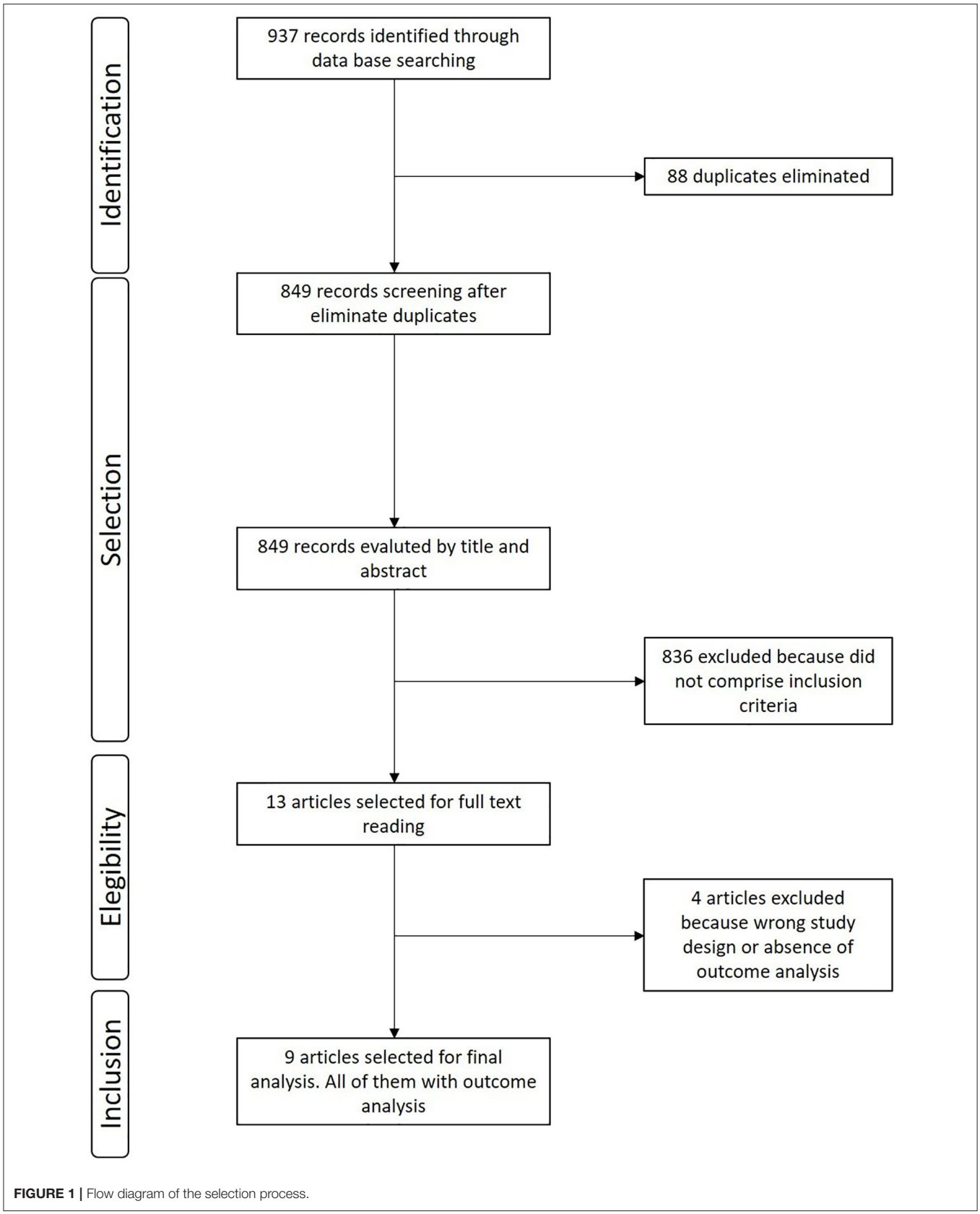

FIGURE 1 | Flow diagram of the selection process.

TABLE 1 | Main characteristics of the included studies.

References	Study design	Number of patients with COVID-19	Exposure	Outcomes	Main results
Argenziano et al. (24)	Cross-sectional	1000	Mean BMI kg/m^2	Level of hospital care	Mean BMI of admitted ICU patients was significantly higher than BMI of admitted patients in all other levels of care (31.2 ± 8.0 vs. 29.9 ±7.24 kg/m^2) (DM 1.30, 95% CI 95% 0.15–2.45; $p = 0.03$)
Bello-Chavolla et al. (25)	Cross-sectional	8261	BMI > 30 kg/m^2 Age > 65 years	Mortality Hospitalization Pneumonia ICU admission Invasive mechanical ventilation	Compared to non-obese, obese patients had a significantly increased risk of: • Mortality (13.6 vs. 7.1%, $p < 0.001$; HR 7.56 95%CI 5.79–9.87) • Hospitalization (47.3 vs. 34.4%, $p < 0.001$) • Pneumonia (36.4 vs. 25.9%, $p < 0.001$) • ICU admission (7.2 vs. 4.2%, $p = 0.034$) • Invasive ventilation (6.9 vs. 4%, $p = 0.029$)
Cummings et al. (18)	Prospective cohort	257	Severe obesity (BMI ≥ 35 kg/m^2)	Rate of in-hospital death	No difference between obese and non-obese patients in mortality (HR 0.94, 95% CI 0.55–1.77)
Lighter et al. (20)	Retrospective cohort	3,615	BMI < 30 vs. BMI 30–34 and BMI ≥ 35 kg/m^2	Age (>60 and <60 years) Hospital admission	Age > 60 years: Compared to non-obese (BMI < 30), there was no difference between groups in: • Admission to acute care: BMI 30–34: RR 0.9, 95% CI 0.6–1.2, $p = 0.39$ BMI ≥35: RR 0.9, 95% CI 0.6–1.3, $p = 0.59$ • Admission to ICU: BMI 30–34: RR 1.1, 95% CI 0.8−1.7, $p = 0.57$ BMI ≥35: RR 1.5, 95% CI 0.9–2.3, $p = 0.10$ Age < 60 years: Compared to non-obese (BMI < 30), obese patients had more: • Admission to acute care: BMI 30–34: RR 2.0, 95% CI 1.6–2.6, $p < 0.0001$ BMI ≥35: RR 2.2, 95% CI 1.7–2.9, $p < 0.0001$ • Admission to ICU: BMI 30–34: RR 1.8, 95% CI 1.2–2.7, $p = 0.006$ BMI ≥35: RR 3.6, 95% CI 2.5–5.3, $p < 0.0001$.
Liu et al. (21)	Retrospective cohort	30	BMI (mean, SD)	COVID-19 severity (mild vs. severe)	Severe COVID patients had a significantly higher mean BMI (27.0 ± 2.5) than mild patients (22.0 ± 1.3) ($p < 0.001$).
Peng et al. (22)	Retrospective cohort	112	BMI ≥ 25 (obese plus overweight) vs. BMI < 24 kg/m^2 (eutrophic or lean)	Mortality	Obese patients had a significant increased risk of mortality comparing to non-obese (18.92 vs. 88.24%, $p < 0.001$); Mean BMI of the critical group (ICU need) was significantly higher than the general group ($n = 16$ vs. 96; $p = 0.003$).
Petrilli et al. (26)	Cross-sectional	4,103	BMI <30 vs. BMI 30–40 and BMI >40 kg/m^2	Hospitalization	• Non-hospitalized group: BMI 30–40: 12.2% (256 patients) BMI >40: 2.3% (48 patients) • Hospitalized group: BMI 30–40: 33.0% (659 patients) BMI >40: 6.9% (137 patients) BMI >40 was significantly associated with hospitalization when compared to BMI <30 (OR 6.2, 95% CI 4.2–9.3)
Simonnet et al. (23)	Retrospective cohort	124	BMI categories: 18.5 to < 25; 25 to < 30; 30 to < 3; ≥35 kg/m^2	Invasive mechanical ventilation	Obese patients (BMI ≥ 35) had a significant increased risk of invasive ventilation need, comparing to non-obese (BMI < 25) (OR 7.36, 95% CI 1.63–33.14, $p = 0.021$)
Zheng et al. (19)	Prospective cohort	66 (with metabolic associated fatty liver disease)	BMI > 25 kg/m^2	COVID-19 severity	Severe patients had a significantly higher proportion of obese than non-severe (89.5 vs. 59.6%, $p = 0.021$). Obese patients with metabolic associated fatty liver diseases had a significantly increased risk of severe COVID-19 (OR 6.32, 95% CI 1.16–34.54, $p = 0.033$)

n, number of participants; BMI, body mass index; ICU, Intensive care unit; SD, Standard deviation; HR, Hazard ratio.

TABLE 2 | Studies excluded after selection.

References	Reason for exclusion
Malavazos et al. (27)	Different study design (narrative review).
Ryan and Caplice (28)	Different study design (narrative review).
Garg et al. (29)	Only data of obesity prevalence, with no outcome association analysis.
Richardson et al. (30)	Only data of obesity prevalence, with no outcome association analysis.

According to COVIDView database of Centers for Disease Control and Prevention (CDC) in the USA, until May 2, 2020 the overall rate for COVID-19-associated hospitalization were 162.2 per 100,00 in individuals 65 years and older, decreasing to 79.0–26.2 for individuals <65 years. Furthermore, preliminary data showed that about 91.5% of hospitalized patients present at least one underlying medical condition. Besides obesity, the most common critical comorbidities observed in the hospitalized COVID-19 patients were hypertension, metabolic disease, cardiovascular and pulmonary diseases (31).

Three of 4 North American studies showed increased BMI among patients who required hospitalization. Argenziano et al. (24) also described that patients who require in-hospital admission had more chronic diseases, such as hypertension, diabetes, and obesity. To date, ICU patients presented significantly higher BMI compared to those admitted in the emergency or inpatient floors. Lighter and colleagues (20) analyzed retrospectively a cohort of 3,615 patients positive for COVID-19 stratified by age. Thirty-eight percent (38%) of these patients presented BMI >30 kg/m^2. An increased risk of hospitalization in acute care or ICU was demonstrated for patients <60 years older with obesity (BMI 30–34 kg/m^2) and severe obesity (BMI ≥35 kg/m^2) compared to patients BMI <30 kg/m^2. Once younger patients generally do not represent higher risk for a severe presentation of COVID-19, authors suggest that obesity may be an unrecognized risk factor for hospital care. In a cross-sectional study, Petrilli et al. (26) showed that hospitalized patients were more likely to be male and present cardiovascular diseases, diabetes and obesity. In fact, as confirmed by a multivariate analysis, obesity (BMI > 40 kg/m^2), older age (≥65 years) and history of heart failure were independent predictors of unfavorable outcome. Cummings et al. (18) observed similar prevalence of obesity among hospitalized patients. However, authors failed to demonstrate that obesity is a predictor of mortality.

Two cohort studies evaluate the severity of COVID-19 disease in Chinese patients. The retrospective study by Liu et al. (21) evaluated 30 medical staff infected with novel coronavirus in January, 2020. Most of them presented a common type of the disease ($n = 26$) and four patients a more severe condition defined as pulmonary insufficiency. Until the end of the study, 80% of the patients were discharged, none of them needed critical hospital care or died. In relation to obesity the authors reported higher BMI in patients with severe compared to the mild presentation. Zheng et al. (19) prospectively evaluated 66 patients with metabolic associated fatty liver disease (MAFLD) stratified by obesity status dividing patients according to severe and non-severe COVID-19 based on the National Health Commission & State Administration of Traditional Chinese Medicine. Frequency of obesity was higher between severe disease patients compared to non-severe, furthermore MAFLD patients with concurrent obesity had more severe presentation of the disease. Indeed, obesity in patients with MAFLD increased the risk of severe illness in almost 6-fold (unadjusted OR 5.77, 95% CI 1.19–27.91, $p = 0.029$). After adjustment for age, sex, smoking, diabetes, hypertension, and dyslipidemia, association with obesity and COVID-19 remained significant and confirmed obesity as an independent marker of critical illness. However, as commented by Hussain et al. (32), MAFLD and obesity are rarely considered as independent conditions, in the cases of concurrent diseases they coexist due to obesity. A third Chinese study (22) demonstrated that mean BMI of the 16 patients who needed ICU care (25.5 kg/m^2) were higher than the general group (22.0 kg/m^2). Between the 17 deaths reported, 88% had BMI >25 kg/m^2. Most of the deceased patients also presented hypertension, coronary heart disease and heart insufficiency.

In a Mexican study (25), obese patients, as expected, had higher proportions of other comorbidities as hypertension, diabetes, cardiovascular disease, asthma, and chronic obstructive pulmonary disease (COPD). Increased lethality of COVID-19 was reported specially in patients with diabetes, early onset diabetes (<40 years), concurrent obesity or several concurrent comorbidities ($p < 0.001$). As presented in **Table 1**, obese patients had higher risks of hospitalization, pneumonia, ICU admission, invasive ventilation and 7-fold increased risk of mortality.

Simonnet et al. (23) described that the distribution of BMI categories in COVID-19 patients admitted to ICU care in France differed from the control patients with non-SARS-Cov-2 respiratory disease. The frequency of obesity (BMI > 30 kg/m^2, 47.6%) and severe obesity (BMI > 35 kg/m^2, 28.2%) were higher among patients with COVID-19 infection compared to control patients (25.2 and 10.8%, respectively). Besides, the median of BMI (31.1 kg/m^2) of the 85 patients who required invasive ventilation was higher than the patients who did not (27.0 kg/m^2, $n = 39$). An univariate logistic regression analysis showed that BMI ≥35 kg/m^2 (vs. BMI <25 kg/m^2) was a risk for need of invasive ventilation (OR 6.75, 95%CI 1.76–25.85, $p = 0.015$), remaining significant after adjustment for age, diabetes and hypertension in a multivariate analysis (OR 7.36 95% CI 1.63–33.14, $p = 0.021$).

This systematic review presents some strengths including the use of stringent methods of Cochrane reviews, reproduced in a short term due to the need of rapid responses to guide clinical decisions during the pandemic. The search for studies was highly sensitive and it was conducted in formal databases, preprint, and gray literature repositories and specific sources for COVID-19 as well.

The present study has some limitations. The included studies adopted different methods to assess obesity as a predictor of poor outcome precluding a meta-analysis. Once COVID-19 is a public health emergency, a considerable amount of

TABLE 3 | Risk of bias of cohort studies: ROBINS-I (16).

Study/Bias domain	Confounding	Selection of participants	Classification of interventions	Deviations from intended interventions	Missing data	Measurement of the outcome	Selection of the reported result	Overall
Cummings et al. (18)	Critical risk of bias It is likely that one or more prognostic variables are present unbalanced among the compared groups	Moderate risk of bias Prospective study; start of follow-up coincide for most participants	Moderate risk of bias Criteria used to define the exposure was described	Moderate risk of bias Probably no deviation happened	Low risk of bias Data from cohort were apparently complete	Low risk of bias Objective outcome assessed (mortality) could not be influenced by outcome assessors	Critical risk of bias Participants selected from a larger group and it is not possible to exclude bias related to the reporting of outcomes	Moderate risk of bias
Lighter et al. (20)	Critical risk of bias It is likely that one or more prognostic variables are present unbalanced among the compared groups	Critical risk of bias Retrospective study	Moderate risk of bias Criteria used to define the exposure was described	Moderate risk of bias Probably no deviation happened	No information No information on which to base a judgement on losses during the study period	Critical risk of bias It is very likely that the subjective outcomes assessed were influenced by knowledge of the prognostic factor	Critical risk of bias Participants selected from a larger group and it is not possible to exclude bias related to the reporting of outcomes	Critical risk of bias
Liu et al. (21)	Critical risk of bias It is likely that one or more prognostic variables are present unbalanced among the compared groups	Critical risk of bias Retrospective study	Moderate risk of bias Criteria used to define the exposure was described	Moderate risk of bias Probably no deviation happened	No information No information on which to base a judgement on losses during the study period	Critical risk of bias It is very likely that the subjective outcomes assessed were influenced by knowledge of the prognostic factor	Critical risk of bias Participants selected from a larger group and it is not possible to exclude bias related to the reporting of outcomes	Critical risk of bias
Peng et al. (22)	Critical risk of bias It is likely that one or more prognostic variables are present unbalanced among the compared groups	Critical risk of bias Retrospective study	Moderate risk of bias Criteria used to define the exposure was described	Moderate risk of bias Probably no deviation happened	Low risk of bias Data from cohort were apparently complete	Critical risk of bias It is very likely that the subjective outcomes assessed were influenced by knowledge of the prognostic factor	Critical risk of bias Participants selected from a larger group and it is not possible to exclude bias related to the reporting of outcomes	Critical risk of bias
Simonnet et al. (23)	Critical risk of bias It is likely that one or more prognostic variables are present unbalanced among the compared groups	Critical risk of bias Retrospective study	Moderate risk of bias Criteria used to define the exposure was described	Moderate risk of bias Probably no deviation happened	Low risk of bias Data from cohort were apparently complete	Critical risk of bias It is very likely that the subjective outcomes assessed were influenced by knowledge of the prognostic factor	Low risk of bias All patients admitted to intensive care for SARS-CoV-2 were analyzed	Critical risk of bias
Zheng et al. (19)	Critical risk of bias It is likely that one or more prognostic variables are present unbalanced among the compared groups	Moderate risk of bias Prospective study; start of follow-up coincide for most participants	Moderate risk of bias Criteria used to define the exposure was described	Moderate risk of bias Probably no deviation happened	Low risk of bias Data from cohort were apparently complete	Critical risk of bias It is very likely that the subjective outcomes assessed were influenced by knowledge of the prognostic factor	Low risk of bias All patients with COVID-19 and with metabolic associated fatty liver disease were analyzed	Moderate risk of bias

Low risk of bias: The study is comparable to a well-performed randomized trial with regard to this domain.
Moderate risk of bias: The study is sound for a non-randomized study with regard to this domain but cannot be considered comparable to a well-performed randomized trial.
Serious risk of bias: The study has some important problems in this domain.
Critical risk of bias: The study is too problematic in this domain to provide any useful evidence on the effects of intervention.
No information: No information on which to base a judgement about risk of bias for this domain.

TABLE 4 | Risk of bias of cross-sectional studies: Cross-Sectional/Prevalence Study Quality, Agency for Healthcare Research and Quality (AHRQ) (17).

Domain	Argenziano et al. (24)	Bello-Chavolla et al. (25)	Petrilli et al. (26)
1 Define source of information (survey, record review)	Y	Y	Y
2 List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications	Y	Y	Y
3 Indicate time period used for identifying patients	Y	N	Y
4 Indicate whether or not subjects were consecutive if not population-based	Y	N	Y
5 Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants	Y	N	Y
6 Describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements)	N	N	N
7 Explain any patient exclusions from analysis	U	Y	N
8 Describe how confounding was assessed and/or controlled	N	Y	Y
9 If applicable, explain how missing data were handled in the analysis	NA	U	Y
10 Summarize patient response rates and completeness of data collection	U	N	U
11 Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained	N	N	N
Number (percentage) of domain agreement	5/10 (50%)	4/11 (36%)	7/11 (63%)

Y, Yes; N, No; U, Unclear; NA, Not applicable.

research is being published every week and it is possible that recent articles may not be included in the final version of our review. For assessing the risk of bias of cohort studies, we slightly adapted the ROBINS-I tool, since there are, as yet, no draft versions of ROBINS-E available. This adaptation was inconspicuous and sought to preserve the definition of domains.

In summary, our systematic review suggests that obesity is likely to be a predictor of poor outcome in patients with COVID-19, in all continents. Obesity is associated with several clinical conditions (e.g., diabetes and hypertension). It is associated with restrictive lung ventilatory defect, which may worsen the severe respiratory failure syndrome. In obesity, the dysfunctional adipocytes produce massive amounts of pro-inflammatory cytokines, which entails a chronic inflammation, harming innate and adaptative immune responses (33–35). The increase in pro-inflammatory cytokines observed among obese patients may add to the inflammatory response triggered by the SARS-CoV-2, and both contribute to poor outcome and high all-cause mortality (7, 8). Likewise, obesity is a well-established risk factor for cardiovascular disease, which triggers diverse physiologic alterations that include activation of renin-angiotensin-aldosterone system, reduction of vasculo-protective effects, upregulation of procoagulant factors, downregulation of anticoagulant factors and chronic oxidative stress and inflammation (36–38). Hence, obese patients with COVID-19 may benefit from an aggressive approach, including eager evaluation and early hospitalization. In addition, health politics may assure obese patients prompt access to the health care system. The investigation of the mechanisms that may be underlying the association between obesity and poor outcome in patients with COVID-19 will certainly help the understanding of this subject. Therefore, further studies with appropriate prospective design are needed to reduce the uncertainty on this evidence.

DATA AVAILABILITY STATEMENT

All datasets presented in this study are included in the article/**Supplementary Material**.

AUTHOR CONTRIBUTIONS

KP contributed to the design, critical review of the literature and data, composition of the manuscript, and final approval. RR and AM contributed to the design, critical review of the literature and data, risk of bias, composition of the manuscript, and final approval. LW contributed to the design, selection of the notable articles for review, critical review of the literature and data, composition of the manuscript, clinical and translational orientation, and final approval. LC contributed to the conception and design, selection of the notable articles for review, critical review of the literature and data, composition of the manuscript, and final approval. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2020.00562/full#supplementary-material

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OPINION
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Obesity and COVID-19

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Keywords: aging, inflammation, nutrition, SARS - CoV-2, body mass Index, sarcopenic obesity, ACE2 (Angiotensin Converting Enzyme-2)

The global pandemic of COVID-19 is putting a strain on the weakness of health care systems. The lack of an established treatment against COVID-19 infection and the rationing of care resulted in a dramatic scenario. Patients with COVID-19 present with very heterogeneous symptoms from asymptomatic forms to severe acute respiratory distress. Infected patients are more likely to have elevated levels of inflammatory markers, and most of those developing severe forms of the disease require mechanical ventilation. The worst-hit population comprises older people and those with multimorbidity. In particular, obesity (usually measured with body mass index, BMI) is repeatedly reported as a major risk factor for severe complications of COVID-19 (1, 2), including respiratory failure, the need for invasive mechanical ventilation, and death (3).

The role of obesity is of great relevance, especially given its high prevalence worldwide. However, it is important to bear in mind that the assessment of obesity *via* BMI is extremely arguable, especially in older people. First, it should be noted that BMI does not purely reflect adiposity because its numerator (i.e., body weight) results from the sum of both fat and fat-free mass. Second, the cut points used to categorize overweight and obesity are arbitrary and based on young and middle-aged cohorts and are, thus, inadequate for older persons (4). Third, with aging, body fat tends to accumulate in parallel with the muscle mass decline. Consequently, obesity is often underestimated in older persons, who may present an excess of adiposity within a normal/overweight body size (the so-called sarcopenic obesity) (5). Finally, ethnic difference may determine major variability in body fat distribution, in particular for what concerns ectopic and visceral fat (4). Body composition is an important aspect to consider in older persons, but it is something not easy to routinely assess even in normal times. Preventive strategies for limiting the spread of the coronavirus as well as the scarce attention frequently given to this evaluation may further accentuate this issue in the period of COVID-19. For this reason, whereas the most accurate techniques (e.g., magnetic resonance imaging, computed tomography, dual energy X-ray absorptiometry) may be difficult to implement or unfeasible during a pandemic, alternatives coming from less accurate methodologies (e.g., bioelectrical impedance analysis) and/or surrogate parameters (e.g., estimates coming from prediction equations) should be considered (6, 7).

Although evidence is still very limited, several reports are starting to indicate a role for adiposity in the COVID-19 susceptibility and severity. Just recently, Watanabe et al. (8) find that visceral fat was significantly higher in COVID-19 patients requiring ICU support—together with age, inflammation markers, and interstitial pneumonia severity. Similarly, Battisti et al. (9) report that COVID-19 severity is associated with abdominal adipose tissue distribution. In another recent study (10), the authors find a positive association between visceral adipose tissue and upper abdominal circumference with COVID-19 severity. What is more, Yang et al. (11) document that, in COVID-

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19 patients, visceral adiposity or high intramuscular fat deposition increases the risk for critical illness.

The contribution of obesity to the severity of COVID-19 may be explained in multiple ways. Obesity is a well-recognized risk factor for diabetes, hypertension, and cardiovascular disease, all of which are predictors of poor outcomes in COVID-19 (12). Obesity may also impair immune response to viral infections and affect diaphragm excursion (thus causing dysventilation) (3, 13). Additionally, the management of obese patients with COVID-19 might be more challenging than routine because the patient's size may limit medical and assistive procedures.

Furthermore, obesity is characterized by abnormal secretion of adipokines and cytokines determining a low-grade systemic inflammation, which may represent the background predisposition to the most severe consequences of COVID-19 (3). At the same time, chronic low-grade inflammation represents a hallmark of aging, responsible for altered metabolism (i.e., elevation of resting energy expenditure) and increased muscle catabolism (14, 15). Inflammation could be the key factor of the muscle decline observed in older individuals, which can be further exacerbated in those with obesity (16). Obesity may also lead to increased fat infiltration of the muscle associated with a decrease in muscle strength and function, mainly due to physical inactivity of obese individuals. As a consequence, muscle decline may lead to a decrease in physical activity, which, in turn, promotes obesity with consequent increased catabolism and anabolic resistance, thus creating a vicious circle of muscle decline (17). In fact, fat mass increase usually precedes a loss of muscle mass. In other words, the increase of adiposity (especially in visceral fat) along with the low-grade chronic inflammation seen with aging could have even more detrimental effects and determine an accelerated muscle decline. Interestingly, intermuscular adipose tissue is shown to contribute to physical impairment, enhancement of insulin resistance, and increased the risk of negative health-related events (18).

Additionally, an association between the SARS-CoV-2 infection and the angiotensin-converting enzyme 2 (ACE2) receptor is widely reported, potentially playing a critical role in the pathological pathway (19–21). Interestingly, the expression of the ACE2 receptor is particularly present in adipose tissue (22, 23), possibly explaining the higher susceptibility, greater severity, and worse prognosis for COVID-19 infection in obese patients (23, 24). A controversy, however, exists about the protective or deleterious role of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in COVID-19 (21).

In this global pandemic, the negative effects of obesity are not confined solely to the acute care setting. In fact, the need for social distancing and isolation during the lockdown may exacerbate depressive symptoms. Furthermore, self-isolation may increase the barriers to accessing healthy and fresh foods with a net shift toward convenience foods, especially in people with a poor socioeconomic status. The self-isolation period due to the lockdown may also lead to the deterioration of the circadian rhythm, resulting in a change of eating habits. Obesity has been widely related to sleep alteration and vice versa (25). In fact, sleep disorders can result in metabolic (i.e., decreased glucose tolerance and insulin sensitivity) and endocrine alterations (i.e., reduced leptin levels, high evening concentrations of cortisol, ghrelin, and increased hunger and appetite), all of which promote obesity (26). Sleep disturbances may also result from high circulating levels of pro-inflammatory cytokines, which are a hallmark of obesity (27). Additionally, high-fat and high-carbohydrate meals may alter sleep indexes (26–29) *via* the elevation of the circulating levels of glucose, insulin, leptin, cholecystokinin (CCK), peptide YY, and enterostatin (28–30).

On the other hand, it should not be neglected that obese individuals may suffer from stigma and depressive symptoms already in normal times. This may render them more likely to restrict their social contacts with detrimental consequences to their physical and psychological domains in the period of COVID-19 (31).

In conclusion, it is necessary that special attention is paid to prevent and control the COVID-19 infection in specific populations, such as obese and older persons, who are already exposed to basal inflammatory status. Inflammation, which is a hallmark of both obesity and the aging process, might have a synergistic role in promoting greater severity of COVID-19. However, as discussed, obesity measured with BMI does not necessarily reflect adiposity. Indeed, it is important to bear in mind that even though the box may look the same, the contents may be different. In this case, it would be better to think inside the box. The role of obesity in COVID-19, given the burden it poses, must no longer be ignored and may have major implications in the public health strategy.

AUTHOR CONTRIBUTIONS

DA contributed to conceptualizing and writing the manuscript. MC edited and revised manuscript. DA and MC approved the final version of manuscript. All authors contributed to the article and approved the submitted version.

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REVIEW
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From Influenza Virus to Novel Corona Virus (SARS-CoV-2)–The Contribution of Obesity

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From the beginning of 2020, the governments and the health systems around the world are tackling infections and fatalities caused by the novel severe acute respiratory syndrome coronavirus (SARS-CoV-2) resulting in the coronavirus disease 2019 (COVID-19). This virus pandemic has turned more complicated as individuals with co-morbidities like diabetes, cardiovascular conditions and obesity are at a high risk of acquiring infection and suffering from a more severe course of disease. Prolonged viral infection and obesity are independently known to lower the immune response and a combination can thus result in a "cytokine storm" and a substantial weakening of the immune system. With the rise in obesity cases globally, the chances that obese individuals will acquire infection and need hospitalization are heightened. In this review, we discuss why obesity, a low-grade chronic inflammation, contributes toward the increased severity in COVID-19 patients. We suggest that increased inflammation, activation of renin-angiotensin-aldosterone system, elevated adipokines and higher ectopic fat may be the factors contributing to the disease severity, in particular deteriorating the cardiovascular and lung function, in obese individuals. We look at the many lessons learnt from the 2009 H1N1 influenza A pandemic and relate it to the very little but fast incoming information that is available from the SARS-CoV-2 infected individuals with overweight and obesity.

Keywords: obesity, SARS-CoV-2, adiposity, COVID-19, novel corona virus, adipocytes

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INTRODUCTION

In the last 50 years, obesity has gradually shaped into a pandemic. Obesity (body mass index (BMI), $\geq$30 kg /m^2) is a combination of genetic, behavioral and environmental variables, and the number of affected individuals has doubled in more than 70 countries. It is not just restricted to developed nations; it is also present in low to middle-income countries (1). With 100 million obese children and 670 million obese adults worldwide, the challenges of tackling obesity involving health, social and economic issues are paramount, and no country is able to reverse the obesity epidemic so far (2, 3).

Many obese individuals may not show any adverse health condition at the onset but if not controlled, checked or reversed, obesity could contribute and develop other co-morbidities such as cardiovascular diseases, diabetes and cancers (3, 4). Many respiratory issues like obstructive sleep apnea, asthma and chronic obstructive pulmonary disease (COPD) have been correlated with obesity (5). Moreover, the incidences of acute respiratory distress syndrome (ARDS) is increased

in parallel with body mass (6). Besides causing non-communicable conditions, in recent years it is suggested that excess adiposity is an ideal set-up for acquiring and spreading of communicable diseases, in particular viral infections (7). Moreover, obesity is also linked to urinary tract, periodontitis, nosocomial and surgical infections (8).

The hallmarks of obesity include increase in hypertrophy and hyperplasia of adipocytes, ectopic fat deposition and adipose inflammation (9, 10). Besides adipocytes and preadipocytes, the other cell types present in adipose tissue comprise of endothelial and resident immune cells (11). During the progression of obesity, the dynamics and the functionality of the adipocytes change leading to altered levels of secreted adipokines and a rise in pro-inflammatory immune cells (12).

Undernutrition, which is still prevalent in many developing countries, was suspected to be the responsible factor for the spread of infection (13). However, observations during the H1N1 influenza virus pandemic indicated that overnutrition along with sedentary lifestyle (factors that mediate obesity) increase the risk of infection. A study by the World Health Organization (WHO), with H1N1 infection involving 70,000 individuals from 19 countries provide evidence that obesity, particularly morbid obesity (BMI $>$ 40), is a risk factor for severe disease (14). Emerging strong evidence suggests that excess adiposity and chronic inflammation increase the susceptibility to infection (15). With elevated levels of pro-inflammatory cytokines, the immune system is dysregulated making it difficult to combat infection (8). A correlation between obesity and infections is suggested by humans and rodent studies (16, 17) and reflects the reduced ability of immune cells from obese individuals to fight viral infection. However, the molecular mechanisms for this correlation are elusive and might even vary between viral infections.

Obesity is an expensive condition costing the society and the health system billions of dollars in treatment (18). With the increased frequency of viral infections, the cost of obesity gets even higher. At this time, when the world is facing a pandemic with the novel corona virus (SARS-CoV-2), it is important to use our current understanding on the connection between viral infection and obesity. In the light of the lessons, we learned from the H1N1 influenza A virus pandemic in an obese setting, this review discusses why obese individuals are at risk during this SARS-CoV-2 pandemic.

OBESITY AND IMMUNE SYSTEM

In healthy adipose tissue, adipocytes and the resident leukocytes maintain a balanced homeostatic state and a steady communication either through messenger cytokines or through cell-cell contact (19). Both the innate and adaptive immune cells reside in the adipose tissue to maintain an anti-inflammatory environment and obesity disturbs this situation (20, 21). Indeed, in obese adipose tissue an increase in macrophage accumulation along with a rise in TNF-α and IL-6 inflammatory molecules has been reported (22, 23). Obesity also results in an increase in ectopic fat accumulation in the bone marrow, which is the site where immune cells develop (24). Thus, the interplay of adipocytes and immune cells is altered in obesity compromising immune cell function and giving rise to inflammation.

Not just resident immune cells, the circulating cells are also affected by obesity. In this regard, the total leukocyte and monocyte count in the blood was shown to be increased in obese individuals as compared to lean counterparts (25). Moreover, the circulating peripheral blood mononuclear cells (PBMCs) secrete higher levels of TNF-α and lower levels of the anti-inflammatory IL-10 in obese individuals establishing a permanent "low-grade inflammatory state" (26). Toll like receptors (TLRs) play a crucial role in innate immune system and their activation in PBMCs from obese individuals indicate an impaired ability to express anti-viral type 1 interferons (IFNs), namely IFN-α and IFN-β (27). The circulating PBMCs differentiate into tissue-resident macrophages, which represent a large proportion of immune cell population in the adipose tissue. It is suggested that with an increase in hypertrophied adipocytes and rise in adipose tissue inflammation, the macrophages switch to a pro-inflammatory M1 type (28). Other immune cells, such as those that mediate the adaptive immune response are also affected by obesity (29). The rise in T cell subpopulations such as Th1 and Th17 cause a pro-inflammatory response in obese adipose tissue (30–32). The pro-inflammatory state in obesity is further enhanced by the depletion of regulatory T cell (Tregs), which is associated with infiltration of immune cells and a rise in inflammation (33). Thus, in obesity the proportion of pro-inflammatory immune cells are increased and together with inflammation from hypertrophied adipocytes they create a robust localized and systemic inflammation.

Adipose tissue was traditionally considered a long-term energy storage organ, but it is now appreciated that it orchestrates metabolic functions by the secretion of adipokines such as adiponectin and leptin (34). Moreover, adipokines have immunomodulatory roles and obesity disturbs this function (35–37). Plasma levels of leptin are highly correlated with BMI in both rodents and humans (38, 39) and influence T cell proliferation and Th1/ Th17-dependent cytokine secretion (40). Leptin affects fat and glucose metabolism and is linked to elevated free fatty acids and glucose levels in obesity and diabetes (38). Such high levels of glucose suppress the anti-viral type 1 IFN production in PBMCs (41, 42) and increase the reactive oxygen species in T cells (43). Elevated free fatty acids activate TLRs, induce inflammatory cytokines in circulating monocytes and enhance inflammation in T cells (44–47).

Thus, excess adiposity mediated by the changes in the levels of cytokines, adipokines and metabolites derails the immune response and shifts the balance to a pro-inflammatory state, which most likely favors and promotes infection.

INFLUENZA VIRUS INFECTION IN OBESITY

Globally 250,000 to 500,000 individuals die of influenza virus and 3 to 5 million individuals, both children and adults, are severely affected annually by this highly contagious virus (48).

Cold-weather months and low relative humidity due to room heating promotes the spread of this virus, which is known to cause severe respiratory tract infection along with rapid onset of high fever, cough, and possible headache, sore throat, body aches, nausea and/ or vomiting (49).

The genetic material of this virus is segmented RNA, which is surrounded by a host lipid envelop and is decorated on the surface by hemagglutinin and neuraminidase viral peptides, which help in attachment to the host cell (50). Influenza A, B, C, and D are the four strains, and A and B are the common strains that infect humans. Most human cases are caused by H1N1 and H3N2 influenza A virus strains (51) and to escape the host immunity, the virus goes through antigenic shift and drift causing seasonal influenza epidemics (50).

One hundred years back, the influenza virus triggered the 1918 "Spanish Flu" pandemic, which caused an extraordinary mortality of 50–100 million deaths (52). However, in those days obesity was not wide spread in the society, rather undernutrition was an issue. Since then other pandemics have taken place, which were caused by zoonotic transfer of the virus from animals to humans, but none of those created such an adverse impact as the Spanish Flu in 1918.

After the 2009 pandemic of influenza A (H1N1) virus, an in-depth analysis of the data revealed that obesity was an independent risk factor for increased morbidity and mortality (53). Obesity is often associated with reduced lung volume, abnormalities in respiratory muscle function and gas exchange compounded by sleep apnea and chronic inflammation (5, 54), and this restricted lung function seems highly conducive for the influenza virus infection and thereby injury in the lungs. Recently, increase in BMI positively correlated with adiposity in airway wall, wall thickness and inflammation causing asthma-related death (55). Influenza virus pathogenicity is not just restricted to lungs (56); it also worsens the cardiovascular function (57).

Using rodent models of obesity, many studies have been performed with influenza virus to understand why obesity is a risk factor for infection. High-fat diet-induced obese (DIO) mice infected with influenza virus develop greater lung damage and inflammation, and exhibit a higher mortality rate (58). Increased leptin levels in DIO mice caused severe lung injury and anti-leptin antibody improved the survival of H1N1 infected obese mice (59). The genetic models of obesity such as the leptin deficient ob/ob mice and leptin receptor-deficient obese db/db mice have increased susceptibility to H1N1 virus infection (60). Increased leptin levels in obesity may promote infection by lowering anti-viral type 1 IFN through the activation of suppressor of cytokine signaling-3 (SOCS-3) expression (42, 61). Indeed disruption of SOCS-3 expression provides protection against influenza A virus infection (62).

The role of antiviral IFNs has also been investigated as it is the key to immunity, and suppressed IFN production could be the link for increased infection in obesity (42). In mice, the reduced IFN response in obese condition was shown to create an ideal microenvironment permitting diversity and emergence of virulent strains and treatment with recombinant IFN reduced the viral diversity (63). Most of the studies on the effect of obesity during infection investigated the lungs, which is the primary site for influenza virus infection. The natural killer (NK) cells assist in eliminating infected cells, and infection in obese mice had diminished NK cell cytotoxicity, lower expression of IFN α/β and delayed expression of pro-inflammatory cytokines like IL-6 and TNFα in the lungs (17), indicating lower immune response. DIO mice had reduced influenza specific CD8+ memory T cells post-infection along with a reduction in leptin receptors in the lungs, suggesting possibility of lung injury (64). Obesity also affected the presence of monocytes, lymphocytes and antigen presentation by dendritic cells during infection leading to impairment of immune response in the lungs (65). However, in contrast to the lungs, adipose tissue have a higher infiltration of inflammatory cells, and increased levels of TNFα, MCP-1, and IL-6 (66), which are known to cause complications like insulin resistant and also dysfunctional adipose tissue. Besides inflammatory mediators, metabolic profiling of serum, adipose tissue, liver, lungs, urine and feces from obese mice infected with influenza virus showed differential increase in specific metabolites such as certain lipids, ascorbate, glucose, 3-hydroxybutyrate, all known to affect the T cell population (67), thus lowering the adaptive immune response.

In humans, the extent of adiposity determines the severity of disease post-infection. The influenza viral RNA was detected in aerosol and there was a positive association with viral aerosol load (indicating shedding) and BMI (68). Higher BMI was shown to be an added risk factor for hospitalization and during the influenza months of the year, the incidences of hospitalization with obese individuals increased (69, 70). Moreover, obese individuals had a longer hospital stay. Indeed, the data suggests that obesity slows the recovery since it delays the clearance of the influenza virus load and prolongs the shedding duration causing long-term transmission (71). Obese individuals infected with H1N1 virus had a two-fold higher chance to end up in Intensive Care Unit (ICU) (72). A multicenter study with 144 ICUs in Spain revealed that obesity was associated with higher ICU resource consumption and hospitalization in H1N1 infected individuals (73). Among patients admitted to ICU due to H1N1 infection, obese and morbidly obese patients were more likely to develop pneumonitis compared to non-obese patients (74). With underlying co-morbidities like obesity and diabetes even younger patients over the age of 20 years had higher hospitalization and mortality (53, 75, 76). Thus, the influenza pandemic data shows that obesity is a risk regardless of age and possible other co-morbidities such as hypertension and diabetes could enhance the severity of the disease.

INFLUENZA VIRUS VACCINATION IN OBESITY

Vaccination is still the best way to prevent the risk of developing infections. Obesity, however, interferes with the protection by vaccination against infectious diseases (7) and indeed obese individuals were reported to show a greater decline in influenza-specific antibody titers at 1 year after vaccination (77). Moreover, vaccinated obese adults had twice the risk of developing influenza

despite a good antibody titer in response to the vaccine (78). PBMCs challenged *ex vivo* with vaccine virus strain showed that obese individuals had decreased $CD8^+$ T cell numbers along with a decline in influenza antibody titers and lower protection to vaccination (77). In a further study by the same group, PBMCs from overweight and obese individuals when stimulated *ex vivo* with H1N1 virus showed a defect in $CD4^+$ and $CD8^+$ T cell activation despite intact dendritic cell functions, suggesting that both overweight and obesity negatively impact the immune function (79).

The above studies with influenza virus show that excess body fat elevates inflammation, weakens the immune response particularly in the lungs, hampers vaccination and creates an ideal environment for influenza viral infection and spreading.

IS OBESITY A RISK FACTOR FOR SARS-COV-2?

Coronaviruses (CoVs) are a family of enveloped RNA viruses that infect mammals and birds. The last two decades saw the emergence of novel coronaviruses that triggered human fatalities. Firstly, in 2002/2003 there was the outbreak of SARS-CoV and then in 2012, the World saw an outbreak of Middle East respiratory syndrome coronavirus (MERS-CoV). Both these viruses originated from animals and infected humans (80). Though these viruses did not spread efficiently from human to human, both SARS and MERS had a high fatality rate of 9.5 and 34.4%, respectively (81). Comorbidities were reported to exist in MERS infected individuals and in one such study obesity was associated with 17% of the MERS infected hospitalized patients (82). The 2002 SARS-CoV infection lowered anti-viral IFNα/β, upregulated TNF receptor, IL-8 and hypoxia related genes (83). Obesity also lowers the IFNs activity and increases hypoxia in adipocytes leading to a heightened inflammation (42, 84). Hence, the combination of the viral infection and obesity probably creates an ideal platform that favors a pro-viral inflammatory "cytokine storm" by lowering the anti-viral immune response.

The 2019 novel coronavirus, referred to as SARS-CoV-2, is closer to SARS as it also binds to human angiotensin-converting enzyme 2 (ACE2). ACE2, which is also referred to as ACE2 receptor acts as the entry point for the coronavirus to infect a wide range of human cells. The viral spike protein S present as transmembrane protein in the viral envelope has a strong affinity for human ACE2 receptor. ACE2 is expressed in a wide variety of human tissues with different expression levels including the small intestine, testis, kidneys, heart, thyroid, lungs, brain and the adipose tissue (85–88). ACE2 is known to generate vasodilator angiotensin-(1-7) from vasoconstrictor angiotensin II, and expression of ACE2 in adipocytes is known to protect against obesity-mediated hypertension (89). ACE2 induces an anti-obesity effect by stimulating brown adipocytes and through browning of white adipose tissue (90). Moreover, activator of ACE2 is reported to reduce adiposity (91). Thus, it is highly probable that the beneficial effects of adipose ACE2 are lost after the binding with SARS-CoV-2. Loss and/ or reduction in ACE2 activity means increase in Ang II levels and indeed Covid-19 patients show increased levels of plasma Ang-II, cardiovascular complications and a linear association with lung injury (92).

Recent studies suggest that COVID-19 patients with obesity are at a greater risk for hospitalization. Obesity was suggested as an independent risk factor for SARS-CoV-2 infection and the proportion of patients in France who required invasive mechanical ventilation increased with BMI (93). In Spain, obesity was the strongest comorbidity among patients admitted to ICU (94). In a retrospective analysis of COVID-19 patients admitted to a hospital in Wuhan, China, 88% of non-survivor patients had a BMI >25 kg/m^2 (95). A report from Intensive Care National Audit and Research Center (ICNARC, UK) from 19 June, 2020 show that of the 9,272 COVID-19 patients admitted in critical care units 39.3% were obese & 35% were overweight (https://www.icnarc.org/Our-Audit/Audits/Cmp/Reports). In USA, which is witnessing an explosion of SARS-CoV-2 infection, 40% of the adult population is obese. In an Editors Speak Out column Ryan et al., suggest that, in USA, obese individuals are at risk of infection and obesity could be an independent risk factor for COVID-19 (96). Data of 5,700 COVID-19 patients from the New York City area with median age of 63 years show that many patients had comorbidities such as obesity (41.7%), hypertension (56.6%) and diabetes (33.8%) (97). A letter communicated by Lighter J et al., on the COVID-19 patient data from a New York City hospital report that in patients younger than 60 years, obesity is a risk factor for hospital admission (98). The authors indicate that of the 3,615 patients admitted in the hospital 38% were with a BMI of $\geq$30 kg/m^2 and that obesity increases the likelihood of admission in critical care unit by 2 times as compared to those with lower BMI in the same age group. Similar data was reported in young obese individuals with H1N1 infection (53). With all the data pouring in, it is still unclear why SARS-CoV-2 infection deteriorates the health and increases the hospitalization of COVID-19 overweight and obese patients.

The driving features of SARS-CoV-2 are reduced levels of anti-viral IFNs along with high levels of chemokine and cytokines like IL-6 (99). Even though inflammation of the lung is the primary symptom in COVID-19 patients, the expression of ACE2 in lungs is very moderate (88). Even with moderate ACE2 expression, it may be enough to drive the lung inflammation. Li et al., found no difference in the expression levels of ACE2 in the lungs of healthy individuals and those with chronic respiratory disease, suggesting that in both groups SARS-CoV-2 could infect the lungs (100). Hence, the additional underlying conditions such as obesity could contribute to worsen the lung function. Obesity is related with chronic obstructive pulmonary disease (COPD) and ACE2 expression is significantly increased in COPD than non-COPD subjects (101). Besides causing acute respiratory distress syndrome (ARDS) and pneumonia, SARS-CoV-2 also causes cardiovascular complications (102).

Until now, most of the studies on SARS-CoV-2 have focused on the lungs even though other organs such as adipose tissue and

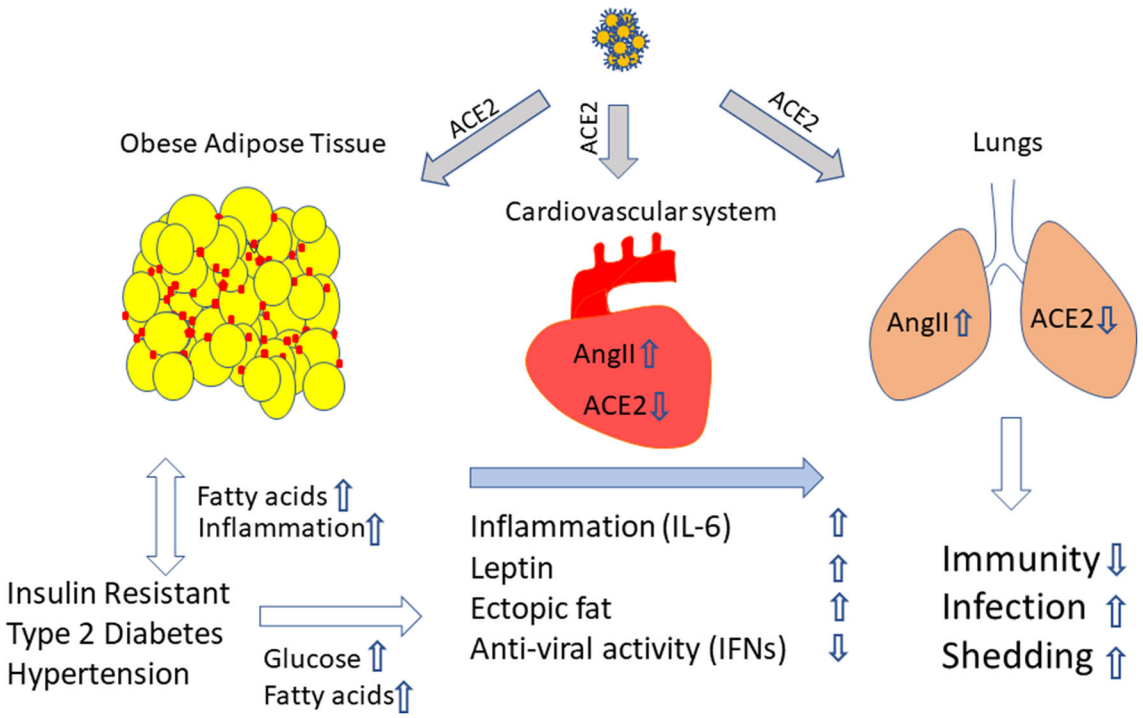

FIGURE 1 | Excess adiposity provides an ideal setting to promote viral infection. We propose that obesity and its associated conditions elevate the cytokines, adipokines and RAAS and increase ectopic fat accumulation. When infection sets in, in this case with SARS-COV-2, through ACE2 receptor on the adipose tissue, the lungs, the heart and the blood vessels, the virus enters, mediates a cytokine storm and creates an imbalance in AngII/ACE-2 levels, elevates leptin levels and lowers anti-viral molecules like IFNs. Moreover, adipose tissue a might serve as a reservoir for viral persistence, which could be the possible source of continuous viral shedding and systemic inflammation. The combination of all the factors deteriorates lungs and the cardiovascular system, weakens the immune response, and promotes viral shedding. Yellow circle indicate adipocytes, red marks indicate inflammatory cells, upwards and downwards arrows indicates upregulation or downregulation of molecules and/ or effect.

heart have higher expression of ACE2 (88). Whether a cross talk exists, by which infection in adipose tissue affects the lung and heart function is a matter of investigation. Based on the present findings, we suggest the following possible factors through which excess adiposity in the presence of SARS-CoV-2 deteriorate health, in particular the lungs and cardiovascular function.

Inflammation

Expression of inflammatory molecules (IL-6, TNFα) and C-reactive protein are increased in overweight and obesity (103, 104) and increased inflammation is shown to deteriorate the lung and the cardiovascular function. High levels of IL-6 is associated with lung lesions after SARS infection (105) and increased levels of circulating IL-6 is connected with systolic blood pressure in hypertensive subjects by increasing the expression of angiotensinogen and angiotensin II receptor (106). Data from COVID-19 patients show that a cytokine storm exist in severe patients and highly elevated IL-6 levels in the serum contributes to the cytokine release syndrome (107, 108), which could probably reduce the immune response in lungs by inhibiting the ability of dendritic cells to activate T cells (109).

Renin-Angiotensin-Aldosterone System (RAAS)

The ACE2-Ang II balance is altered by both obesity and by SARS-CoV-2 infection. Activation of RAAS results in higher blood pressure and elevated levels of Ang II induces endothelial dysfunction (110). Moreover, SARS-CoV-2 viral elements have been reported within endothelial cells along with an accumulation of inflammatory cells (111), which could further worsen the cardiovascular system. In the lungs, downregulation of ACE2 receptors is shown to cause immune-cell infiltration and expression of inflammatory cytokines leading to lung edema and acute lung failure, which appear to be mediated by Ang II (112).

Adipokines

Leptin levels are increased in obesity and elevated leptin levels deteriorate lung and cardiovascular function (59, 113). It is reported that COVID-19 patients with high BMI have significantly higher levels of serum leptin (doi: https://doi.org/10.1101/2020.04.30.20086108).

Ectopic Fat

An increase in ectopic fat, in obesity, may worsen the function of the organ that is in close proximity to the adipose tissue. For example: the epicardial adipose tissue (EAT) which is in close proximity with the myocardium could be a possible source for myocarditis and indeed myocarditis is reported in COVID-19 patients (114). Fat embolism in lungs through the action of the released lipid droplets from necrotic adipose tissue could be another way by which obesity affects lung function upon viral infection (115).

Even though there are several similarities between influenza and SARS-CoV-2 virus and both these viruses worsen the lung and cardiovascular function in obese setting, some differences also exist. Both viruses utilize different entry points to bind and enter the cells. Even though there is a report which suggests that influenza virus utilizes ACE2 to induce acute lung damage (116) however for SARS-CoV-2 infection, ACE2 is the main route to infection. It is highly important for clinicians and health workers to distinguish between the two types of infections, which have almost the same readouts. It is suggested that COVID-19 patients have a higher median age, higher proportions male subjects, a history of cardiovascular diseases as compared to H1N1 patients (117). The case fatality risk (CFR) suggest that COVID-19 is more severe than H1N1 infected hospitalized individuals (118).

Even though the information coming out on SARS-CoV-2 is very rapid, some open questions remains.

Some Important Open Questions

1. Does SARS-CoV-2 infect the adipose tissue and enhance the inflammation?
2. Do COVID-19 obese individuals have a longer virus shedding duration and therefore need longer isolation period?
3. If SARS-CoV-2 reduces memory $CD8^+$ T cells in obesity, then how effective a vaccine will be for obese individuals?
4. Will countries with less obese individuals per million of population, have a lower morbidity and mortality rate to SARS-CoV-2?

CONCLUSION

Based on the studies, we suggest that obesity favors viral infection (both influenza and COVID-19). At this stage of the COVID-19 pandemic, it is evident that obesity and infection together build up a cytokine storm that determines the severity of the disease. Moreover, increased inflammation in particular elevated IL-6 levels, activation of RAAS, rise in Ang II levels, higher leptin and increased ectopic fat favor COVID-19 disease progression and severity, and thus worsen the lung and cardiovascular function (**Figure 1**). The lower levels of anti-viral IFNs and weakened immune response in COVID-19 patients make the fight against this infection more difficult and the effect of a potential vaccine questionable in obese individual. Therefore, overweight and obese individuals should be informed that they belong to a risk group and should avoid the risk of SARS-CoV-2 infection by any means.

AUTHOR CONTRIBUTIONS

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SYSTEMATIC REVIEW
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Obesity Increases the Severity and Mortality of Influenza and COVID-19: A Systematic Review and Meta-Analysis

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Since December 2019, COVID-19 has aroused global attention. Studies show the link between obesity and severe outcome of influenza and COVID-19. Thus, we aimed to compare the impacts of obesity on the severity and mortality of influenza and COVID-19 by performing a meta-analysis. A systematic search was performed in MEDLINE, EMASE, ClinicalTrials.gov, and Web of Science from January 2009 to July 2020. The protocol was registered onto PROSPERO (CRD42020201461). After selection, 46 studies were included in this meta-analysis. The pooled odds ratios (ORs) with 95% confidence intervals (CIs) were analyzed. We found obesity was a risk factor for the severity and mortality of influenza (ORsevere outcome = 1.56, CI: 1.28-1.90; ORmortality = 1.99, CI: 1.15-3.46). For COVID-19, obesity was a significant risk factor only for severe outcome (OR = 2.07, CI: 1.53-2.81) but not for mortality (OR = 1.57, CI: 0.85-2.90). Compared with obesity, morbid obesity was linked with a higher risk for the severity and mortality of both influenza (OR = 1.40, CI: 1.10-1.79) and COVID-19 (OR = 3.76, CI: 2.67-5.28). Thus, obesity should be recommended as a risk factor for the prognosis assessment of COVID-19. Special monitoring and earlier treatment should be implemented in patients with obesity and COVID-19.

Keywords: obesity, COVID-19, influenza, mortality, severe outcome

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INTRODUCTION

Since December 2019, countries globally have been suffering from the spread of COVID-19, which is also known as SARS-CoV-2 (1, 2). The latest information indicates that there are more than 48 million COVID-19 cases around the world, according to the data on November 6, 2020. Based on the 1918 "Spanish" influenza pandemic and 2009 influenza A (H1N1) pandemic (3), studies show the close relationship between obesity and virus infection as well as mortality (4, 5). Significantly, special attention should be paid to obese patients. Due to the prolonged pandemic of COVID-19, tons of expenses have been spent on medical fields, which has influenced the social economy extremely (6). Thus, investigating the influencing factors and susceptible population are the most

important things to prevent the pandemic of COVID-19. Evidence from previous influenza studies might provide referential and warning values for the understanding and control of COVID-19.

Obesity is one of the most important diseases affecting people's health with dramatically increased morbidity year by year (7, 8). Studies indicate that obesity is linked with increased influenza infection. Because of the disturbed immune regulation and metabolic homeostasis, patients with obesity present higher risks for the severe outcome and mortality of influenza (9, 10). Similarly, the latest studies show that COVID-19 patients with obesity are more likely to be admitted to the intensive care unit (ICU), be on mechanical support, and have a severe outcome (11, 12). Although some reviews and meta-analyses have been published on the topic of obesity and severe outcome of COVID-19, the data are updated every minute (13). An available and timely meta-analysis is urgent. Moreover, the differences and comparisons of severity, outcome, and mortality between influenza and COVID-19 in patients with obesity are unknown so far. Thus, to compare the effect of obesity on influenza and COVID-19 is of great value and importance for us to learn about COVID-19.

In the present study, we aimed to systematically review and compare the effects of obesity on the infection, hospitalization, disease severity, and mortality of both influenza and COVID-19 based on the available evidence. In addition, we updated the meta-analysis by including the latest studies from other countries. We hope this meta-analysis provides more valuable information for the management of the COVID-19 pandemic.

METHODS

Literature Search Strategy

A systematic search was conducted to identify papers available on MEDLINE, EMASE, ClinicalTrials.gov, and Web of Science for relevant studies from January 2009 to July 2020. The review protocol was registered onto PROSPERO (CRD42020201461). We developed a search strategy for MEDLINE based on medical subject heading (MeSH®) terms and text of target papers. Different possible variations and combinations of the following search terms were used: influenza, influenza A, influenza B, H1N1, H7N9, COVID-19, SARS-CoV-2, coronavirus, 2019 nCoV, obesity, obese, BMI, severity, outcome, and mortality. We also reviewed the reference lists of all included papers and relevant review papers to identify studies that the database searches might have missed. To minimize selection bias, two persons completed this work independently. Disagreements were resolved by consensus and by a third person. In the initial search, no filter for language preference was used. The literature search process is based on the PRISMA form (14).

Inclusion and Exclusion Criteria

Articles were included or excluded on the basis of full-text articles. The following inclusion criteria were applied: 1) For the diagnosis of obesity, BMI was applied for classification according to the American Endocrine Society Scientific Statement on obesity management (15): ①normal weight: 18.5 kg/m^2 < BMI < 25 kg/m^2; ②overweight: 25 kg/m^2 ≤ BMI < 30 kg/m^2; ③obesity: BMI ≥ 30 kg/m^2; ④morbid obesity: BMI ≥ 35 kg/m^2. 2) COVID-19 infection is diagnosed according to the criteria established by the China National Health Commission (16) based on laboratory examinations, such as nasopharyngeal and oropharyngeal swab tests. Detection tests for coronavirus include reverse-transcription polymerase chain reaction (RT-PCR), real-time RT-PCR (rRT-PCR), and reverse transcription loop-mediated isothermal amplification (RT-LAMP). To identify patients earlier, two one-step quantitative RT-PCR (qRT-PCR) assays were developed to detect two different regions (ORF1b and N) of the SARS-CoV-2 genome. For patients suffering from fever, sore throat, fatigue, coughing, or dyspnea coupled with recent exposure, COVID-19 infection should be diagnosed with typical chest computerized tomography (CT) characteristics despite negative RT-PCR results. 3) Influenza infection is diagnosed with clinical manifestations and laboratory tests (17). The RT-PCR test is the most traditional yet powerful approach for identification of influenza viruses in most diagnostic labs around the world. Rapid influenza diagnostic tests are also applied by many countries, using monoclonal antibodies that target the viral nucleoprotein and employ either an enzyme immunoassay or immunochromatographic techniques. 4) Included studies should present data that could be extracted straightforwardly, and detailed characteristics on the population and studies should be provided. 5) Severe outcome of influenza and COVID-19 refers to admission to the ICU, requiring mechanical support, hypoxia requiring oxygen therapy, and increased mortality and death. 6) Only papers published in English were included in the present study, but abstracts of non-English papers were also reviewed to prevent missing information.

Studies were excluded if subjects had diabetes or other fatal chronic diseases or medication history. Fatal chronic disease refers to disease that could induce the severity of COVID-19 or influenza besides obesity, which might make it difficult to discuss the role of obesity on the risk and outcome of COVID-19 or influenza. For instance, fatal chronic diseases include cancer, severe autoimmune disease, chronic kidney disease, diabetes, cirrhosis, liver failure, and so on. As for medication history, it does not mean all kinds of treatment are excluded. Only medications that could cause interference in the outcome or mortality of COVID-19 or influenza were excluded. Case reports, reviews, meta-analyses, conference abstracts, and letters to the editor were also excluded.

Data Extraction and Analysis

Both investigators (XZ and QH) initially screened all relevant titles and abstracts to confirm if the studies were related to the topics of present study. After the first round of reviewing, full-text articles were read by two persons. Data were extracted from studies meeting our inclusion criteria according to our self-made forms. Data on population characteristics, group descriptions, and odds ratio or relative risk (OR/RR) values were extracted. One investigator performed the data extraction (XZ), which was verified by a second investigator (QH). Data from influenza and COVID-19 studies were analyzed through meta-analysis guidelines. For influenza studies, we aimed to analyze the data on the influenza infection, hospitalization, disease severity, and mortality in patients with obesity or morbid obesity. For

COVID-19 studies, we aimed to analyze the data on the disease severity and mortality in patients with obesity or morbid obesity. OR/RR and 95% confidence interval (95% CI) were presented as effect size for case control or cohort studies. Before data synthesis, heterogeneity was estimated using the Q test and I^2 statistic. When $P < 0.1$ or I^2>50%, indicating the existence of possible heterogeneity among studies, the random-effect model was applied. Sensitivity analyses were performed to explore the resources of heterogeneity in instances in which sufficient data were collected. The Begg's test was used to evaluate publication biases. All analyses were completed with the software STATA 15.1 (StataCorp, College Station, TX, USA). All statistical tests were 2-tailed.

Methodological Quality Assessment

The 9-star Newcastle-Ottawa Scale (NOS) was applied to assess the quality of the studies (18). The methodologies of studies that achieved 6/9 or more were classified as high quality, whereas those that scored less than 5/9 were classified as low quality.

RESULTS

Literature Search and Study Characteristics

After careful selection, a total of 46 studies were included in the present meta-analysis; 11/46 studies were COVID-19 studies (11, 19–28), and 35/46 studies were influenza studies (29–61). A total of 4,023,895 patients were included for the studies on influenza, and 9,787 patients were included in the COVID-19 studies. The procedure of literature selection based on the PRISMA statement is shown in **Figure 1**. Details about the characteristics of the included studies are shown in **Tables 1** and **2**. The included studies were published between 2009 and 2020. Of the included COVID-19 studies, 4 were conducted in the United States, 3 were from China, and 1 each was from France, Singapore, Italy, and Mexico, respectively. Of the included influenza studies, 12 were conducted in the United States, 4 were from Spain, 6 were from China, 3 were from Canada, 2 were from UK, and 1 each was from the following countries: Mexico, Serbia, France, Iran, Romania, France, Brazil, Australia, and South Africa. The studies varied in sample size from 48 to 3,076,699. In addition, 41/46 studies enrolled both males and females, and 5 did not show the gender characteristic. Study quality assessment according to NOS is shown in **Tables 1** and **2**.

Obesity Increases the Risk of Influenza Infection and Hospitalization

A total of 7 studies were included for the meta-analysis of obesity and influenza infection risk (30, 33, 34, 36, 40, 55, 60). Our pooled analysis shows that patients with obesity had a significantly higher risk for influenza infection (OR: 1.29, 95% CI: 1.11-1.49, I^2: 61.5%, *n*=7). This result is presented in **Figure 2**. Due to the heterogeneity between the included studies, we

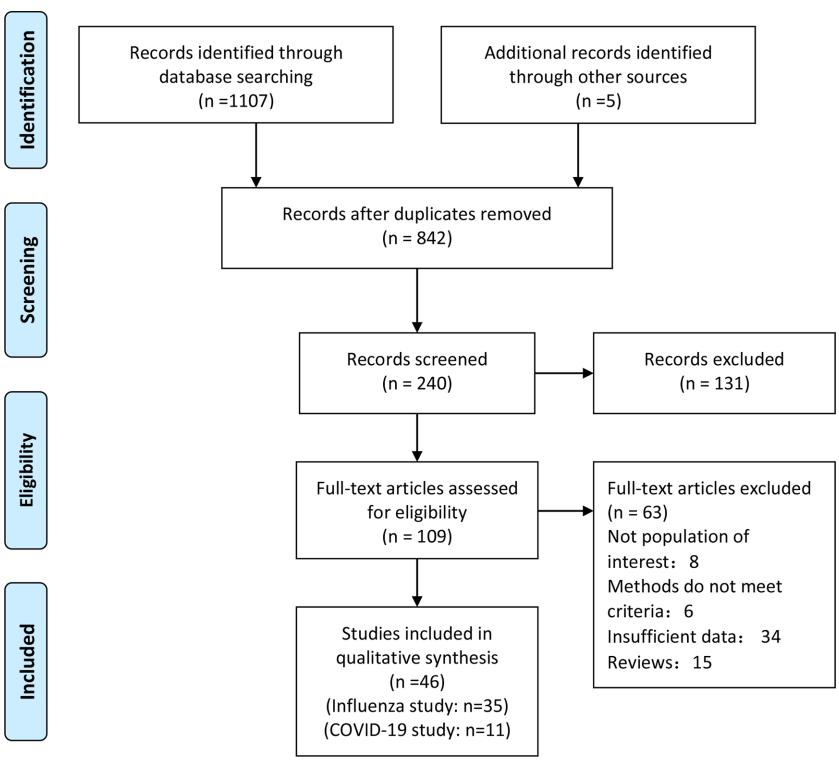

FIGURE 1 | Flowchart on the literature selection process in this meta-analysis.

TABLE 1 | Characteristics of included studies on the infection, hospitalization, severity, and mortality of influenza.

Author	Country	Year	Number	Women (%)	Age	Groups	Disease outcome	OR or RR (95% CI)	NOS
Ren et al. (29)	China	2013	686	48.40%	5-60	Overweight; Obesity	Severe influenza manifestation	Overweight: 3.70(2.04, 6.72) Obesity: 35.61 (7.96, 159.21)	7
Maier et al. (30)	US	2018	1783	74%	0-92	Obesity	Influenza	2.04 (1.35, 3.09)	6
Segaloff et al. (31)	US	2017	48	23%	21-91	Obesity Morbid obesity	Severe influenza outcomes	Obesity: ICU: 2.9 (0.5, 20.9); LRD: 2.1 (0.5, 8.6) Morbid obesity: ICU: 7.9 (0.9, 87.1); LRD: 4.0 (0.6, 35.0)	6
Moser et al. (32)	Mexico	2018	3248	64.25%	41.2 ± 16.2	Underweight; Obesity; morbid obesity	hospitalization	Underweight: 5.20 (1.67, 16.01) Obesity: 3.18 (1.73, 5.91) Morbid obesity: 18.4 (7.83, 47.4)	5
Neidich et al. (33)	US	2017	1022	64.68%	54 ± 15	Obesity	Influenza risk	Obesity: 2.01 (1.12, 3.06)	5
Murphy et al. (34)	UK	2016	6984	53.94%	35-63	Obesity	Influenza-like illness	Obesity: 1.16 (0.97, 1.38)	6
Yang et al. (35)	China	2013	66820	65.75%	65+	Underweight; Overweight; Obesity; Morbid obesity	influenza-associated mortality	Underweight: 1.081 (1.013, 1.154) Overweight: 0.981 (0.936, 1.028) Obesity: 1.018 (0.980, 1.058) Morbid obesity: 1.062 (0.972, 1.162)	6
Cocoros et al. (36)	US	2014	8266	59.63%	48+	Overweight; Obesity	Influenza-like illness	Overweight: 1.54 (0.56, 4.27) Obesity: 1.90 (0.68, 5.27)	6
Dragana et al. (37)	Serbia	2017	777	48.26%	65+	Obesity	Admission to ICU	Obesity: 3.32 (1.36, 8.14)	6
Charland et al. (38)	US	2012	3076699	N/A	0-80+	Obesity	Hospitalization	Obesity: 1.12 (1.07, 1.17)	6
Braun et al. (39)	US	2015	9048	65.6%	20+	Underweight; Overweight; Obesity; Morbid obesity	Influenza severity (admission to ICU)	Underweight: 1.13 (0.86, 1.49) Overweight: 0.80 (0.70, 0.94) Obesity: 0.90 (0.76, 1.08) Morbid obesity: 0.91 (0.77, 1.09)	5
Coleman et al. (40)	US	2012	2623	65.42%	45 ± 17	Obesity; Morbid obesity	Influenza	Obesity: 0.95 (0.75, 1.20) Morbid obesity: 1.10 (0.8, 1.52)	6
Morgan et al. (41)	US	2010	594	N/A	N/A	Obesity; Morbid obesity	Hospitalization; Death	Obesity: hospitalization: 1.5 (0.8, 2.8); death: 4.9 (2.4, 9.9) Morbid obesity: hospitalization: 3.1 (1.5, 6.6); death: 7.6 (2.1, 27.9)	6
Halvorson et al. (42)	US	2018	2811	61%	22+	Overweight; Obesity; Morbid obesity	Hospitalization	Overweight: 0.8 (0.6, 1.0) Obesity: 0.7 (0.5, 1.0) Morbid obesity: 0.9 (0.6, 1.2)	6
Van Kerkhove et al. (62)	US	2015	11086	10.5%	28-40	obesity	Hospitalization severe outcomes	Obesity: 1.6 (1.2, 2.1)	7
Louie et al. (43)	US	2010	534	52%	46 (20, 92)	Morbid obesity	Death	Morbid obesity: 2.8 (1.4, 5.9)	6
Jime´nez-Garcı´a et al. (44)	Spain	2012	11499	54.2%	18+	Obesity	Death	Obesity: 1.88 (1.07, 3.92)	5
Díaz et al. (45)	Spain	2011	416	41.93%	43.1 ± 12.2	Obesity	Death	Obesity: 1.56 (0.95, 2.54)	6
Tempia et al. (46)	South Africa	2016	465	64.95%	5+	Obesity	Hospitalization	Obesity: 12.1 (1.6, 88.8)	6
Martin et al. (47)	US	2013	161	35.4%	40-46	Obesity	Hospitalization; death	Hospitalization: 2.93(1.50, 5.71) death: 5.33 (0.61, 46.71)	5
Bijani et al. (48)	Iran	2016	55	43.6%	25.7 ± 16.9	Obesity	Severe manifestation	Obesity: 0.89 (0.08, 10.43)	5
Cui et al. (49)	China	2010	68	N/A	41 (18, 66)	Obesity	Death	Obesity: 23.06 (0.95, 2.54)	7
Santa-Olalla Peralta et al. (63)	Spain	2010	3025	N/A	38 (0,94)	Obesity	Severe outcomes	Obesity: 2.01 (1.38, 2.94)	6
Gilca et al. (50)	Canada	2011	716	54.05%	5+	Obesity; Morbid obesity	Hospitalization; ICU or death	Obesity: hospitalization: 1.3 (0.8, 2.0); death: 1.0 (0.5, 2.3) Morbid obesity: hospitalization: 2.0 (0.6, 6.2); death: 0.4 (0.09, 2.0)	6
Lenzi et al. (51)	Brazil	2011	4740	53.31%	0-90	Obesity	Hospitalization	Obesity: 2.994 (1.638, 5.472)	5

(Continued)

TABLE 1 | Continued

Author	Country	Year	Number	Women (%)	Age	Groups	Disease outcome	OR or RR (95% CI)	NOS
Yu et al. (52)	China	2011	9966	44%	22 (11, 39)	Obesity	Severe outcomes	Obesity: 1.54 (1.35, 1.76)	6
Viasus et al. (53)	Spain	2010	585	48.7%	39 (16, 87)	Morbid obesity	Severe outcomes	Morbid obesity: 6.7 (2.25, 20.19)	6
Tang et al. (53)	China	2010	457	42.23%	25 (6, 42)	Overweight; Obesity	Severe outcomes	Overweight: 3.13 (1.83, 5.36) Obesity: 4.05 (1.72, 9.52)	6
Karki et al. (55)	Australia	2018	246494	46.99%	50+	Obesity; Morbid obesity	Influenza incidence; Hospitalization	Incidence: Obesity: 1.27 (1.10, 1.46) Morbid obesity: 1.69 (1.24, 2.29) Hospitalization: Obesity: 1.57 (1.22, 2.01); Morbid obesity: 4.81 (3.23, 7.17)	9
Zhou et al. (56)	China	2015	65841	66.14%	65+	Obesity	Influenza mortality	Obesity: 1.19 (1.01, 1.42)	8
Campitelli et al. (57)	Canada	2014	396581	48.92%	18-64	Overweight; Obesity; Morbid obesity	Acute respiratory infection for influenza	Overweight: 1.10 (1.07, 1.13) Obesity: 1.17 (1.13, 1.22) Morbid obesity: 1.19 (1.12, 1.25)	8
Kwong et al. (58)	Canada	2011	82545	50.49%	18+	Obesity; Morbid obesity	Hospitalization	Obesity: 1.45 (1.03, 2.05) Morbid obesity: 2.12 (1.45, 3.10)	9
Pițigoi et al. (59)	Romania	2019	345	55.9%	74 (68, 80)	Obesity	Hospitalization	Obesity: 2.1 (1.3, 3.4)	7
Guerrisi et al. (60)	France	2019	6992	61%	0-75	Underweight Overweight; Obesity	Influenza-like illness	Underweight:0.92(0.77,1.11) Overweight:1.18(1.08,1.29) Obesity:1.28(1.14,1.44)	8
Myles et al. (61)	UK	2012	1520	52.6%	26(9,44)	Obesity	Severe outcomes	Obesity:2.22(1.18,4.18)	7

TABLE 2 | Characteristics of included studies on the severity and mortality of COVID-19.

Author	Country	Year	Number	Women (%)	Age	Group	Outcome	OR (95%CI)	NOS score
Simonnet et al (11).	France	2020	124	27%	60 (51, 70)	Obesity; Morbid obesity	Severe manifestation; ICU	Obesity:3.45(0.83,14.31) Morbid obesity: 7.36 (1.63, 33.14)	6
Cai et al (19).	China	2020	383	52.21%	48 (39, 54)	Overweight; Obesity	Severe manifestation; ICU	Overweight: 1.84 (0.99, 3.43) Obesity: 3.4 (1.4, 8.26)	7
Wu et al (20).	China	2020	280	46%	43.12 ± 19	Obesity	Severe influenza outcomes	Obesity: 1.3 (1.09, 1.54);	5
Lighter et al (21).	US	2020	3615	N/A	N/A	Obesity; morbid obesity	Severe manifestation; ICU	Obesity: 1.8 (1.2, 2.7) Morbid obesity: 3.6 (2.5, 5.3)	5
Ong et al (22).	Singapore	2020	182	60%	43 (27, 52)	Obesity	Severe manifestation; ICU	Severe manifestation: 6.32 (1.23, 32.34) ICU: 3.13 (0.57, 17.13)	5
Gao et al (23).	China	2020	150	37.3%	35-63	Obesity	Severe manifestation and ICU	Obesity: 3 (1.22, 7.38)	6
Pettie et al (24).	US	2020	238	52.5%	58.5 ± 17	Obesity	mortality	Obesity: 1.7 (1.1, 2.8)	6
Hajifathalian et al (24).	US	2020	770	39.2%	64 ± 16.7	Obesity	ICU and mortality	ICU: 1.76 (1.24, 2.48) mortality: 1.15 (0.62, 2.14)	7
Busetto et al (26).	Italy	2020	92	38.1%	70.5 ± 13.3	Obesity	Admission to ICU; death	ICU: 11.65 (3.88, 34.96) mortality: 0.27 (0.03, 2.05)	6
Palaiodimos et al (27).	US	2020	200	51%	64 (54, 73.5)	Morbid obesity	mortality	Morbid obesity: 3.78 (1.45, 9.83)	7
Denova-Gutiérrez et al (28).	Mexico	2020	3844	42%	45.4 ± 15.8	Obesity	Severe outcome; ICU	Obesity: 1.43 (1.11, 1.83)	6

performed subgroup analysis according to different regions. The results show that the heterogeneity was decreased in non–North American countries (**Supplement Figure 1**).

As for the risk of hospitalization, 18 studies were included in this part. To specify the effect of obesity classes on influenza hospitalization, 12 studies focused on the link between obesity and influenza hospitalization (32, 38, 41, 42, 46, 47, 50, 51, 55, 58, 59, 62). Among these, 6 studies focused on the link between morbid obesity and influenza hospitalization (32, 41, 42, 50, 55, 58). Our results show that patients with obesity had an increased risk for hospitalization because of influenza (OR: 1.62, 95% CI: 1.28-2.04, I^2: 82.3%, *n*=12). In addition, patients with morbid obesity had extremely higher risk for hospitalization (OR: 3.08, 95% CI: 1.43-6.62, I^2: 92%, *n*=6). The overall analysis showed consistent results (OR: 2.00, 95% CI: 1.54-2.59, I^2: 89.7%, *n*=18). This result is presented in **Figure 3**. As for the subgroup analysis, the heterogeneity between the included studies did not show any decrease after subgroup analysis by different regions (**Supplement Figure 1**).

Obesity Aggravates Disease Severity and Increases the Risk of ICU Admission in Both Influenza and COVID-19

The severe outcomes consist of severe manifestations, admission to ICU, and requirement for mechanical supports. In this section, 12 influenza studies and 9 COVID-19 studies were included (11, 19–23, 25, 26, 28–31, 37, 39, 48, 52, 54, 56, 57, 61, 62). The pooled analysis results show that patients with obesity had an increased risk for severe outcome of both influenza (OR: 1.56, 95% CI: 1.28-1.90, I^2: 85.1%, *n*=12) and COVID-19 (OR: 2.07, 95% CI: 1.53-2.81, I^2: 70.9%, *n*=9). Compared with influenza, obesity patients with COVID-19 might present a higher risk for ICU admission and worse outcomes. This result is presented in **Figure 4**. To further explore the heterogeneity between the included studies, subgroup analysis was applied by different regions (**Supplement Figure 1**). The heterogeneity was significantly decreased in each subgroup of COVID-19 studies, indicating the region characteristic for the COVID-19 studies (**Figure 5**).

Obesity Increases the Mortality of Influenza but Has No Adverse Effect on the Mortality of COVID-19

In addition to the severe outcome of both diseases, we then detected the effects of obesity on the mortality of influenza and COVID-19. In this section, 7 studies on influenza and 4 studies on COVID-19 were included (24–27, 35, 41, 44, 45, 47, 49, 50). Our results show that patients with obesity presented higher mortality of influenza (OR: 1.99, 95% CI: 1.15-3.46, I^2: 82.7%, *n*=7). However, inconsistent with influenza studies, our results show no link between obesity and mortality of COVID-19 (OR: 1.57, 95% CI: 0.85-2.90, I^2: 57%, *n*=12). This result demonstrates that, although obesity could aggravate the severe outcome of COVID-19, obesity does not increase the death rate based on available studies. This result is presented in **Figure 6**. To further explore the heterogeneity of the included studies, subgroup analysis was applied by different regions (**Supplement Figure 1**).

Morbid Obesity Is Linked to Severity and Mortality of Both Influenza and COVID-19

To detect the effects of different obesity classes on the severity and mortality of influenza and COVID-19, we applied the

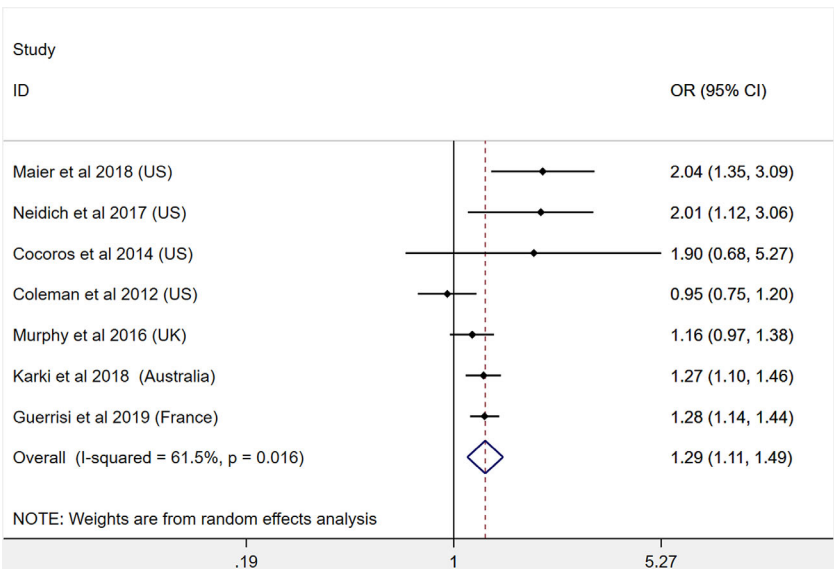

FIGURE 2 | Odds ratios for influenza infection in patients with obesity versus patients without obesity.

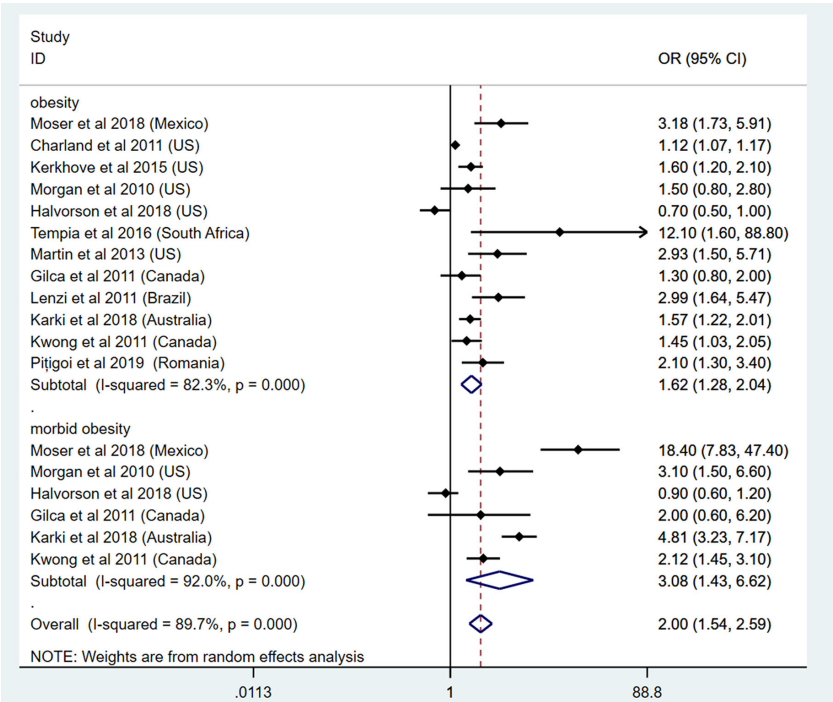

FIGURE 3 | Odds ratios for influenza-induced hospitalization in patients with obesity and morbid obesity.

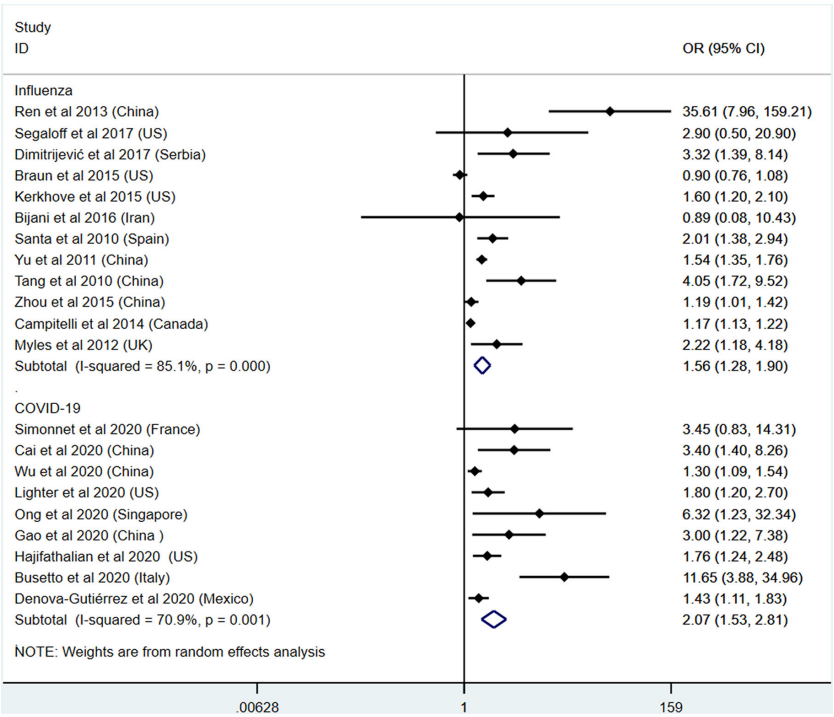

FIGURE 4 | Odds ratios for severe outcome or admission to ICU in patients with obesity and influenza or COVID-19.

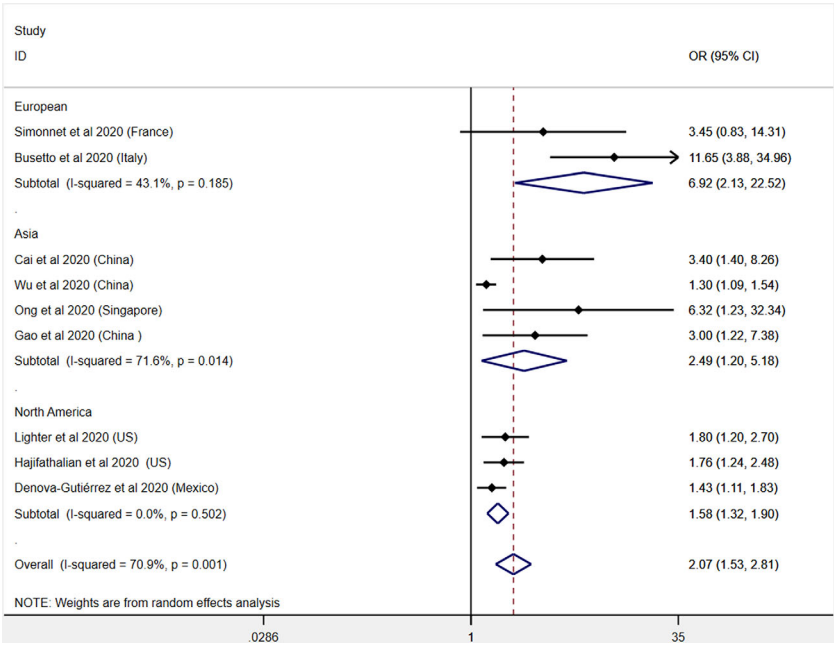

FIGURE 5 | Subgroup analysis (by region) on the effects of obesity on the severity and mortality of COVID-19.

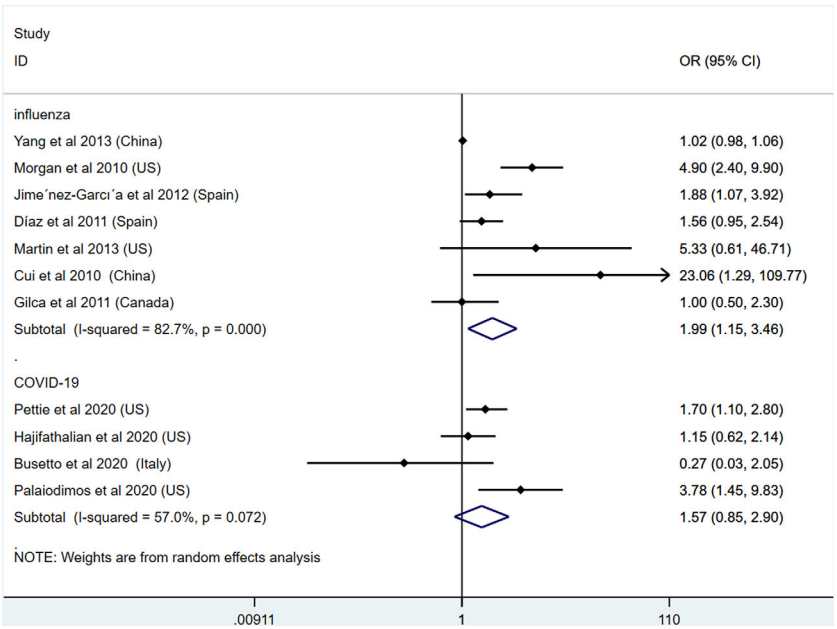

FIGURE 6 | Odds ratios for the mortality of patients with obesity and influenza or COVID-19.

meta-analysis on morbid obesity studies. In this section, 7 studies on influenza and 3 studies on COVID-19 were included (11, 21, 27, 31, 35, 41, 43, 50, 53, 57). The results show that morbid obesity is a significant predictor or risk factor for the severe outcomes and death of influenza (OR: 1.40, 95% CI: 1.10-1.79, I^2: 81.7%, *n*=7) and COVID-19 (OR: 3.76, 95% CI: 2.67-5.28, I^2: 0%, *n*=3). Compared with influenza, COVID-19 infection in patients with morbid obesity induced higher mortality. This result is presented in **Figure 7**. Due to the limited number of studies, subgroup analysis was not performed.

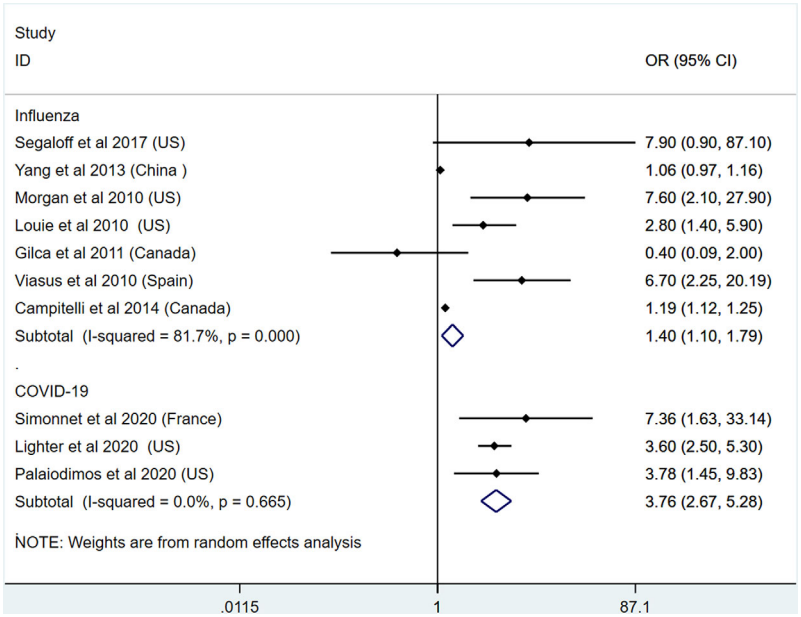

FIGURE 7 | Odds ratios for severe outcome and mortality in patients with morbid obesity and influenza or COVID-19.

Publication Bias Assessment and Sensitivity Assessment

Begg's tests were applied to evaluate publication bias. Because of the limited number of studies included in each section, no conclusive information was found after Begg's tests and sensitivity assessment. The results are shown in **Supplement Figure 1**.

DISCUSSION

The Influence of Obesity on the Severity and Mortality of Influenza and COVID-19

In the present meta-analysis, we systematically reviewed studies focusing on the influence of obesity on the severity and mortality of influenza and COVID-19. The results show obesity could increase the risk and severe outcomes of both influenza and COVID-19. Higher mortality of influenza was found in patients with obesity. Compared with influenza, COVID-19 patients with obesity present higher risk of severe outcomes and admission to ICU but not mortality. These results indicate the characteristic of COVID-19, which is higher infection rate and lower mortality. Thus, more strategies on weight control and physical regulation should be encouraged to decrease the risk of COVID-19 infection and its development.

The impact of different obesity classes on the severity and mortality of COVID-19 was unclear so far. In the present meta-analysis, we analyzed the relationship between morbid obesity and severity or mortality of COVID-19. The results show patients with morbid obesity have higher risk for the severe outcome of COVID-19. Different from patients with obesity, morbid obesity is linked with higher mortality. Thus, patients with morbid obesity should be given more attention, especially when they are infected with COVID-19. However, available evidence in this field is extremely limited. More studies should be conducted to explore the different impacts of obesity classes on the outcome of COVID-19.

Because the severe outcomes of COVID-19 are influenced by multiple factors (64), obesity might be one of the important influencing factors. Obesity could induce and aggravate the severe clinical manifestations of COVID-19 through influencing metabolism, inflammation, immune responses, and other pathways (65). At the same time, other factors, such as age, diabetes, hypertension, and cardiovascular diseases, can also cooperate with obesity to play a part in the development of COVID-19 (66). Thus, to discuss more influencing factors of severe COVID-19 is of great value.

In the present meta-analysis, we performed a subgroup analysis to discuss the heterogeneity of the included studies. Different regions were chosen as parameters to evaluate the heterogeneity. The results show significant decreased heterogeneity in the regions of Europe and North America in COVID-19 studies, indicating the existence of specific regional characteristics of COVID-19 (67). For the included studies on influenza, we did not find a valuable factor that could be used as a parameter to decrease the heterogeneity. Common parameters used for subgroup analysis, such as age and sex, are not suitable in the present studies. Because some studies did not provide enough information on these influencing factors, it is difficult to conduct subgroup analysis. Future studies should pay more attention to detecting more influencing factors on the severity and mortality of COVID-19.

Numerous studies have indicated the influenza vaccination could help to protect patients with obesity from the risk of influenza (68). However, its effect on COVID-19 is not clear so far, and available information is controversial. Because of the coming winter, it will be a great challenge for the global healthcare systems because the epidemic of influenza season is on the way. Due to the lack of a COVID-19 vaccine, the immunization for influenza might be helpful to prevent the epidemic wave of seasonal influenza and the co-circulation of both influenza and COVID-19 (69). A study from Zanettini et al. shows the influenza vaccination is helpful to reduce the mortality of COVID-19 in the elderly population (70). However, the effect of the influenza vaccination on other populations in preventing COVID-19 risk is quite limited and needs more evidence in this field (71). High influenza vaccine uptake rates in a well-matched season between the circulating influenza strains and the vaccine influenza strains could reduce the epidemiological noise of influenza during the COVID-19 epidemic. Thus, for patients with obesity, children, elders, pregnant women, and patients with chronic diseases, the influenza vaccination is highly advised.

Strengths

To our knowledge, this is the first meta-analysis to compare the effects of obesity on the severity and mortality of influenza and COVID-19. In addition to a rigorous methodology to conduct the meta-analysis, we also applied subgroup analysis, evaluation of publication bias, and sensitivity analysis. To further explore the risk-increasing effect of obesity specifically, we also performed analysis comparing BMI classes with each other.

Limitations

One significant limitation of the present study is that the majority of the included studies are retrospective studies. Because the pandemic of influenza and COVID-19 are not designed or planned, it is difficult to conduct the cohort study further. Besides this, the high heterogeneity of included studies does limit the ability to accurately estimate the size of the effects. Moreover, the BMI definition and the criteria for the admission to ICU might be different across different countries, which might influence the final results to some degree. For the assessment of publication bias, we tried to apply the Begg's test. Sensitivity analysis was also performed. However, due to the limited number of included studies and high heterogeneity, no conclusive information was provided.

Implications for Future Research

Based on available evidence, obesity or BMI should be considered as an important parameter for a COVID-19 risk assessment model. More studies in this field are encouraged to further examine whether obesity is an independent risk factor or predictor. Besides this, future studies should include detailed anthropometric parameters of patients with COVID-19. Moreover, basic research exploring the underlying mechanism of COVID-19 and obesity are urgently needed in the near future.

CONCLUSION

Consistent with influenza, COVID-19 patients with obesity and morbid obesity present with a higher risk for severe outcome and admission to ICU. No correlation was found between obesity and mortality of COVID-19. Thus, obesity or BMI should be recommended as important parameters for COVID-19 risk assessment. Special monitoring and earlier treatment should be implemented in COVID-19 patients with elevated BMI. Furthermore, prevention of obesity and regular physical activity are important methods to fight against the COVID-19 pandemic.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

XZ and GW designed the study. XZ and QH wrote the paper. XG and GH selected the paper. ZL and YL did the data extraction and analysis. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2020.595109/full#supplementary-material

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SYSTEMATIC REVIEW
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Prevalence of Obesity and Its Impact on Outcome in Patients With COVID-19: A Systematic Review and Meta-Analysis

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Background and Objective: Obesity has been reported as a risk factor for adverse outcomes in COVID-19. However, available studies presenting data on obesity prevalence in patients with COVID-19 have conflicting results. The objective of this systematic review and meta-analysis is to evaluate the prevalence of obesity in these patients and to stratify the estimates by illness severity.

Methods: We performed a literature search with the use of Medline/PubMed and Google Scholar database from December 1, 2019 to June 27, 2020 and systematically reviewed studies reporting the number of obese patients with real-time reverse transcriptase polymerase chain reaction (rRT-PCR)-confirmed SARS-CoV-2 infection.

Results: Nineteen studies were identified. The pooled obesity prevalence rates were 0.32 (95% CI: 0.24–0.41) in hospitalized patients, 0.41 (95% CI: 0.36–0.45) in patients admitted to intensive care unit, 0.43 (95% CI: 0.36–0.51) in patients needing invasive mechanic ventilation (IMV), and 0.33 (95% CI: 0.26–0.41) in those who died. Obesity was associated with a higher risk for hospitalization [Odds ratio (OR): 1.3, 95% CI: 1.00–1.69; I^2 52%, $p = 0.05$], ICU admission (OR: 1.51, 95% CI: 1.16–1.97; I^2 72%, $p = 0.002$), and IMV requirement (OR: 1.77, 95% CI: 1.34–2.35; I^2 0%, $p < 0.001$). The increase in risk of death did not reach statistical significance (OR: 1.28, 95% CI: 0.76–2.16, p = 0.35) which might be due to obesity survival paradox and/or unidentified factors.

Conclusions: Our data indicate that obese subjects may be at higher risk for serious illness if infected and obesity may play a role in the progression of COVID-19.

Keywords: obesity, body mass index, COVID-19, SARS-CoV-2, prognosis

INTRODUCTION

Coronavirus disease 19 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly spread and become a global pandemic, with more than 13 million confirmed cases resulting in over 585,000 confirmed deaths as of July 17, 2020 (1). Clinical manifestations of COVID-19 vary in a broad spectrum, ranging from asymptomatic or mild infection to life-threatening acute respiratory distress syndrome and multiorgan failure. Older age and the presence of comorbidities including hypertension (HT), type 2 diabetes (T2DM), and cardiovascular disease (CVD) seems to be associated with a more severe course of COVID-19 (2–4).

Obesity represents a major and urgent global health problem (5). It tends to increase with increasing age and is a known risk factor for the abovementioned comorbidities identified as predisposing factors for adverse outcomes in COVID-19 (5). Although there are several reports evaluating the burden of obesity on the clinical course of COVID-19, it has not been fully documented whether people living with obesity have a higher risk of getting COVID-19. Most of the earlier studies on COVID-19 did not provide information about body mass index (BMI) or other measures of adiposity of the patients (2–4, 6–8). Other studies which present data on obesity prevalence in patients with COVID-19 have conflicting results, reporting similar, lower, or higher rates of obesity compared to general population (9–12). The aim of this systematic review and meta-analysis was, therefore, to evaluate the prevalence of obesity in patients with COVID-19 and to stratify the estimates by illness severity.

MATERIAL AND METHODS

Protocol and Registration

We report this systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (13). The review protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42020199145).

Literature Search Strategy

The following medical subject titles, key words, and their combinations were used to search on Medline/PubMed and Google Scholar database for retrospective cohorts, cross-sectional and longitudinal studies including gray literature as pre-prints, conference papers, and reports which were accessed online between December 1, 2019 and June 27, 2020: 2019 nCoV, SARS-CoV-2, COVID-19, coronavirus disease 2019, obesity, body mass index, BMI, clinical features, risk factors. Reference lists of relevant articles were also screened to capture other potentially eligible studies. The literature search was concluded by June 27, 2020 and only reports written in English language were assessed.

Eligibility Criteria and Study Selection

The primary outcome measure was to evaluate the overall prevalence of obesity in COVID-19 infection and stratify the estimates by disease severity and geographic region. Studies reporting the number of obese patients with real-time reverse transcriptase polymerase chain reaction (rRT-PCR)-confirmed SARS-CoV-2 infection at least in two of the following groups were included in the meta-analysis: all cases, hospitalized patients, patients admitted to an intensive care unit (ICU), patients needing invasive mechanical ventilation (IMV), and patients who died. Duplicate publications, reviews, perspectives and letters not presenting original data, studies lacking information on BMI or obesity were excluded, as well as studies including any intervention, pediatric population, patients with any specific condition (e.g., malnutrition, pregnancy), or fewer than 50 patients. Among studies involving the same patient groups, the largest cohort was selected. Studies that applied a BMI cut-off value other than ≥30 kg/m^2 for obesity were also excluded; however, studies defining obesity as BMI ≥28 kg/m^2 in Asian Pacific populations were eligible. To avoid selection bias, two reviewers (NH and ND) identified and selected articles that met the inclusion criteria. The full text of each study was assessed independently by these reviewers and any disagreement among them was discussed and resolved by consensus or discussion with a third reviewer (BY).

Data Extraction and Quality Assessment

Information on first author, publication year, country, study design, time and duration of follow-up, total sample size, gender composition, obesity criteria, numbers reported for obesity at different outcome levels were extracted from all included studies. The methodological quality of studies was evaluated through the National Heart, Lung, and Blood Institute Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (14). Data extraction and quality assessment was conducted independently by two reviewers (NH and NE). Disagreements were resolved by joint discussion or by the third reviewer (BY).

Statistical Analyses

All statistical analyses were done through metaprop and metabin commands in meta package version 4.13 in R software ver. 3.6.3. Meta-analysis of obesity prevalence was performed through the DerSimonian-Laird, random-effects method, to account for a high heterogeneity with 95% confidence interval. The Freeman–Tukey double arcsine transformation was applied for prevalences to normalize and stabilize the variance of the sampling distribution. Higgins' I^2 was used to assess heterogeneity with significance set at >75%.

RESULTS

Literature Search

Initial search strategy identified a total of 3,883 records, of which 2,470 remained after the removal of duplicates. After assessment of titles and abstracts of these records, 72 articles were found to be potentially relevant. Full texts of these articles were reviewed and finally, 19 studies (9–12, 15–29) that met the inclusion criteria were included in this systematic review and meta-analysis. A PRISMA study flow diagram of this search and selection process is shown in **Figure 1**.

Study Characteristics

The main characteristics of the included studies are summarized in **Table 1**. The results of the risk of bias assessment of individual studies are shown in **Table 2**. All included studies were observational cohort studies. Their sample size ranged from 50 to 51,633, describing a total of 68,214 patients having confirmed COVID-19. The research time period of the included studies ranged from January 11 to May 18, 2020. Out of 19 studies, eight were conducted in the U.S., two in Mexico, six in Europe, two in China, and one in Kuwait respectively.

Five studies with 58,419 patients provided data for the combined analysis (inpatient + outpatient), 15 studies with 7,758 patients reported on hospitalization, 17 studies with 10,391 patients reported on ICU admission, and 9 studies with 5,107 patients reported on IMV requirement.

Anthropometric measurements were performed at hospital admission in only two studies (16, 22). In the rest, data from previous medical records were used to define obesity. Out of 19 studies, five had missing BMI data of the patients (9, 11, 20, 21, 29). The proportion of patients without BMI data ranged from 4.5 to 45.3% in these studies.

Prevalence of Obesity in Patients With COVID-19

The pooled obesity prevalence rate in all cases (admitted + non-admitted) with COVID-19 was 0.34 [95% confidence interval (CI): 0.22–0.46] as presented in **Figure 2A**. The pooled obesity prevalence rate was 0.35 (95% CI: 0.22–0.49) in non-admitted patients (**Figure 2B**). There was significant heterogeneity among studies. I^2 estimates were 100 and 95%, respectively ($p < 0.01$ for both).

The pooled obesity prevalence rates were 0.32 (95% CI: 0.24–0.41) in hospitalized patients (**Figure 3**), 0.30 (95% CI: 0.21–0.39) in patients admitted to non-critical care wards (**Figure 4**), 0.41 (95% CI: 0.36–0.45) in patients admitted to an ICU (**Figure 5**), 0.43 (95% CI: 0.36–0.51) in patients with IMV requirement (**Figure 6**), and 0.33 (95% CI: 0.26–0.41) in those who died (**Figure 7**) respectively. Studies from the U.S., Europe, and Asia were included in these analyses. All rates were significantly higher than the 13.2% worldwide prevalence of obesity (30). I^2 estimates were 98, 98, 92, 94, and 94%, indicating significant heterogeneity among studies (all $p < 0.01$).

Subgroup analysis according to the geographic region were as follows:

In the U.S., the prevalence rates of obesity were 0.45 (95% CI: 0.38–0.52) in hospitalized patients (**Figure 3**), 0.42 (95% CI: 0.34–0.50) in patients admitted to non-critical care wards (**Figure 4**), 0.48 (95% CI: 0.40–0.57) in patients admitted to ICU (**Figure 5**), 0.56 (95% CI: 0.45–0.67) in patients with IMV requirement (**Figure 6**), and 0.40 (95% CI: 0.11–0.73) in those who died (**Figure 7**) respectively. Obesity rate was higher only in patients who required IMV compared to the background general population prevalence of obesity in the U.S., which is 42.4% (31).

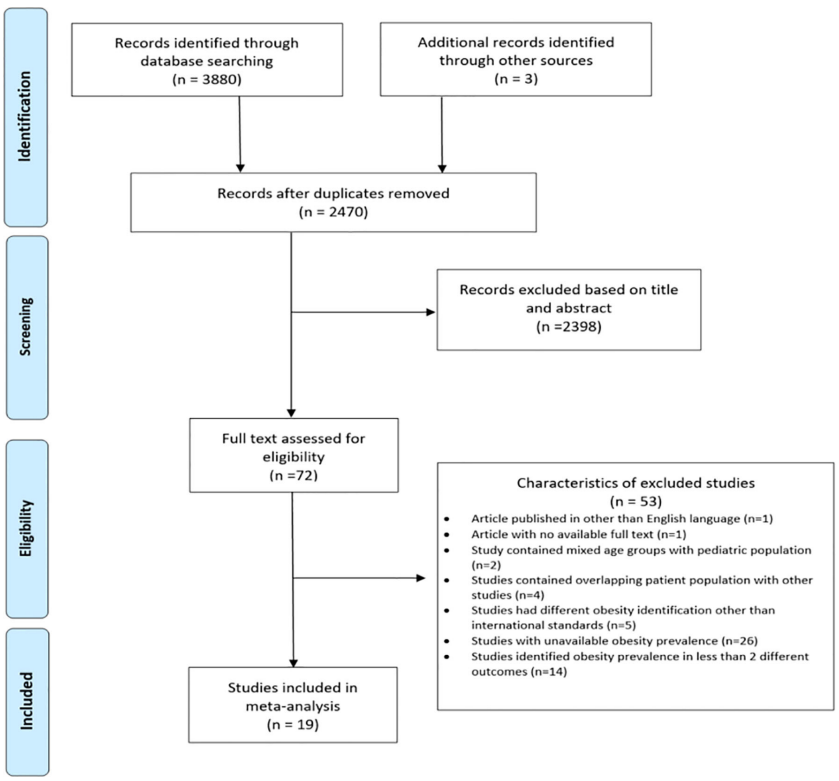

FIGURE 1 | PRISMA study flow diagram of the search and selection process.

TABLE 1 | Characteristics of the included studies.

Author	Country	Design	Period	Sample size/male (%)	Age*	Ethnicity	Obesity, n (%)	Missing BMI data (%)	Outcome
North America									
Argenziano et al.	U.S.	Retrospective	March 1–April 5, 2020	1,000/59.6	63 (50–75)	White 18%, Hispanic 31%, Black 22%, Asian 2%, other 27%	352 (41.9)	15.9	Hospitalization, ICU admission, IMV, mortality
Ebinger et al.	U.S.	Retrospective	March 8–21,2020	442/57.9	52.7 ± 19.7	White 69%, Black 14%, Asian 8%, other 9%	71 (16)	0	Clinical illness severity
Hajifathalian et al.	U.S.	Retrospective	March 4–April 9, 2020	770/60.8	63.5 ± 16.7	White 41%, Black 14%, Asian 16%, other 29%	277 (36)	0	ICU admission, IMV, mortality
Hur et al.	U.S.	Retrospective	March 1–April 8, 2020	486/55.8	59 (19–101)	White 39%, Hispanic 23%, Black 23%, Asian 4%, other 4%	259 (53.3)	0	IMV
Kaligeros et al.	U.S.	Retrospective	February 17–April 5, 2020	103/61.2	60 (50–72)	White 41%, Hispanic 23%, Black 34%, Asian 2%,	49 (47.5)	0	ICU admission, IMV
Petrilli et al.	U.S.	Prospective	March 1–April 8, 2020	5,279/49.5	54 (38–66)	White 40%, Hispanic 27%, Black 17%, Asian 8%, other 8%	1865 (35.3)	4.5	Hospitalization, critical illness, mortality
Pettit et al.	U.S.	Prospective	March 1–April 18, 2020	238/47.5	58.5 ± 17	White 5%, Hispanic 1%, Black 91%, Asian 1%, other 3%	146 (61.3)	0	Length of stay, IMV, ICU admission, mortality
Suleyman e al.	U.S.	Retrospective	March 9–27, 2020	463/44.1	57.5 ± 16.8	Black 72%, other 28%	262 (57.6)	0	Hospitalization, ICU admission, IMV
Bello-Chavolla et al.	Mexico	Retrospective	Until May 18, 2020	51,633/57.7	46.7 ± 15.8	NR	10708 (20.7)	0	Hospitalization, ICU admission, IMV, mortality
Ortiz-Brizuela et al.	Mexico	Prospective	February 26–April 11, 2020	309/60.7	43 (33–54)	NR	67 (39.6)	45.3	Hospitalization, ICU admission
Asia									
Al-Sabah et al.	Kuwait	Retrospective	February 24–April 7, 2020	1,158/81.6	40.5 (32–52)	Indian 47.5%, Kuwaiti 26%, other 26.5	148 (20.4)	37.2	ICU admission
Cai et al.	China	Retrospective	January 11–February 21, 2020	383/47.8	Range 28–62	NR	41 (10.7)	0	Clinical illness severity, mortality
Hu et al.	China	Retrospective	January 8–February 20, 2020	323/51.4	61 (23–91)	NR	13 (4)	0	Clinical illness severity, unfavorable outcome
Europe									
Caussy et al.	France	Retrospective	February 27–April 8, 2020	291/NR	NR	NR	96 (33)	0	IMV
Dreher et al.	Germany	Retrospective	February–March 2020	50/66	65 (58–76)	NR	17 (34)	0	ARDS, ICU admission, mortality
Giacomelli et al.	Italy	Prospective	February 21–March 19, 2020	233/69.1	61 (50–72)	NR	38 (16.3)	0	Mortality
ICNARC	UK	Registry-based cohort	March 1–April 19, 2020	6720/71.8	60 (52–68)	White 72%, Black 12%, Asian 17%, other 9%	2310 (38.5)	10.6	Hospitalization, ICU admission, IMV, mortality
Rottoli et al.	Italy	Retrospective	February 28–March 28, 2020	296/65.2	Obese 68.3 ± 13.5, non-obese 63 ± 16.8	NR	70 (23.6)	0	Hospitalization, discharge, respiratory failure, ICU admission, mortality
Simonnet et al.	France	Retrospective	February 27–April 5, 2020	124/73	60 (51-70)	NR	59 (47.6)	0	IMV

ARDS, acute respiratory distress syndrome; BMI, body mass index; ICNARC, Intensive Care & National Audit Research Center; ICU, intensive care unit; IMV, invasive mechanical ventilation; NR, not reported; UK, United Kingdom; U.S., United States.
**Data are reported as median (interquartile range) or mean ± standard deviation.*

TABLE 2 | Quality assessment of enrolled studies.

Study	Question number[a]														Quality
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Argenziano et al.	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	No	Yes	No	NA	No	Good
Ebinger et al.	Yes	Yes	CD	No	No	Yes	No	No	Yes	No	Yes	No	NA	Yes	Fair
Hajifathalian et al.	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	No	Yes	No	NA	Yes	Good
Hur et al.	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	No	NA	Yes	Good
Kaligeros et al.	Yes	Yes	CD	No	No	Yes	Yes	Yes	Yes	No	Yes	No	NA	Yes	Good
Petrilli et al.	Yes	Yes	CD	No	No	Yes	Yes	Yes	Yes	No	Yes	No	CD	Yes	Good
Pettit et al.	Yes	Yes	CD	No	No	Yes	Yes	Yes	Yes	No	Yes	No	NA	Yes	Good
Suleyman et al.	Yes	Yes	CD	No	No	Yes	No	Yes	Yes	No	Yes	No	NA	Yes	Good
Ortiz-Brizuela et al.	Yes	Yes	Yes	CD	No	Yes	Yes	No	Yes	No	Yes	No	NA	No	Good
Bello-Chavolla et al.	Yes	Yes	Yes	CD	No	Yes	CD	No	Yes	No	Yes	No	CD	Yes	Good
Al-Sabah et al.	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	No	NA	Yes	Good
Hu et al.	Yes	Yes	CD	CD	No	Yes	Yes	No	Yes	No	No	No	NA	No	Fair
Cai et al.	Yes	Yes	CD	CD	No	Yes	Yes	No	Yes	No	Yes	No	NA	Yes	Good
Caussy et al.	Yes	Yes	CD	CD	No	Yes	Yes	Yes	Yes	No	Yes	No	NA	No	Good
Dreher et al.	Yes	Yes	CD	CD	No	Yes	CD	No	Yes	No	Yes	No	NA	No	Fair
Giacomelli et al.	Yes	Yes	CD	CD	No	Yes	No	No	Yes	No	Yes	No	CD	Yes	Fair
ICNARC	No	Yes	Yes	No	No	Yes	Yes	No	Yes	No	Yes	No	CD	No	Fair
Rottoli et al.	Yes	Yes	CD	CD	No	Yes	Yes	No	Yes	No	Yes	No	NA	Yes	Good
Simonnet et al.	Yes	Yes	CD	CD	No	Yes	Yes	Yes	Yes	No	Yes	No	NA	No	Good

[a]*The questions are those of the National Heart, Lung, and Blood Institute Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (14).*

#1. Was the research question or objective in this paper clearly stated?

#2. Was the study population clearly specified and defined?

#3. Was the participation rate of eligible persons at least 50%?

#4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?

#5. Was a sample size justification, power description, or variance and effect estimates provided?

#6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?

#7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?

#8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?

#9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?

#10. Was the exposure(s) assessed more than once over time?

#11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?

#12. Were the outcome assessors blinded to the exposure status of participants?

#13. Was loss to follow-up after baseline 20% or less?

#14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

CD, cannot determine; NA, not applicable.

In Europe, the prevalence rates of obesity were 0.23 (95% CI: 0.15–0.31) in hospitalized patients (**Figure 3**), 0.18 (95% CI: 0.14–0.23) in patients admitted to non-critical care wards (**Figure 4**), 0.39 (95% CI: 0.35–0.44) in patients admitted to ICU (**Figure 5**), 0.43 (95% CI: 0.36–0.51) in patients with IMV requirement (**Figure 6**), and 0.37 (95% CI: 0.32–0.42) in those who died (**Figure 7**) respectively. Prevalence rates of obesity in patients admitted to ICU, in patients needing IMV, and in those who died were significantly higher than the obesity prevalence of the countries where the included studies were conducted, which are 27.8% in UK, 22.3% in Germany, 21.6% in France, and 19.9% in Italy (32).

In Asia, the prevalence rates of obesity were 0.11 (95% CI: 0.03–0.23) in hospitalized patients (**Figure 3**), 0.11 (95% CI: 0.03–0.22) in patients admitted to non-critical care wards (**Figure 4**), 0.19 (95% CI: 0.06–0.36) in patients admitted to ICU (**Figure 5**), 0.14 (95% CI: 0.04–0.28) in patients with IMV requirement (**Figure 6**), and 0.33 (95% CI: 0.00–0.94) in those who died (**Figure 7**) respectively. Among the included studies, one was conducted in Kuwait (approximately 48% of included patients were Indian), two in China. Compared to the general obesity prevalences, which are 6.2% in China, 3.9% in India, and 37.9% in Kuwait (32), these rates are not significantly increased. However, the wide confidence intervals should be considered while interpreting these results.

Association Between Obesity and Disease Severity

Our pooled analyses showed that COVID-19 patients with obesity had a borderline higher risk for hospitalization [Odds ratio (OR):1.3, 95% CI: 1.00–1.69, p = 0.05; I^2 52%, $p_{heterogeneity}$ = 0.08] (**Figure 8**). Obesity was related to significantly higher risk for ICU admission (OR:1.51, 95% CI: 1.16–1.97, p = 0.002; I^2 72%, $p_{heterogeneity}$ < 0.01) (**Figure 9**), and IMV requirement (OR:1.77, 95% CI: 1.34–2.35, p < 0.001; I^2 0%, $p_{heterogeneity}$ = 0.64) (**Figure 10**). However, obesity was not associated with increased risk for death in patients with COVID-19 (OR:1.28, 95% CI: 0.76–2.16, p = 0.35; I^2 80%, $p_{heterogeneity}$ < 0.01) (**Figure 11**).

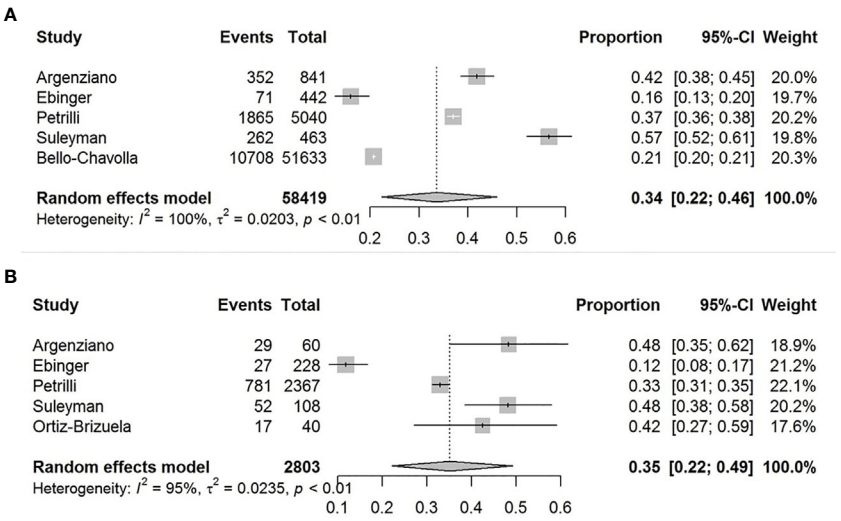

FIGURE 2 | Forest-plots showing the prevalence rates of obesity in all cases **(A)** and in non-admitted patients with COVID-19 **(B)**.

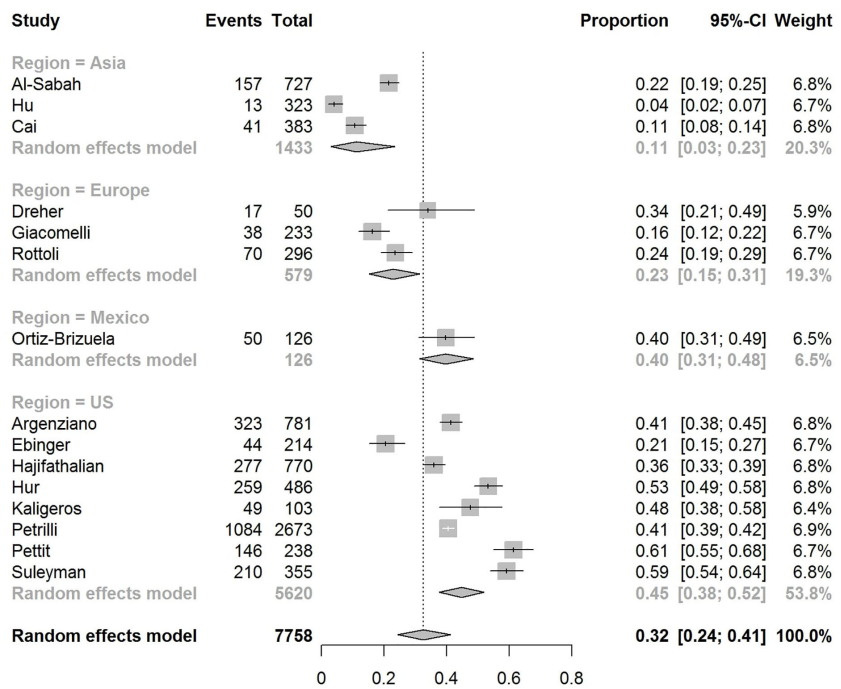

FIGURE 3 | Forest-plot showing the prevalence rate of obesity in hospitalized patients with COVID-19.

Publication Bias

The funnel-plot analysis for the association between obesity and risk of admission to ICU showed an asymmetrical shape (**Figure 12**), indicating the possibility of publication bias. Funnel-plot analysis was not performed for obesity and risk of hospitalization, IMV, and death because the number of included studies were less than 10.

DISCUSSION

In this systematic review and meta-analysis, we found that the pooled obesity prevalence rates were higher in patients with COVID-19 who were hospitalized, admitted to an ICU, or in need for IMV. Our pooled analysis revealed 1.3 times increased risk for hospitalization, 1.5 times increased risk for ICU

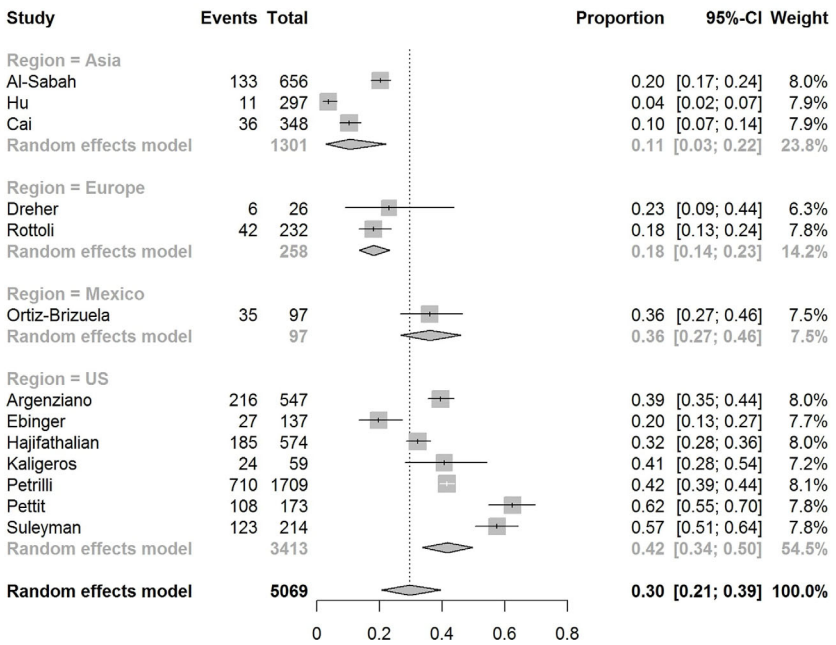

FIGURE 4 | Forest-plot showing the prevalence rate of obesity in patients with COVID-19 admitted to non-critical care wards.

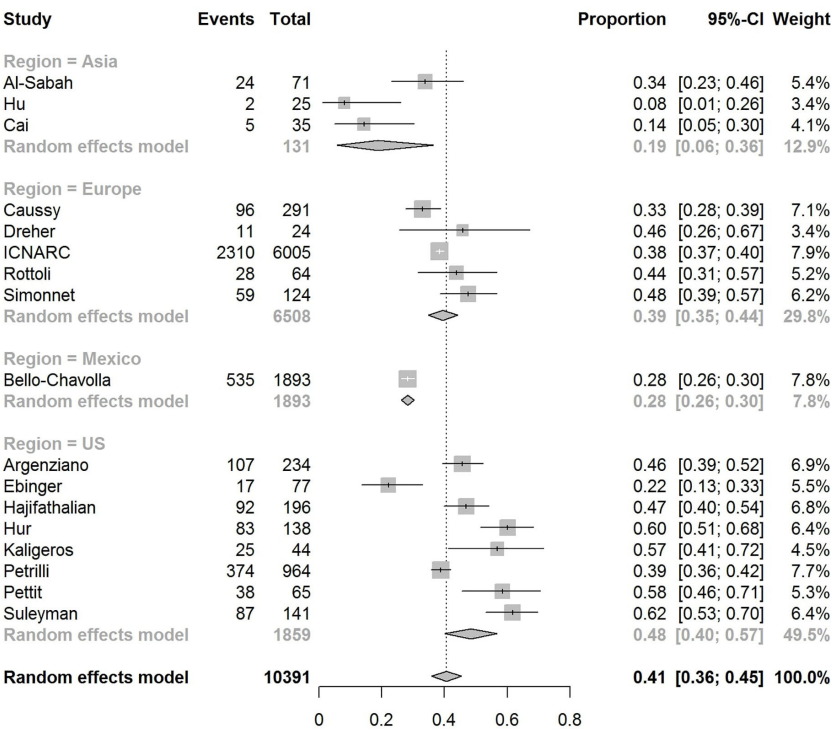

FIGURE 5 | Forest-plot showing the prevalence rate of obesity in patients with CVOID-19 admitted to intensive care unit (ICU).

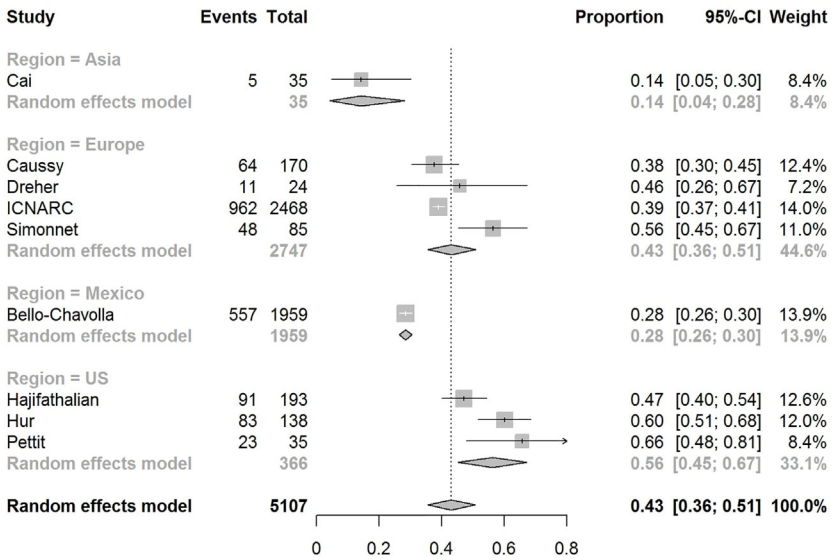

FIGURE 6 | Forest-plot showing the prevalence rate of obesity in patients with COVID-19 needing invasive mechanical ventilation (IMV).

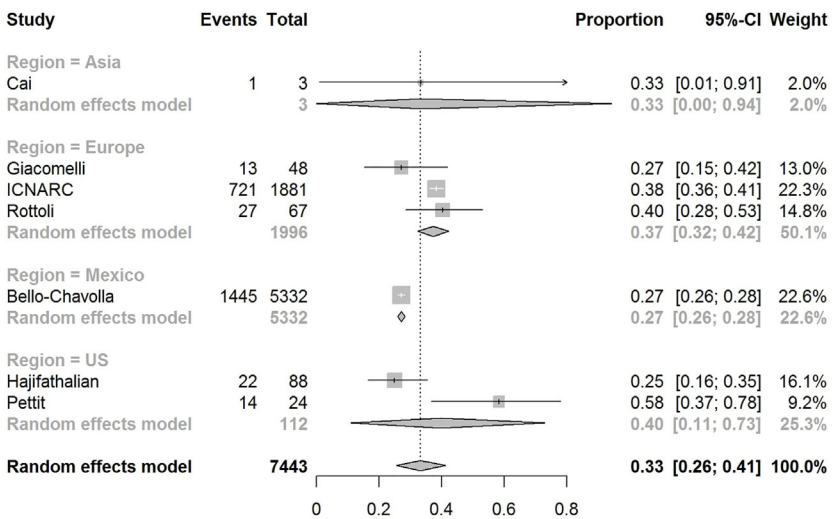

FIGURE 7 | Forest-plot showing the prevalence rate of obesity in deceased patients with COVID-19.

admission, and approximately 1.8 times increased risk for IMV requirement among patients with obesity compared to patients without obesity.

In the fast-moving field of COVID-19, other meta-analyses have also assessed the relationship between this disorder and obesity. Using various inclusion criteria and definitions for the outcome variables, most of these meta-analyses indicated that in patients with COVID-19, obesity is significantly related to increased risk of severe disease and composite poor outcomes with reported ORs varying from 1.39 to 2.35 (33–41). A few meta-analyses presenting separate analyses for different outcomes reported increased risk of hospitalization with ORs varying from 1.4 to 2.13 (34, 42, 43), ICU admission with ORs varying from 1.21 to 1.74 (34, 43, 44), and IMV requirement with ORs varying from 1.66 to 2.29 (34, 36, 42–44) in obese patients with COVID-19. Our findings are in line with these reports in that we found 1.3 times higher risk for hospitalization, 1.51 times higher risk for ICU admission, and 1.77 times higher risk for IMV in obese patients with COVID-19 suggesting that obesity increases the severity of this disorder.

Prevalence of obesity varies across geographic region and obesity prevalence observed in hospitalized patients or in ICUs may depend on the local prevalence of obesity. Thus, we performed subgroup analysis by geographic region and found

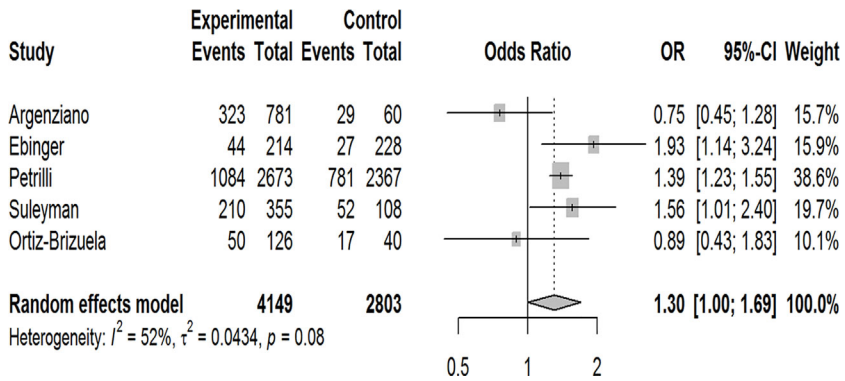

FIGURE 8 | Forest-plot showing the association between obesity and hospitalization in patients with COVID-19.

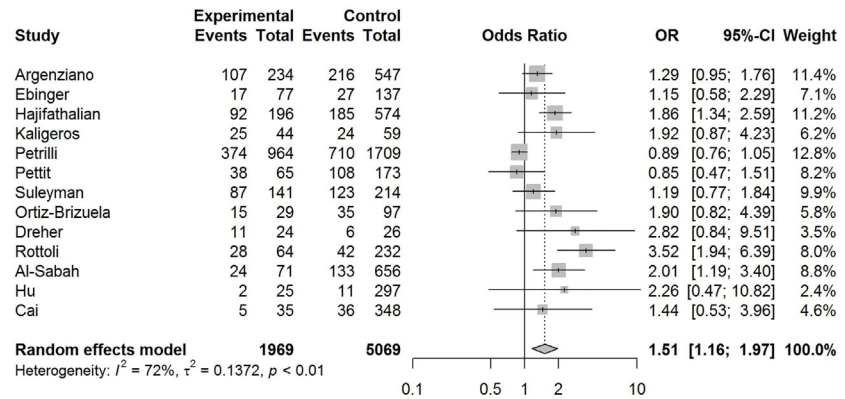

FIGURE 9 | Forest-plot showing the association between obesity and admission to intensive care unit (ICU) in patients with COVID-19.

that in European countries, obesity was more common in patients with COVID-19 who needed ICU admission, IMV, or in those who died compared to background population. On the other hand, obesity rates only in COVID-19 patients requiring IMV exceeded the background general population prevalence of obesity in the U.S. In addition to the differences of obesity in the general population, the inconsistencies between Europe and the U.S. regarding the measured outcomes may be related with missing data, confounding factors, and variations in reporting methods and management protocols.

In our study, pooled prevalence rates of obesity seem to increase progressively with increasing disease severity, being highest in patients with IMV requirement. However, pooled obesity prevalence rate in patients who died was lower than that of those admitted to ICU or those with IMV requirement. Similar results were obtained in subgroup analysis by geographic region in the U.S. and Europe. Accordingly, our results showed that risk of death due to COVID-19 was not significantly increased in patients with obesity (OR:1.28, 95% CI: 0.76–2.16, p = 0.35). Consistent with our results, another meta-analysis including 34 studies from 9 different countries reported that obesity was significantly related to the increased risk of IMV during ICU admission, but not associated with excess mortality (OR: 1.15, 95% CI: 0.98–1.34) (36). These observations may be in agreement with obesity survival paradox. That is, despite the increased risk of pneumonia, pneumonia mortality might be lower in overweight and moderate obese individuals compared to those with normal BMI, as shown in a previous meta-analysis (45). Several hypothetical explanations have been proposed for this inverse association between obesity and risk of mortality, including clinicians' lower threshold for ICU admission of obese patients, confounding, reverse causality, secretion of immunomodulatory substances by adipocytes (e.g., leptin, interleukin-10, and soluble TNF-α receptor) that may attenuate the inflammatory response, and the increased metabolic reserve provided by excess fat stores and lean body mass in obese patients that may counteract the increased catabolic stress and improve survival during critical illness (46). However, during the 2009 H1N1 pandemic, severe obesity (BMI ≥40 kg/m^2) was identified as an independent risk factor for admission to ICU and death (47). Similarly, obesity has been reported to be associated with increased mortality due to COVID-19 in some of the very recently published meta-analyses

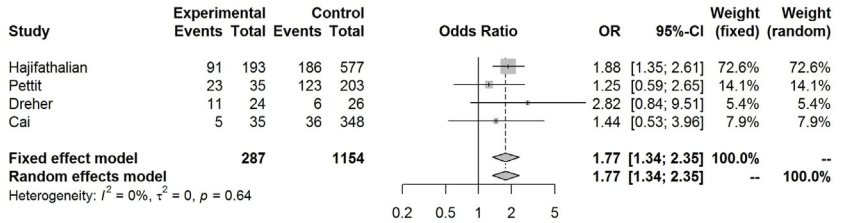

FIGURE 10 | Forest-plot showing the association between obesity and invasive mechanical ventilation (IMV) requirement in patients with COVID-19.

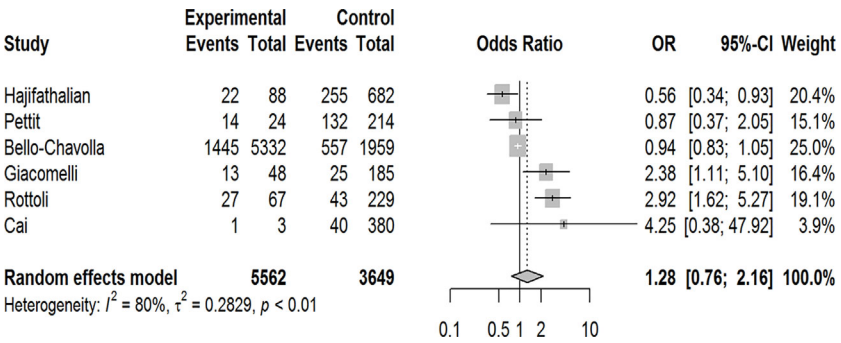

FIGURE 11 | Forest-plot showing the association between obesity and death in patients with COVID-19.

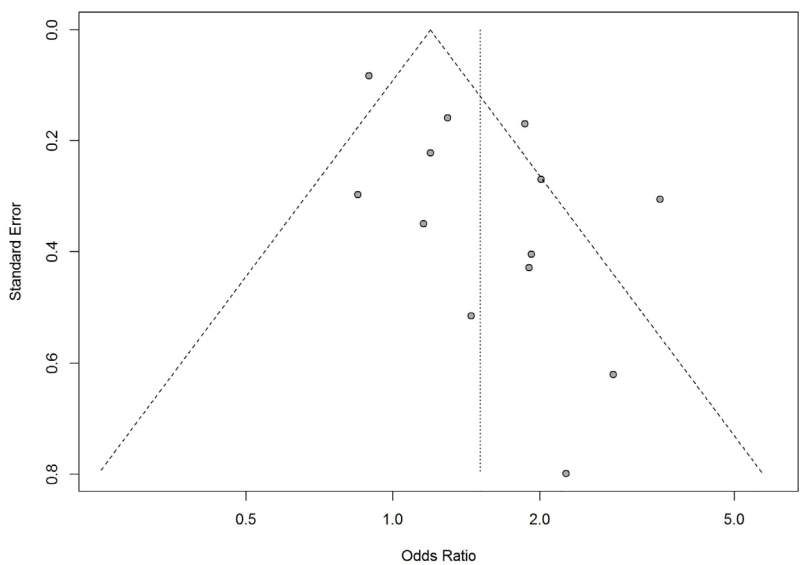

FIGURE 12 | Funnel plot analysis for obesity and admission to intensive care unit (ICU).

with ORs varying from 1.37 to 3.68 (34, 35, 42, 43, 48) challenging the obesity survival paradox in COVID-19 in contrast to our results. The differences in the study populations and the discrepancies in the cut off values for BMI to define obesity among the included studies as well as the differences between healthcare systems, testing strategies, and indications for hospitalization, ICU admission, or IMV might explain these inconsistencies.

In the present study, we found that the pooled prevalence of obesity in all cases (admitted + non-admitted) with COVID-19 was

34% (22–46%). Among five studies that included both inpatient and outpatient confirmed COVID-19 cases, four were conducted in the U.S (9–12). and one in Mexico (19). Compared with the obesity prevalence in the general population of the U.S., this result suggests that obesity may not be associated with a higher test positivity for COVID-19. This contradicts the result of a study conducted in the United Kingdom (UK) (49). In this study, Yates et al., used UK Biobank data, in which 882 of 2,494 tests were positive for COVID-19. Although limited by possible selection bias, authors reported that both BMI and waist circumference were associated with testing positive for COVID-19 in a dose-response fashion. After adjustment for possible confounders, the OR for overweight, obese, and severe obese subjects was 1.31, 1.55, and 1.57, respectively, compared to those with healthy weight (49).

Overall, our data indicate that obese subjects may be at higher risk for serious illness if infected and obesity may play a role in the progression of COVID-19. Several mechanisms have been proposed about the association between obesity and poor COVID-19 outcomes (**Figure 13**). Higher expression of angiotensin-converting enzyme 2 (ACE-2; an important functional receptor for SARS-CoV-2 invasion) in adipose tissue may lead to prolonged viral shedding and exposure in patients with obesity, increasing the susceptibility to SARS-CoV-2 infection and the risk of disease aggravation (35). Obesity driven chronic inflammation, aberrant cytokine activation, decreased adiponectin and increased leptin secretions, and dysfunction of innate and adaptive immunity may contribute to worse clinical outcomes in patients with COVID-19 (50–52). Obesity is also associated with hypercoagulability and increased risk of thrombosis (53), which seems to be one of the important factors leading to a more severe clinical course in infected patients. Moreover, obesity, particularly when it is severe, is associated with significant changes in pulmonary mechanics and respiratory muscle performance, which predispose patients to develop respiratory failure in the case of lung infection (54). Although these are plausible mechanisms, future studies are needed to prove that they are actually linked to COVID-19 outcomes.

This study, with its large sample size and inclusion of studies from different regions worldwide, presents further evidence about the relationship between obesity and COVID-19 outcomes. However, several limitations exist in this work. There was a significant heterogeneity among studies, probably due to the differences in sample sizes and baseline characteristics of the patients. Most included studies were retrospective and analyzed data of patients who were hospitalized, leading to a selection bias towards those with a more severe disease. Sampling and testing strategies, indications for hospitalization or admission to ICU, or indications for IMV were not adequately defined in most reports. Moreover, studies included in this analysis were short-term observational studies; outcomes could be different with a longer time of observation. Anthropometric measurements were not performed in most studies; using data from previous medical records may have led to incorrect BMI assessment and categorization. Besides, a substantial proportion of patients had missing BMI data in some studies. Furthermore, confounding factors including age, sex, ethnicity, deprivation, and comorbidities were not addressed in some reports. Given that obesity is related to these factors, it is difficult to interpret the

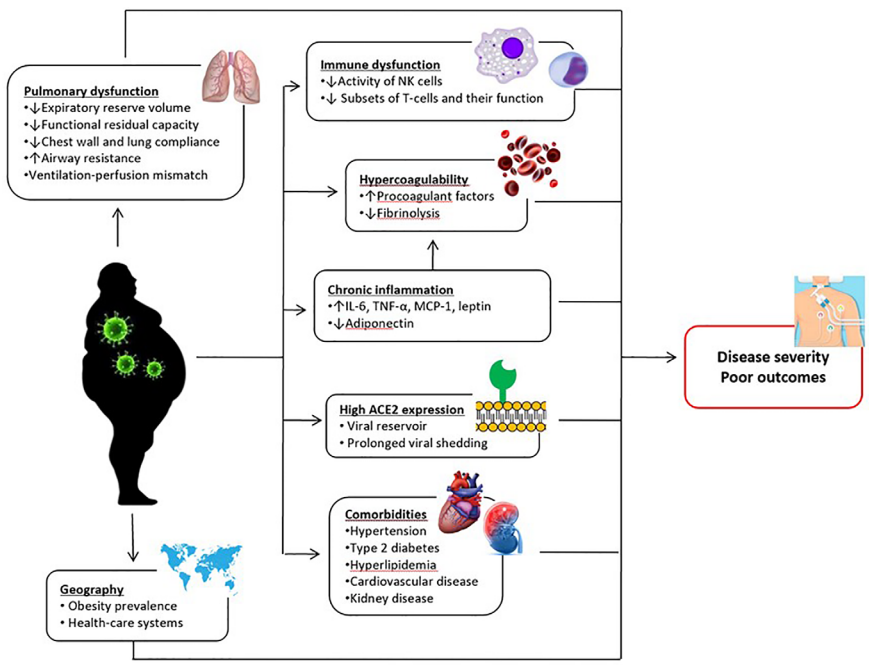

FIGURE 13 | Postulated mechanisms underlying the relationship between obesity and poor COVID-19 outcomes. IL-6, interleukin-6; MCP-1, monocyte chemoattractant protein-1; NK, natural killer; TNF-α, tumor necrosis factor alpha.

potential role of obesity as an independent risk factor for poor COVID-19 outcomes. It should also be kept in mind that variations in treatment protocols over time across studies may have affected reported outcomes. Lastly, due to the small number of studies in subgroup analyses, strong conclusions could not be drawn on geographic variation of observations regarding the association between obesity and outcomes of COVID-19.

Despite its limitations, available data and results of our study consistently suggest that people living with obesity are at increased risk of poor COVID-19 outcomes. Thus, measurement of anthropometric parameters should be routinely performed in patients tested positive for COVID-19 as a part of risk assessment. Obese patients with COVID-19 should be followed and treated as a higher risk population. Testing priority, close monitoring, and earlier intensive treatment may be considered in these patients to avoid unfavorable clinical outcomes.

Special attention to obesity is also important in the aspect of disease prevention. Restriction on leaving home for several weeks was introduced in many countries as a measure to reduce rapid transmission of COVID-19. This may result in physical inactivity and, in long term, increase the susceptibility of people to develop obesity (55). Eventually, this may increase the number of individuals who will likely have a more severe course when infected with COVID-19. Thus, people should be encouraged to increase physical activity and gain healthy eating habits during pandemic.

In conclusion, our systematic review and meta-analysis indicated that the prevalence of obesity is higher in patients with severe COVID-19 and obesity is associated with increased risk for hospitalization, ICU admission, and IMV. However, abovementioned limitations of the included studies should be kept in mind while interpreting the results. Prospective cohort studies with a large sample size and addressing all potential confounding factors including age, sex, ethnicity, deprivation, and comorbidities are needed to clarify the independent role of obesity on the risk of COVID-19 and its clinical course. The pathogenesis of COVID-19 in patients with obesity should also be investigated to identify the causal mechanisms and interfere with prophylactic and therapeutic measures.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

BY supervised the project. BY and NE conceptualized the meta-analysis protocol. NH, NE, and BY screened the literature search results and assessed for the eligibility criteria. EK quantitatively synthesized the results of involved studies. NH and NE produced original form of the manuscript. BY reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

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Poor Metabolic Health Increases COVID-19-Related Mortality in the UK Biobank Sample

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Previous studies link obesity and components of metabolic health, such as hypertension or inflammation, to increased hospitalizations and mortality of patients with COVID-19. Here, in two overlapping samples of over 1,000 individuals from the UK Biobank we investigate whether metabolic health as measured by waist circumference, dyslipidemia, hypertension, type 2 diabetes, and systemic inflammation is related to increased COVID-19 infection and mortality rate. Using logistic regression and controlling for confounding variables such as socioeconomic status, age, sex or ethnicity, we find that individuals with worse metabolic health (measured on average eleven years prior to 2020) have an increased risk for COVID-19-related death (adjusted odds ratio: 1.75). We also find that specific factors contributing to increased mortality are increased serum glucose levels, systolic blood pressure and waist circumference.

Keywords: COVID-19, obesity, diabetes, hypertension, dyslipidemia

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INTRODUCTION

Since the beginning of the COVID-19 pandemic, mounting evidence supports an association between obesity and poor outcomes (1–12). The association holds for both obesity and obesity-associated metabolic health – hypertension, diabetes, dyslipidemia, and systemic inflammation (13). Similarly, obesity and excess adipose tissue have also been associated with higher risk of SARS-CoV-2 infection (10, 14, 15).

Previous studies, however, have tended to use small sample sizes, focus predominantly on the effects of body mass index (BMI) as a measure of obesity, or not account for confounding factors, such as ethnicity or socioeconomic status (14, 16–18). Since ethnicity and socioeconomic status are themselves associated with obesity and metabolic health (19, 20), they could confound interpretation of analyses in patients with COVID-19.

Here, we aim to present a comprehensive evaluation of obesity-associated metabolic risk factors that might be related to poor health outcomes in SARS-CoV-2 infected patients while controlling for confounding variables and limiting potential collider bias, which has previously resulted in incorrect epidemiological conclusions (21–23). We investigate whether metabolic health is related to higher chance for SARS-CoV-2 infection, but also COVID-19-related death.

MATERIALS AND METHODS

Participants

In this study, we used the UK Biobank dataset – a large scale study with extensive phenotyping carried out in the United Kingdom (24). This study was performed under UK Biobank application ID 35605. SARS-CoV-2 real-time PCR test results in the UK Biobank dataset are derived from the Public Health England microbiology database Second Generation Surveillance System that is dynamically linked to the UK Biobank database (25). Here we only included individuals who were recorded as tested for SARS-CoV-2. We distinguished between two samples for two aims of our project: Sample 1 – a larger sample (n=12,659) of all individuals who were tested for SARS-CoV-2 between 16th March 2020 and 24th August 2020, to investigate the risk of COVID-19 infection and how it is related to metabolic health; and Sample 2, a subset of Sample 1 consisting of individuals who tested positive for SARS-CoV-2 (n=1,152). We also obtained data on mortality from COVID-19 for all the individuals included in our study population.

Sample characteristics can be found in **Table 1**. The discrepancies in number of patients who tested positive in both samples is due to outlier exclusions (see section: *'Measures used in the study'*). Participants were classified as having metabolic syndrome based on the criteria in (26). All participants signed written informed consent prior to participating in the UK Biobank study, which was approved by the North-West Multicentre Research Ethics Committee (11/NW/0382). All UK Biobank actions are overseen by the UK Biobank Ethics Advisory Committee.

Measures Used in the Study

To investigate how metabolic health is related to SARS-CoV-2 infection and mortality rate, we used the following measures: waist circumference, serum triglyceride (TG), serum high density lipoprotein cholesterol (HDL), glycated hemoglobin (HbA1c), serum glucose (corrected for fasting times prior to blood drawing), serum C-reactive protein (27), previous type 2 diabetes diagnosis, resting systolic and diastolic blood pressure (mean of two measurements each), and hypertension diagnosis. In our analyses,

TABLE 1 | Participants characteristics.

Measure	Sample 1 (n=12,659)			Sample 2 (n=1,148)		
	SARS-CoV-2 positive patients mean (SD)	SARS-CoV-2 negative patients mean (SD)	p-value	SARS-CoV-2 positive survivors mean (SD)	SARS-CoV-2 positive deceased mean (SD)	p-value
n	*1,138*	*11,521*		*970*	*178*	
COVID-19 mortality rate		*1.42%*			*15.51%*	
Age in years	*68 (8)*	*70 (8)*	***<0.001***	*67 (9)*	*74 (6)*	***<0.001***
Sex distribution	*47.36% women*	*52.32% women*	***0.002***	*49.07% women*	*36.52%*	***0.003***
Waist circumference (cm)*	*93.38 (13.89)*	*92.07 (13.69)*	***0.003***	*92.56 (13.63)*	*98.49 (14.31)*	***<0.001***
Body mass index (kg/m^2)*	*28.40 (5.15)*	*27.87 (4.90)*	***<0.001***	*28.22 (4.96)*	*29.57 (6.06)*	***0.006***
Obesity (BMI>30kg/m^2)*	*38.14%*	*28.01%*	*0.136*	*29.38%*	*35.96%*	*0.096*
Metabolic syndrome*	*1.58%*	*1.56%*	*1.000*	*1.24%*	*4.49%*	***0.006***
Serum HDL (mmol/l)*	*1.36 (0.34)*	*1.43 (0.38)*	***<0.001***	*1.37 (0.45)*	*1.34 (0.31)*	*0.366*
Serum TG (mmol/l)*	*1.78 (1.04)*	*1.77 (1.02)*	*0.545*	*1.78 (1.05)*	*1.88 (1.01)*	*0.207*
HbA1c (mmol/mol)*	*35.83 (4.51)*	*35.76 (4.33)*	*0.637*	*35.73 (4.63)*	*36.94 (5.19)*	***0.004***
Serum glucose (mmol/l)*	*4.98 (0.64)*	*5.00 (0.63)*	*0.318*	*4.95 (0.63)*	*5.20 (0.74)*	***<0.001***
Serum C-reactive protein (mg/l)*	*3.00 (5.23)*	*2.84 (4.45)*	*0.308*	*2.82 (4.73)*	*4.01 (7.25)*	***0.036***
Systolic blood pressure (mmHg)*	*137.20 (18.59)*	*138.55 (18.55)*	***0.019***	*135.68 (18.15)*	*145.74 (18.43)*	***<0.001***
Diastolic blood pressure (mmHg)*	*82.46 (10.25)*	*82.24 (9.94)*	*0.484*	*82.19 (10.30)*	*83.99 (10.06)*	***0.030***
Diabetes*	*9.23%*	*7.61%*	*0.055*	*8.66%*	*15.17%*	***0.010***
Hypertension*	*41.65%*	*42.32%*	*0.685*	*38.14%*	*62.36%*	***<0.001***
Liver disease	*2.46%*	*2.63%*	*0.807*	*2.68%*	*1.69%*	*0.605*
Pulmonary disease	*25.3%*	*25.22%*	*0.979*	*24.85%*	*29.21%*	*0.256*
Cardiovascular disease	*14.94%*	*16.22%*	*0.279*	*13.40%*	*25.28%*	***<0.001***
Kidney disease	*7.64%*	*6.86%*	*0.349*	*7.11%*	*10.67%*	*0.137*
Townsend deprivation index*	*0.14 (1.04)*	*-0.07 (0.96)*	***<0.001***	*-0.06 (0.98)*	*0.04 (1.03)*	*0.215*
Cigarette smokers*	*12.57%*	*11.89%*	*0.197*	*12.58%*	*12.36%*	*0.108*

SD, standard deviation; BMI, body mass index; HDL, high density lipoprotein cholesterol; TG, triglycerides; HbA1C, hemoglobin A1c. Uncorrected p-values reflect significance of within samples differences calculated with t-tests in case of numerical variables and chi-squared tests in case of categorical variables.

Note that measures with an asterisk were obtained on average 11 years prior to 2020, while the other measures are from the time of testing.

Bold values indicate significant between-group differences.

we also controlled for age, sex, socioeconomic status [Townsend deprivation index (28)], highest achieved educational qualifications, mean family income, smoking status, and ethnic background, the laboratory where COVID-19 testing was performed, and the origin of the sample used for COVID-19 test (e.g. nose, throat etc.). Based on the previous literature, we also controlled for past liver disease (ICD10 identifiers K7), cardiovascular disease (ICD10 identifiers I2 and I3), pulmonary disease (ICD10 identifiers J), and kidney disease (ICD10 identifiers N1) in all our analyses, as they are all related to the severity of COVID-19 (29–32). For Sample 2, we used mortality data provided by the UK Biobank – COVID-19-related death was described using the ICD10 identifier U07.1. All variables related to metabolic health and all confounding variables were collected on average 11 years prior to COVID-19 tests.

Prior to the analyses, all numeric variables were z-scored, all serum level values were log-transformed, and we excluded outliers from the samples (2.2 interquartile range below 1st or above 3rd quartile). No other exclusions were applied. If participants were tested for SARS-CoV-2 more than once, they were considered positive if at least one test result was positive.

Statistical Analyses

The same analyses were performed for each of the two population samples. Data were analyzed using R (v. 3.6.0). First, using confirmatory factor analysis in lavaan (v. 0.6-7), we estimated the fit of a latent variable 'metabolic health', which consisted of waist circumference, serum C-reactive protein levels, a latent variable 'dyslipidemia' [serum HDL and TG levels; with loadings constrained to be equal between the two variables (33)], and two other latent variables, diabetes and hypertension. The latent variable 'diabetes' consisted of serum glucose and HbA1c levels, and type 2 diabetes diagnosis, while the latent variable 'hypertension' consisted of blood pressure measurements (systolic and diastolic blood pressure), and hypertension diagnosis (**Figure 1**). The model was estimated using robust maximum likelihood estimation and model's fit was evaluated using common indices: comparative fit index (CFI), root mean square error of approximation (RMSEA), and standardized root mean square residual (SRMR). Acceptable fit was defined as CFI>0.9, RMSEA<0.1, and SRMR<0.08.

Next, we extracted components of the latent variable 'metabolic health' for each participant and entered them in a logistic regression. The outcome variable in logistic regression for Sample 1 was COVID-19 test result, while for Sample 2 the outcome variable was COVID-19-related death.

In the analyses we used a set of confounding variables to calculate adjusted odds ratio: age, sex socioeconomic status, smoking status, ethnic background, test laboratory, and sample origin (6, 34–36).

Finally, for Sample 2 we explored how individual factors contributed to the COVID-19-related mortality by using a logistic regression with individual components of metabolic health, instead of the latent variable 'metabolic health'.

Overall, analyses using a latent variables approach allowed us to maximize information shared between different measured variables within the same metabolic domains, e.g. serum glucose levels, HbA1C levels and type 2 diabetes diagnosis for the latent variable 'diabetes'. Furthermore, adding continuous measures in this study, such as glucose levels or blood pressure, instead of only using type 2 diabetes or hypertension diagnosis, enabled us to use more information that is available in the dataset and investigate in depth how continuous metabolic health measures are related to SARS-CoV-2 infection and COVID-19 mortality.

A script for the analysis of the data as well as the output of statistical software can be found at https://github.com/FilipMorys/COVID_MetS.

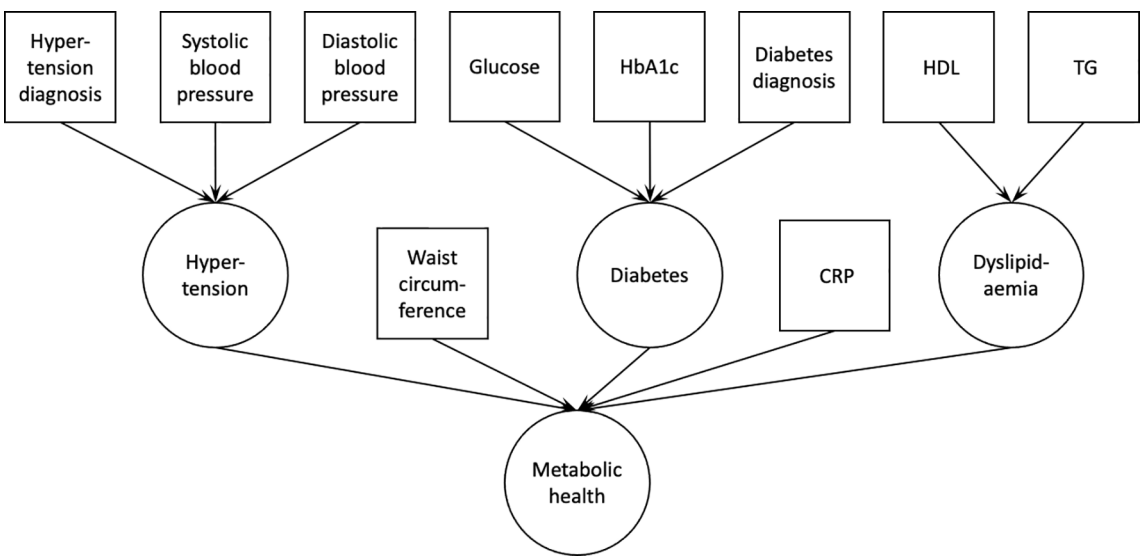

FIGURE 1 | Confirmatory factor analysis model used to derive the latent variable 'metabolic health'. Squares indicate measured variables; circles indicate latent variables. HbA1c, glycated hemoglobin A1c; HDL, high density lipoprotein cholesterol; TG, triglycerides; CRP, C-reactive protein.

RESULTS

Metabolic Health and the Risk of COVID-19 Infections

In Sample 1, the confirmatory factor analysis provided an acceptable model fit (CFI=0.932, RMSEA=0.065, SRMR=0.040). In the logistic regression the relation between metabolic health and the chance of having a positive SARS-CoV-2 test did not reach our pre-set statistical significance threshold (p=0.059; odds ratio 1.10; 95% confidence intervals (CI): 1.00-1.22).

Metabolic Health Is Related to an Increased COVID-19-Related Mortality

Among the individuals who tested positive, 178 people (16%) died from COVID-19, allowing us to investigate how metabolic health influences COVID-19-related mortality. Here, the confirmatory factor analysis provided an acceptable model fit (CFI=0.919, RMSEA=0.068, SRMR=0.049). Logistic regression showed that obesity-associated metabolic impairment was related to an increased mortality rate among COVID-19 positive individuals (p<0.001) – adjusted odds ratio: 1.75 (95% CI: 1.30-2.37), pointing to a 75% increase for each unit increase on the metabolic health latent variable (**Figure 2**). Each unit increase on the metabolic health variable means increased serum glucose levels by 0.21 mmol/l, HbA1c levels by 3.21 mmol/mol, C-reactive protein levels by 2.18 mg/l, triglyceride levels by 0.67 mmol/l, systolic blood pressure by 7.17 mmHg, diastolic blood pressure by 4.27 mmHg, waist circumference by 18.72 cm, and decreased HDL cholesterol levels by 0.24 mmol/l.

Exploratory analysis with individual components of metabolic health revealed that higher systolic blood pressure, higher serum glucose, and higher waist circumference increased the chance of COVID-19-related mortality – the adjusted odds ratio were 1.32 (95% CI: 1.02-1.70), 1.27 (95% CI: 1.04-1.55), and 1.34 (95% CI: 1.05-1.72), respectively (systolic blood pressure: p=0.035, glucose levels: p=0.020, waist circumference: p=0.019; **Figure 2**).

DISCUSSION

We investigated whether obesity-associated poor metabolic health, here defined by increased waist circumference, increased TG levels, decreased HDL levels, systemic inflammation, increased glucose and HbA1C levels, increased systolic and diastolic blood pressure, and the presence of type 2 diabetes and hypertension, is a risk factor for COVID-19 infection and mortality. We were able to show that a one unit increase of the latent variable 'metabolic health' results in a 75% higher risk of death because of COVID-19. In contrast, the relation between metabolic health and the likelihood of test positivity was weaker, with an odds ratio of only 1.1 and a confidence interval that included the null effect. In sum, poor metabolic health contributes little to no risk of test positivity but substantially increases the odds of an adverse outcome. A strength of our analysis lies in the fact that the risk factor variables were measured prior to COVID-19 diagnosis and therefore were not influenced by the disease itself or possible treatment. Another strength is that we controlled for known shared risk factors between obesity and COVID-19 outcomes, such as socioeconomic status, ethnicity, and sex. We also used history of pulmonary, cardiovascular, kidney, and liver disease as covariates in our analyses, as these have been linked to COVID-19 severity and mortality (29–32).

The results of our study are in line with previous reports linking obesity and individual components of metabolic health with poor COVID-19 outcomes and death (1, 5, 7, 10, 12, 18, 37). In particular, the fact that waist circumference was related to COVID-19 mortality is consistent with a study showing that

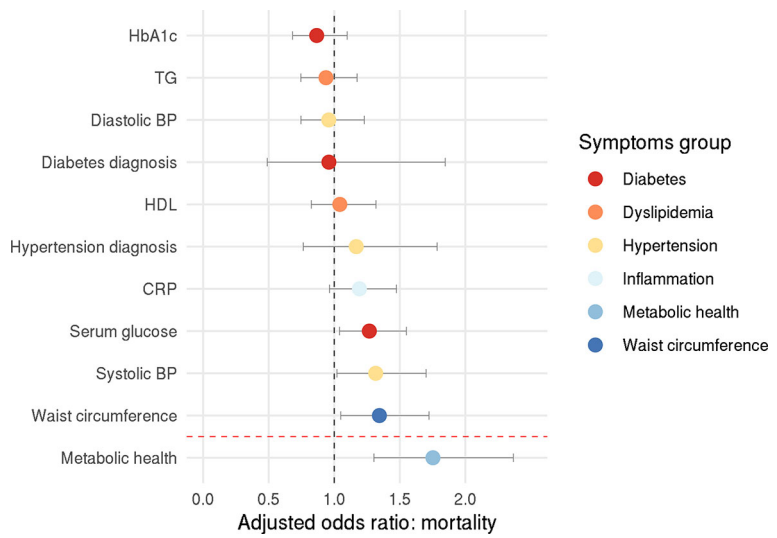

FIGURE 2 | Odds ratio for COVID-19-related death. Circles represent adjusted odds ratios, error bars represent 95% confidence intervals.

visceral adipose tissue is significantly related to the risk of admission to an intensive care unit in COVID-19 patients (38). Here, the authors argue that this might be in part due to increased local and systemic inflammation. In their review, Bansal et al. discuss some of the physiological mechanisms that might mediate the relationship between obesity, related comorbidities and worse outcomes of COVID-19 (39). These include an enhanced expression of the angiotensin converting enzyme 2 (ACE2), diabetes-related microvascular dysfunction, increased expression of pro-inflammatory cytokines, or activation of the renin-angiotensin-aldosterone system related to hypertension (39–41). Recent reports especially highlight the role of interleukin-6 (IL-6) in the pathogenesis of COVID-19, but also the role of IL-6 inhibitors in COVID-19 therapy (42, 43). This is important given that adiposity is associated with chronic systemic inflammation, which generally delays immune response to pathogens and can also lead to worse outcomes in COVID-19 patients (37, 39, 40, 44). In general, our results suggest that a number of these mechanisms might also contribute to increased mortality from COVID-19.

Previous studies investigating COVID-19 in the UK Biobank used positive test results obtained between March 16th and April 26th as a proxy of severe COVID-19 (18, 45). The rationale for this is that, during this time, only patients admitted to hospitals and with COVID-19-like symptoms were tested for SARS-CoV-2. Here, we decided to not use this approach for several reasons. First, it is possible that individuals with COVID-19-like symptoms for which they were admitted to a hospital but who did not have COVID-19 were only infected after being admitted. In those cases, positive tests would not reflect COVID-19 severity. Second, it is not possible to determine the exact reason for which inpatients were tested for SARS-CoV-2; positive test results might therefore not only reflect severity of COVID-19 disease, but also testing in anticipation of isolating patients admitted for other reasons. For example, patients having to undergo unrelated medical procedures might have received precautionary testing. We therefore recommend that studies that used this approach as a proxy for COVID-19 severity be interpreted with caution.

For the interpretation of our and similar results from the UK Biobank, it is important to note that the UK Biobank is not a sample representative of the entire UK population and therefore the findings might not be generalizable (46). Infection and mortality rates calculated here should not be used as an indicator of true prevalence and mortality rate in the general population. Furthermore, observational studies such as ours are prone to collider bias, which has already been identified in UK Biobank COVID-19 investigations (23). Collider bias occurs when the sample population is conditioned on a variable that correlates with the variables of interest. For example, during the time period of the current study, it is thought that health workers were more likely to be tested for SARS-CoV-2, which may have contributed to incorrect conclusion that cigarette smoking is protective, as health care workers have a lower incidence of smoking (23). Our study population includes individuals who were seen in a health care setting, who may therefore have a higher incidence of obesity and poorer metabolic health than the general population. However, it is difficult to see how this would account for the effect of obesity on death from COVID-19 among people who tested positive for the virus.

In addition, COVID-19 testing in the UK during the time period of this study was generally restricted to individuals with symptoms such as fever, cough, or loss of smell or taste – asymptomatic COVID-19 individuals were less likely to be tested. This might further increase the extent of collider bias in this and similar studies investigating the predictors of COVID-19 severity or mortality. Current strategies to account for such bias or measure the extent thereof rely on models and strong assumptions that might be incorrect. We therefore suggest that our findings be interpreted with caution. Nonetheless, our model did account for potential collider variables or confounds such as socioeconomic status, ethnicity and age.

Finally, in this study we only used limited data pertaining to COVID-19 diagnosis or mortality. Information on the seriousness of illness, treatment administered, or actual cause of death were not available.

In sum, we used the UK Biobank dataset to confirm that, in individuals who tested positive for COVID-19 in the early stages of the pandemic, metabolic health, and especially visceral adiposity, hypertension, and serum glucose levels, were associated with an increased risk of death.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The dataset can be obtained from the UK Biobank. Requests to access these datasets should be directed to https://www.ukbiobank.ac.uk.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by North-West Multi-centre Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Both authors contributed equally to all stages of the research. All authors contributed to the article and approved the submitted version.

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REVIEW
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Review: Obesity and COVID-19: A Detrimental Intersection

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Obesity has been recognized as an independent risk factor for critical illness and major severity in subjects with coronavirus disease 2019 (COVID-19). The role of fat distribution, particularly visceral fat (often linked to metabolic abnormalities), is still unclear. The adipose tissue represents a direct source of cytokines responsible for the pathological modifications occurring within adipose tissue in obese subjects. Adipokines are a crucial connection between metabolism and immune system: their dysregulation in obesity contributes to chronic low-grade systemic inflammation and metabolic comorbidities. Therefore the increased amount of visceral fat can lead to a proinflammatory phenotypic shift. This review analyzes the interrelation between obesity and COVID-19 severity, as well as the cellular key players and molecular mechanisms implicated in adipose inflammation, investigating if adipose tissue can constitute a reservoir for viral spread, and contribute to immune activation and cytokines storm. Targeting the underlying molecular mechanisms might have therapeutic potential in the management of obesity-related complications in COVID-19 patients.

Keywords: obesity, low-grade inflammation, COVID-19, adipose tissue, visceral fat

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INTRODUCTION

Obesity is more prevalent in developed countries, because of increased consumption of sugars, and saturated fats with low levels of fibers and antioxidant molecules. This diet can lead to enhancement of the innate immune system and delay of the adaptive immune system (interfering with T and B lymphocyte function), potentially via augmented oxidative stress (1). Obesity seems to increase the risk of both COVID-19 complications and mortality (2). Our perspective about COVID-19 is changing from a viral agent responsible for a respiratory disease toward a facilitator of complication and increased mortality in obese patients, with a dose-response curve, where higher body mass index result to be at most risk. This finding suggests a bidirectional relationship between COVID-19 and metabolic diseases: on the one hand, pre-existing metabolic diseases potentiate the severity of COVID-19, on the other hand, this viral infection exacerbate precedent metabolic frailty (3).

The amplified risk of obese patients to develop severe COVID-19 manifestations can depend on numerous factors, such as the chronic systemic phlogistic state, the decreased immune response, and even the adipose tissue itself, which represents a reservoir for the virus (4). Adipose tissue is also a fount of many proinflammatory mediators and hormones. High baseline serum C-Reactive Protein (PCR) and interleukin 6 (IL-6) levels, as well as hypoadiponectinemia and hyperleptinemia/leptin resistance (typical of obesity) elucidates the preexisting inflammatory

microenvironment in obese patients, making them more susceptible to worse outcomes and even fatality. The perspective of obesity as a persistent low grade systemic inflammation is very interesting because of the multiple overlapping areas with the immune system. White adipose tissue produces adipokines, molecules that are involved in the etiopathogenesis of some major metabolic disorders such as dyslipidemia, diabetes, hypertension, and other cardiovascular disorders, which share a central role in the metabolic syndrome. Most adipokines with proinflammatory properties are overproduced, while others with anti-inflammatory or insulin-sensitizing properties (such as adiponectin) are reduced. This adiposity-linked dysregulation of adipokine secretion can contribute to obesity-related complications (5).

Two signaling pathways are activated by the proinflammatory cytokines in obesity: the nuclear factor-kB (NF-kB) and the c-Jun NH2-terminal kinase (JNK) pathway, which downregulates the anti-inflammatory transcription factors thus propagating inflammatory processes. Adipocyte hypertrophy is linked not only to mitochondrial dysfunction, DNA damage and cell death (6) but also to altered intracellular signaling: enlarged omental adipocytes resulted to be hyper-responsive to TNF-α with an increased constitutive NF-kB activity, thus leading to adipokine overproduction. Another crucial step in increased obesity-related inflammation is the massive infiltration of adipose tissue by phagocytosis mediators: monocyte chemoattractant protein-1 (MCP-1), whose circulating levels are elevated in obese, recruits monocytes and macrophages into the adipose tissue as well as into the arterial vessel wall. This process can contribute to cardiovascular events, which represent a frequent complication in COVID-19 patients (7).

Adipose tissue can regulate cardiac function through its endocrine effects, exerted not only by adipokines but also by lipokines (such as palmitoleate), batokines and exosomal miRNAs: a series of bioactive molecules contributing to the dialogue with metabolic tissues and influencing whole-body metabolism (8). Consequently, increased adiposity determines a dysregulation of endocrine functions, with consequent insulin resistance and higher cardiovascular risk. An impairment of immune system could also be present, due to the dysregulation of the factors produced by adipose tissue.

Obesity could also worsen the clinical outcome in COVID-19 also by respiratory compromise because of pulmonary restriction, impaired pulmonary perfusion, endothelial dysfunction and critical care management obstacles. In fact, obesity significantly interferes with respiratory function by reducing the expiratory reserve volume and the functional residual capacity. Further, the respiratory strength might be significantly reduced because of the ineffectiveness of the respiratory muscles, with the body fat distribution influencing the respiratory efficiency, due to the direct mechanical obstacle of visceral fat storage in the abdominal regions. These concurrent factors can lead to inspiratory overload and increase respiratory effort and oxygen request with a high likelihood of decompensation into respiratory failure and insufficiency.

VISCERAL FAT: THE INDEPENDENT RISK FACTOR FOR COVID-19?

Preliminary data indicate that COVID-19 cases are mostly prevalent among obese subjects. Obesity constitutes a primary and independent risk factor for its complications in obese adults, where ectopic and visceral fat stores are the leading markers of such a risk. Even if growing evidence supports that obesity leads to an increased inflammation and fibrosis together with a decreased expression levels of the anti-inflammatory adiponectin also in the subcutaneous adipose tissue (8), visceral fat accumulation (the so-called "abdominal obesity" or "central obesity"), is usually more markedly characterized by an impaired profile of adipokines, with increased proinflammatory signals (9). In severe abdominal obesity, the adipokine profile is unbalanced in favor of leptin secretion and low-grade inflammation in spite of adiponectin. This deregulated adipokine profile links various metabolic disorders to inflammatory manifestations (9). This link has been recently evidenced in a cross-sectional analysis including 30 patients (aged 65.60 ±13.11 years) with COVID-19 diagnosis. An increase in visceral fat area by 10 cm^2 at the level of the first lumbar vertebra was related to a 1.37-fold higher possibility of intensive care unit treatment and a 1.32-fold higher risk of invasive mechanical ventilation. One additional centimeter of waist circumference defines a more severe clinical course of COVID-19 with a 1.13-fold higher risk of intensive care unit treatment and a 1.25-fold higher possibility of assisted mechanical ventilation (10). Some authors also evidenced that computed tomography (CT) imaging of fatty liver and epicardial adipose tissue (EAT) were found in severely and critically ill young COVID-19 subjects, in comparison with patients experiencing milder disease (11). The increased risk of obese patients to develop severe COVID-19 cardiac and pulmonary damage could be referred not only to the mentioned factors (chronic phlogistic status in visceral obesity, unpaired immune response, and adipose tissue serving as a possible reservoir for the virus), but also to an additional mechanism: ectopic fat accumulation. Deng's findings tried to extricate the complex physiopathology leading to COVID-19 organ injuries: they proposed that not simply obesity, but visceral fat is an independent risk factor for COVID-19 complications in young patients (12) because abdominal adiposity may promote and amplify the inflammatory answer (13, 14). Their study analyzed CT data of ectopic fat depots in young COVID-19 patients, such as intrahepatic and heart epicardial adipose tissue (EAT), which have been evidenced to play a role in COVID-19 myocardial phlogosis (15–17). EAT is an inflammatory depot with conspicuous macrophage infiltrates and proinflammatory cytokines, such as interleukin-6 (IL-6), which is secreted by numerous cells (monocytes, fibroblasts, endothelial cells, adipocytes), overexpressed in COVID-19 patients (18). Circulating levels and adipocyte release of IL-6 are augmented in obese individuals: specifically, visceral adipose tissue displayed to release three times more IL-6 than subcutaneous fat. Similarly, serum IL-6 levels resulted to be 50% higher in the portal vein

than in the radial artery of obese patients; this portal vein IL-6 concentration resulted to be closely related to systemic C-reactive protein (CRP) levels. Visceral fat is a central site for IL-6 release, regulating the hepatic production of acute-phase reactants and providing a link between visceral adipose tissue and inflammation (19). EAT proinflammatory cytokines can reach out to the myocardium via vasa vasorum (since they share the same microcirculation) or through paracrine pathways (20), thus determining myocardial inflammation and concurring to cardio-respiratory failure. A profibrotic remodeling of extracellular matrix also plays a role in the pathogenesis of obesity complications, such as fibrosis of EAT.

The EAT is a metabolically active tissue releasing proatherogenic and proinflammatory molecules and leading to a low-grade inflammatory and pro-fibrotic environment. It was evidenced that EAT, through its secretion of adipo-fibrokines, such as Activin A (a member of the TGF-β family) and MMP8, may represent a complementary mechanism contributing to the genesis of myocardial fibrosis, implicated in the increased risk of arrhythmias in obese patients (21).

Peri-renal and liver fat infiltration may also play a pivotal role in severe COVID-19: visceral accumulation [often present in severely and critically ill young individuals with obesity (22)], may concur to hypoalbuminemia, insulin resistance, and hyperglycemia: all measurable predictors of COVID-19 complications, as recently evidenced (23). Another study (24) retrospectively examined EAT from CT scans of 41 patients, admitted for COVID-19 infection. Chest CT scan was performed on the admission day, investigating the presence of pulmonary embolism. EAT and subcutaneous adipose tissue densities were retrospectively obtained and defined as mean attenuation expressed in Hounsfield units (HU). EAT HU resulted significantly higher than subcutaneous adipose tissue HU (-95 HU versus -118, $p<0.01$); mean EAT thickness was 5.5 mm. EAT attenuation significantly augmented with the increase in COVID-19 severity. Subjects with more severe COVID-19 had more significant EAT attenuation, which was importantly linked to peripheral oxygen saturation (SpO2) and body temperature, and reflected inflammatory changes within the fat depot (25). Specifically, EAT showed imaging signs of augmented inflammation in patients with more severe COVID-19, directly increasing with COVID-19 severity. On the contrary, subcutaneous adipose tissue attenuation did not progress with the severity of COVID-19. Consequently, CT-measured EAT attenuation might play a diagnostic and prognostic role in COVID-19 patients with obesity (26), serving as a reliable (even if expensive) indicator of phlogosis in COVID-19 patients.

Hepatic and cardiac imaging could help to phenotype and stratify younger individuals with visceral obesity at higher risk of COVID-19 morbidity and mortality. Furthermore, visceral and ectopic fat can be targeted with lifestyle, such as weight loss and n-3 PUFA supplementation.

N-3 PUFAs can modulate the transcription of inflammatory genes through the regulation of key transcription factors (27), for example inhibiting nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and activating peroxisome proliferator-activated receptors-α/γ (PPARα/γ). N-3 PUFA-containing diets in severe ARDS showed to reduce the duration of mechanical ventilation, improved oxygenation and reduced stay in intensive care units (28).

A randomized controlled study (29) demonstrated that 1.5 g EPA and 1.0 g DHA 4 weeks daily supplementation can consistently decrease serum levels of TNF-α, IL-6,and IL-1β, suggesting n-3 PUFAs as an effective low-risk dietary intervention to mitigate the cytokine storm thus modulating inflammation. Similarly, the parenteral supplementation of 4g/die EPA and DHA in severe COVID-19 disease (30) inhibited cytokine production and mitigated the inflammatory response, thus attenuating the complex inflammatory state of pre-existing health conditions, such as obesity and elderly age, often associated with poorer clinical outcomes.

OBESITY AND COVID-19 PATHOGENESIS

Although COVID-19 symptoms usually resolve in about 10 days, some patients develop respiratory insufficiency and become ventilator dependent (31–33) and need to be admitted to the intensive care units with respiratory failure: these patients are obese/overweight with extensive visceral fat in almost 90% cases (34). Visceral fat, lung tissue, and leptin production are closely interconnected. Leptin produced in visceral fat could contribute to deterioration in mechanical ventilation. In a cross-sectional study (35), COVID-19 patients displayed significantly increased leptin levels: the mean serum leptin level was 21.2 ug/L vs. 5.6 ug/L for COVID-19 patients and controls respectively. Within the same study, 90% of respiratory failure cases presented a body mass index over 25 kg/m^2. Similarly, in the Seattle cohort individuals requiring mechanical ventilation presented a mean BMI of 33 kg/m^2 (32, 33). An excessive adipose mass seems to contribute to the hyperinflammatory state, pulmonary phlogosis, and subsequent respiratory failure. A complex biological framework could explain these clinical observations. ACE2 receptor, which is a constituent of renin-angiotensin system (RAS), exerts a central role in the pathogenesis of SARS CoV2 COVID-19 infection. ACE2 receptors are expressed not only in the apical surfaces of well-differentiated ciliated cells, but also in endothelial cells, kidneys, pancreas, adrenals, and adipocytes. Intracellular invasion of COVID-19 is mediated by ACE2 receptor: the virus spike protein "S" is cleaved into S1 and S2 domains. The S1 fragment is internalized into the host cell through ACE2 receptor. The S2 domain is further cleaved further by the host cell (trans-membrane serine protease), (TMPRSS2), that determines membrane fusion with dissemination of the virus into the host (36). ACE2 receptor is present in the respiratory tract, lungs, and visceral fat; its expression is upregulated on alveolar epithelial cells and in visceral fat, particularly abundant in obese subjects. In addition, it has been very recently identified that the liver also expresses ACE2 and its priming protease TMPRS22, with obese patients with nonalcoholic steatoepatitis (NASH) showing increased

hepatic expression of these critical viral entry points. In obese patients with NASH higher expressions of these genes have been evidenced, pointing that advanced stages of nonalcoholic fatty liver disease (NAFLD) could make subjects prone to COVID-19 infection (37). Specifically, expression of ACE2 receptor results to be upregulated because of obesity, air pollution, and smoking (38). This upregulation, more prominent in adipocytes of diabetic and/or obese subjects, could turn fat into a potential viral target and reservoir, thus explaining the reason why diabetes and overweight/obesity are dangerous comorbidities for COVID-19 infection, significantly augmenting the severity of the local pulmonic response (39). ACE2 is more expressed in visceral adipose tissue because of its antiobesity action in adipose tissue with stimulation of brown adipose tissue and browning of pre-existing white adipose tissue (40). The ACE2 utilization by the virus determines a local pulmonary inflammation due to ACE2-ATII disbalance. This may be enhanced by an increased leptin secretion (induced by COVID-19 infection of visceral adipose tissue): leptin receptors in the lungs are hyper-activated, thus enhancing local pulmonary inflammation. Since ACE2 reduces leptin levels through activation of the MrgD-receptor/c/Src/p38MAPK pathway, a compromised ACE2 function ends up in an additional elevation in leptin levels (41), resulting in a hyper-inflammatory local pulmonary answer embroiling local leptin receptors and local ACE2-ATII derangement. This disruption of the renin-angiontensin system by the virus impairs the energetic functions of these pathways during COVID-19 infection, leading to abnormalities in the inflammatory response through their influence on immune balance and cytokine generation (42). The major presence of ACE2 receptors in obese individuals is also due to a more abundant volume of adipose tissue. Weight loss achieved by bariatric surgery determines a significant reduction in adipose tissue volume, and also downregulates ACE 2 gene expression in the subcutaneous adipose tissue, which might also constitute a putative protective mechanism against severe COVID-19. Roux-en-Y gastric bypass was demonstrated to positively impact numerous comorbidities obesity-related (often linked to poorer COVID-19 outcomes), resulting independently associated with a reduced risk of mechanical ventilation and death in obese patients with COVID-19 (43).

ENDOTHELIAL ACTIVATION: EXACERBATION OF INFLAMMATION

The chronic low-grade inflammatory state in obesity has been confirmed by high baseline CRP in overweight individuals (44, 45). A Korean multicentric study evaluated the correlation between high sensitivity-CRP and sarcopenic obesity: CRP resulted to be significantly higher in obese patients in comparison with the normal weight control group (46). This complex framework can explain respiratory failure in obese COVID-19 infected patients. Additionally, other obesity-related clinical features (such as tachypnea, minor lung capacity, reduced chest wall compliance, and aberrant respiratory muscle adaptations) can lead to severe respiratory failure requiring mechanical ventilation.

However, COVID-19 is associated not only with dysregulated inflammation but also with augmented coagulation and thrombotic accidents, which were extensively found in infected patients (47). In numerous ARDS patients, not only venous thromboembolism but also thrombocytopenia, renal failure, and disseminated intravascular coagulation have often been reported. In situ thrombi were found in pulmonic arteries and in other organs, including liver and kidneys, in subjects who died of COVID-19 (48).

A very recent study compared seven lungs from subjects dead from COVID-19 with seven lungs from subjects dead from H1N1-related ARDS infection and with age-matched uninfected control lungs after autopsy. The peripheral lungs from both COVID-19 and H1N1 presented a histologic pattern with a pervasive alveolar injury and perivascular T-cell infiltration. A COVID-19 peculiarity consisted of severe endothelialitis and damage, related to intracellular presence of virus and disrupted cell membranes, with diffuse alveolar capillary thrombosis and microangiopathy. Additionally, a greater amount of new vessel growth through a mechanism of intussusceptive vascular neoangiogenesis was reported (49). These autopsy findings raise the hypothesis that widespread endothelial hyper-activation in COVID-19 can trigger thrombotic events, with intra-alveolar deposits of hyper-activated leukocytes and fibrin contributing to pulmonary failure (50). The mechanism of this coagulopathy is not completely clear, however, dysregulated immune responses orchestrated by lymphocyte death, inflammation, hypoxia, and endothelial hyper-activation/injury are implicated (51). Specifically, endothelial cells could be hyper-activated by adipocyte secretory products; this activation results in intracellular signaling pathways leading to the generation of cell adhesion molecules, adipokines and proinflammatory cytokines, which address inflammatory cells to the endothelium and underlying tissues, stimulating them to become fully activated. Circulating levels of soluble intercellular (ICAM-1) and vascular (VCAM-1) adhesion molecules, as well as endothelial E-selectin result to be augmented in obese adults and reduced after weight loss. Similarly, incubation of human adipose tissue-derived endothelial cells with mature adipocytes resulted in the upregulation of endothelial cell adhesion molecules with augmented monocytes diapedesis. This process leads to firm adhesion of monocytes to the endothelium and increased diapedesis of macrophages through the endothelium junctions into the adipose tissue (52), so that adipokines and cell adhesion molecules can be directly involved in thrombosis. Additionally, both endothelium and adipose tissue generate plasminogen activator inhibitor-1, whose increased levels (mostly induced by TNF-α, thrombospondin-1 and oxidative stress) typical of obesity can determine hypofibrinolysis, thus configuring a pro-thrombotic state (53). Although the poorest outcomes in COVID-19 subjects certainly derive from multifactorial

cofactors, thrombotic complications exert a pivotal role in their prognosis (54). The development of safe thromboprophylaxis strategies for these thrombotic complications goes through a full understanding of its pathophysiologic basis in COVID-19 patients.

METAINFLAMMATION IN OBESE PATIENTS: THE ROLE OF LEPTIN AND TLR3 IN ABNORMAL VIRAL RESPONSES

Adipocyte dysfunction in visceral adipose tissue is closely related to low-grade chronic phlogosis, the so-called "metainflammation", induced by both proinflammatory and hypoxic signals from adipocytes, which represents the starting point of metabolic diseases in obesity (55). The metainflammation often originates from the leptin-activated macrophages present in the white adipose tissue, which produce IL-6, TNF-α,and IL-1β, with the activation of the NF-kB pathway. This activation can be inhibited by adiponectine, whose effect is easily overwhelmed by this proinflammatory drive in cases of severe obesity (56).

Leptin is the leading adipokine, whose anorexigen activity modulates satiety and food intake; its blood levels are proportionate to the amount of white adipose tissue and BMI. Leptin is an essential pulsatile hormone, responsible for energy homeostasis and numerous neuroendocrine functions. It stimulates the migration of resident macrophages in the WAT and promotes their shift toward a proinflammatory profile, and unbalances lymphocyte Th profiles, by reducing regulatory T-cells and inducing Th17 polarization (57). The typical modern diet-induced obesity is characterized by hyperleptinemia (elevated levels of leptin) and resistance to the body weight reducing effects of leptin (58). Leptin resistance upsets the endothelial leptin signaling, predisposing to atherogenesis in obese subjects, and it is responsible for the proinflammatory microenvironment, often leading to cardiovascular complications (59, 60). Leptin also addresses hematopoiesis in the bone marrow toward granulocyte lines and promotes neutrophils survival: higher levels of neutrophils can be found in obese patients. This makes neutrophil recruitment more powerful in obese patients than in normal weight subjects during inflammatory processes (61). Additionally, this adipokine also induces vasodilatation by inhibiting angiotensin II-induced vasoconstriction and inducing nitric oxide release from vascular smooth muscle and endothelial cells, with leptin resistance blunting this vasodilatory effect (62).

However, obese patients not only suffer proinflammatory environments, but they also exhibit abnormal responses to viral infection. Specifically, patients with visceral adipose accumulation show not only a strong cytokine production, especially IL-6, IFN type I and III groups, interferon gamma-induced protein 10, but also a lower toll-like 3 receptor (TLR3) expression in adipocytes, muscle cells, and adipose tissue-resident macrophages (63). TLR3 belongs the toll-like receptor family, with a pivotal role in both microorganism recognition and stimulation of innate immune system. It identifies the double-stranded RNA of some viruses: upon recognition, TLR3 induces the production of type I IFN, which signals other cells to increase their antiviral defenses. Consequently, the reduced activation of TLR3 may exacerbate the metainflammation, thus contributing to the more severe septic states of obese patients with COVID-19. This suggests that their antiviral answer is less effective, but the overall phlogosis is higher than in normal weight subjects with viral infections. Additionally, individuals with metabolic abnormalities and visceral adipose accumulation could have a constitutional lower titer of angiotensin 1-7 (64), which limits the metainflammation as a guardrail, and a consequent higher inflammation; the inappropriate inflammatory response, added to the reduced activation of TLR3 in obese patients, can lead to unrestrained inflammation. This could contribute to the easier development of ARDS in obese patients.

CONCLUSION

Obesity is a comorbidity that drives COVID-19 infected subjects toward a dangerous downhill slope. A low-grade chronic inflammation in obese people, as indicated by increased baseline serum levels of CRP, TNF-α, and IL-6 (positively correlated with BMI, waist circumference and visceral adipose tissue), is responsible for initiating the cytokine storm and can determine numerous underlying pathological situations and complications. Adipose tissue contains not only adipocytes (with significant intrinsic inflammatory properties) but also monocytes, macrophages, vascular components, and other cells contributing to inflammation. Additionally, adipocytes express numerous receptors, which are sensitized by infectious agents, thus activating cytokine-mediated signal transduction cascades and releasing proinflammatory cytokines and acute phase reactants. Up-regulation of ACE2 receptors in adipocytes is another reason why obese patients are more susceptible to infection with SARS-CoV 2 COVID-19 and progress into more critical forms of the disease. In this established interrelation between BMI-based obesity and severe course of COVID-19 disease, body fat distribution seems to be crucial, with visceral fat significantly raising the possibility of a more severe course of COVID-19: CT-based quantification of visceral adipose tissue and upper abdominal circumference can represent a simple promising strategy for risk assessment in COVID-19 infected subjects providing experimental proof of the association between visceral fat amount and COVID-19 severity: however it is not cost effective and expose the patients to radiations.

AUTHOR CONTRIBUTIONS

MG projected the manuscript and wrote the draft. ND'O supervised the process and contributed to editing. All authors contributed to the article and approved the submitted version.

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Obesity and Its Impact on Adverse In-Hospital Outcomes in Hospitalized Patients With COVID-19

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Background: An increasing level of evidence suggests that obesity not only is a major risk factor for cardiovascular diseases (CVDs) but also has adverse outcomes during COVID-19 infection.

Methods: We used the German nationwide inpatient sample to analyze all hospitalized patients with confirmed COVID-19 diagnosis in Germany from January to December 2020 and stratified them for diagnosed obesity. Obesity was defined as body mass index ≥30 kg/m^2 according to the WHO. The impact of obesity on in-hospital case fatality and adverse in-hospital events comprising major adverse cardiovascular and cerebrovascular events (MACCE), acute respiratory distress syndrome (ARDS), venous thromboembolism (VTE), and others was analyzed.

Results: We analyzed data of 176,137 hospitalizations of patients with confirmed COVID-19 infection; among them, 9,383 (5.3%) had an additional obesity diagnosis. Although COVID-19 patients without obesity were older (72.0 [interquartile range (IQR) 56.0/82.0] vs. 66.0 [54.0/76.0] years, $p < 0.001$), the CVD profile was less favorable in obese COVID-19 patients (Charlson comorbidity index 4.44 ± 3.01 vs. 4.08 ± 2.92, $p < 0.001$). Obesity was independently associated with increased in-hospital case fatality (OR 1.203 [95% CI 1.131–1.279], $p < 0.001$) and MACCE (OR 1.168 [95% CI 1.101–1.239], $p < 0.001$), ARDS (OR 2.605 [95% CI 2.449–2.772], $p < 0.001$), and VTE (OR 1.780 [95% CI 1.605–1.973], $p < 0.001$) and also associated with increased necessity of treatment on intensive care unit (OR 2.201 [95% CI 2.097–2.310], $p < 0.001$), mechanical ventilation (OR 2.277 [95% CI 2.140–2.422], $p < 0.001$), and extracorporeal membrane oxygenation (OR 3.485 [95% CI 3.023–4.017], $p < 0.001$).

Conclusions: Obesity independently affected case fatality, MACCE, ARDS development, VTE, and other adverse in-hospital events in patients with COVID-19 infection. Obesity

should be taken into account regarding COVID-19 prevention strategies, risk stratification, and adequate healthcare planning. Maintaining a healthy weight is important not only to prevent cardiometabolic diseases but also for better individual outcomes during COVID-19 infection.

Keywords: COVID-19, human resources, obesity, ventilation, intensive and critical care

INTRODUCTION

The first severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in Germany was reported on January 27, 2020 (1, 2), about 2 months after the first pneumonia patient-cases of unknown origin were identified in Wuhan, China (3, 4). Patients with detected SARS-CoV-2 infection have been documented both in hospitals and in family settings (4). The first reports from China indicated mild symptoms in the majority (approximately 4/5) of patients with SARS-CoV-2 infection, about one-fifth were hospitalized, and among them, one-fourth were admitted to intensive care units (ICUs) (3, 5, 6). From China, the SARS-CoV-2 pandemic spread worldwide and affected nearly every country (1, 5, 7, 8). In order to avoid a critical overload of the healthcare system, many countries, like Germany, have implemented lockdown strategies (5, 8, 9). Since the beginning of the COVID-19 pandemic, deaths related to COVID-19 counted more than 5 million people worldwide (10). In particular, the case-fatality rate of COVID-19 patients who have to be treated in ICUs with mechanical ventilation (MV) is very high (2, 5, 9). Studies have shown an association between COVID-19 and cardiovascular disease (CVD) (11, 12). Particularly, preexisting CVD seems to be linked with poor outcomes in patients with COVID-19 (11, 12). Although the predominant clinical manifestation of COVID-19 is pneumonia, COVID-19 infection can also induce CVD such as acute coronary syndrome with myocardial injury, arrhythmia, and venous thromboembolism (VTE) (2, 11, 12). Vascular response to cytokine production of SARS-CoV-2 and interaction between severe acute respiratory syndrome in COVID-19 and angiotensin-converting enzyme 2 receptor might lead to a significant reduction regarding cardiac contractility and result in myocardial dysfunction (12).

Another ongoing pandemic is the increase of obesity worldwide (13, 14). Obesity is a major healthcare concern, not only in high-income countries but even in middle-income and low-income countries, because of its continuous increase in the populations and of its association with chronic diseases, such as CVD, diabetes mellitus (DM), chronic kidney disease (CKD), and some cancer entities (13, 14). In the context of the COVID-19 pandemic, many studies (but not all) identified obesity as a strong risk factor for adverse outcomes in patients with SARS-CoV-2 infection (2, 13, 15–21).

Obesity is accompanied by a well-known chronic inflammatory condition (21). Obesity and its effects on immunity might aggravate disease severity of pneumonia and acute respiratory distress syndrome (ARDS), which are important causes of death due to SARS-CoV-2 infection (21). Adipocytes of the adipose tissue produce and secrete the hormone leptin in proportion to individuals' body fat mass (21). Increasing levels of circulating plasma leptin are typical for obesity and associated with a leptin-resistant state (21). Leptin, which regulates appetite and immunity, functions in immunity as a cytokine coordinating a host's innate as well as adaptive responses by promoting the Th1 type of the immune response (21). Leptin is an important factor regarding proliferation and different functions of antigen-presenting cells, T-helper cells, and monocytes, subsequently influencing the pro-inflammatory cytokine secretions by these cells including TNF-a, IL-2, and/or IL-6 (21). Scarcity of leptin levels and leptin resistance correlate with dysregulation of cytokine secretion resulting in autoimmune disorders, inflammatory responses, and especially increased susceptibility towards infections (21, 22). Thus, higher leptin levels and leptin activity in obese individuals contribute to higher mortality rates during SARS-CoV-2 infection (21, 22). In addition, the increased susceptibility to SARS-CoV-2 infection documented in obesity suggests an initial defect in the defense mechanisms, most likely caused by the aforementioned higher systemic metabolic inflammation, which is regulated by NLRP3 inflammasome as a master regulator of metaflammation with a pivotal role in obesity (23–25). NLRP3 inflammasome over-activation contributes to the development of cardiometabolic disorders, while NLRP3 deficiency is accompanied by decreased immune cell activation and, therefore, plays a key role in the immune defense of the host against pathogens, including viruses (23–25). Moreover, increased abdominal visceral adiposity compromises pulmonary function, decreases diaphragmatic excursion, and impairs lung ventilation resulting in reduced oxygen saturated blood levels (22).

The objectives of the present study were to investigate differences in patient characteristics, treatments, and adverse in-hospital events and outcomes of COVID-19 patients with and without obesity as well as the impact of obesity on adverse in-hospital events and outcomes of COVID-19 patients in Germany.

METHODS

Data Source

The statistical analyses of this study were performed on our behalf by the Research Data Center (RDC) of the Federal Bureau of Statistics (Wiesbaden, Germany). Aggregated statistical results were provided by the RDC on the basis of generated SPSS codes (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. IBM Corp: Armonk, NY, USA), which we had created and sent to the RDC (source: RDC of the Federal

Statistical Office and the Statistical Offices of the federal states, DRG Statistics 2020, own calculations) (2, 26, 27).

In the present data study-analysis of the German nationwide inpatient sample, we aimed to investigate temporal trends of all hospitalized patients with a confirmed COVID-19 diagnosis (ICD code U07.1) during the observational period between January 1 and December 31, 2020, and stratify the included COVID-19 hospitalizations for additionally coded obesity as well as identify independent predictors of in-hospital death of obese COVID-19 patients.

Study Oversight and Support

There was no commercial support regarding our present study and no foreign influence on the preparation of this report. Since our study did not contain direct access by us (as the investigators) to individual patient data and we had only access to summarized results provided by the RDC, approval by an ethics committee as well as patients' informed consent was not required, in accordance with German law (26, 27).

Coding of Diagnoses, Procedures, and Definitions

Shortly after the beginning of the century (since the year 2004), diagnosis- and procedure-related remunerations were introduced and implemented in the German healthcare system for German hospitals. Coding according to the German Diagnosis Related Groups (G-DRG) system with the coding of patient data on diagnoses, coexisting conditions, and surgeries as well as diagnostic and interventional procedures is required, and the transfer of these codes to the Institute for the Hospital Remuneration System is mandatory for German hospitals to get their remuneration regarding rendered and provided services (15, 16). In this context, patients' diagnoses are coded according to the International Statistical Classification of Diseases and Related Health Problems (of the 10th revision with German modification, ICD-10-GM) (19, 20). In addition, diagnostic, interventional, and surgical procedures are coded according to special OPS codes [Operationen- und Prozedurenschlüssel (surgical and procedural coding). With this present analysis of the German nationwide inpatient sample, we were able to identify all patients with confirmed COVID-19 diagnosis (ICD code U07.1] hospitalized in German hospitals during the year 2020 (COVID-19 as main or secondary diagnosis).

To obtain data of coexisting conditions, comorbidities, complications, and treatments, the aforementioned available diagnostic and procedural codes were used for acute and chronic conditions (OPS and ICD-10-GM codes).

The selected COVID-19 patients were stratified for additionally coded obesity (defined as body mass index [BMI] ≥30 kg/m^2 according to the WHO; ICD code E66). Patients with obesity were further classified in mild obesity (obesity class I: BMI 30 to <35 kg/m^2, ICD codes E66.00, E66.10, E66.20, E66.80, and E66.90), moderate obesity (obesity class II: BMI 35 to <40 kg/m^2, ICD codes E66.01, E66.11, E66.21, E66.81, and E66.91), and severe obesity (obesity class III: BMI >40 kg/m^2, ICD codes E66.02, E66.12, E66.22, E66.82, and E66.92).

Post-COVID was defined as the status of previous survived COVID-19 infection before the patient's hospitalization with the actual (and therefore at this time recurrent) COVID-19 infection.

Study Outcomes and Adverse In-Hospital Events

The primary study outcome was defined as case fatality with death due to all causes during in-hospital stay (in-hospital case fatality). In addition, we analyzed the prevalence of major adverse cardiovascular and cerebrovascular events [MACCE, composite of all-cause in-hospital death, acute myocardial infarction (ICD code I21), and/or ischemic stroke (ICD code I63)] as well as that of the adverse in-hospital events ARDS (ICD code J80), VTE (ICD codes I26, I80-I82), acute renal failure (ICD code N17), myocarditis (ICD code I40), myocardial infarction (ICD codes I21-I22), ischemic or hemorrhagic stroke (ICD codes I61-I64), cardiopulmonary resuscitation (CPR, OPS code 8-77), ICU, OPS codes 8-980, 8-98d, and 8-98f), MV (OPS codes 8-71), gastrointestinal bleeding (ICD code K92.0-K92.2), intracerebral bleeding (ICB; ICD code I61), and transfusion of blood constituents (OPS codes 8-800).

Statistical Analysis

For the objective, to compare COVID-19 patients with and without obesity, we analyzed the differences between these two groups. The differences in patient characteristics between the groups of hospitalized COVID-19 patients with and without obesity were calculated with the help of the Wilcoxon–Whitney U test for continuous variables and Fisher's exact or chi (2) test for categorical variables, as appropriate. We used Bonferroni's correction method for multiple testing. For the reported differences between patient characteristics and adverse in-hospital events of both groups (COVID-19 cases with and without obesity) (presented in **Table 1**), Bonferroni's correction method for multiple testing was used and indicated that only p-values <0.00139 and not p-value <0.05 identified a significant difference.

Since COVID-19 is a new disease with the first cases in Germany diagnosed in January 2020 and a learning process regarding pathomechanism, risk factors, and treatments in the years 2020 (1, 2), it is of outstanding interest to analyze the time trends of these patients. Temporal trends of the total numbers of hospitalizations of COVID-19 patients, obesity classes, treatment in ICUs, use of MV, VTE events, and in-hospital mortality over time and with increasing age were estimated by means of linear regression analyses. Results were presented as β-estimates and 95% CIs.

Univariate and multivariate logistic regression models were computed in order to investigate associations between obesity and adverse in-hospital events and invasive treatments. The multivariate regression models were adjusted for age, sex, cancer, heart failure, coronary artery disease, peripheral artery disease, chronic obstructive pulmonary disease, essential arterial hypertension, hyperlipidemia, renal insufficiency (glomerular filtration rate [GFR] <60 ml/min/1,73 m^2), DM, and atrial fibrillation/flutter. We selected this epidemiological approach regarding this adjustment to test the widespread independence of obesity as an influencing factor on adverse in-hospital events of these outstanding

TABLE 1 | Patients' characteristics, medical history, presentation, and adverse in-hospital events of the 176,137 hospitalized patients with confirmed COVID-19 infection in Germany in the year 2020 stratified for obesity.

Parameters	COVID-19 with obesity (n = 9,383; 5.3%)	COVID-19 without obesity (n = 166,754; 94.7%)	p-Value*
Age	66.0 (54.0/76.0)	72.0 (56.0/82.0)	**<0.001**
Age ≥ 70 years	3,879 (41.3%)	90,450 (54.2%)	**<0.001**
Female sex	4,704 (50.1%)	79,245 (47.5%)	**<0.001**
In-hospital stay (days)	10.0 (5.0/19.0)	8.0 (4.0/14.0)	**<0.001**
Cardiovascular risk factors			
Diabetes mellitus	4,293 (45.8%)	40,939 (24.6%)	**<0.001**
Essential arterial hypertension	5,510 (58.7%)	76,970 (46.2%)	**<0.001**
Hyperlipidemia	2,066 (22.0%)	25,507 (15.3%)	**<0.001**
Comorbidities			
Coronary artery disease	1,692 (18.0%)	23,882 (14.3%)	**<0.001**
Heart failure	2,293 (24.4%)	24,826 (14.9%)	**<0.001**
Peripheral artery disease	438 (4.7%)	5,202 (3.1%)	**<0.001**
Atrial fibrillation/flutter	2,147 (22.9%)	32,013 (19.2%)	**<0.001**
Chronic obstructive pulmonary disease	1,077 (11.5%)	11,077 (6.6%)	**<0.001**
Chronic renal insufficiency (glomerular filtration rate <60 ml/min/ 1,73 m^2)	2,010 (21.4%)	25,362 (15.2%)	**<0.001**
Cancer	394 (4.2%)	8,607 (5.2%)	**<0.001**
Mild liver disease	276 (2.9%)	1,369 (0.8%)	**<0.001**
Severe liver disease	389 (4.1%)	3,750 (2.2%)	**<0.001**
Charlson comorbidity index	4.44 ± 3.01	4.08 ± 2.92	**<0.001**
Respiratory manifestations of COVID-19 and post-COVID-19 status			
Pneumonia	6,505 (69.3%)	100,408 (60.2%)	**<0.001**
Acute respiratory distress syndrome	1,464 (15.6%)	10,130 (6.1%)	**<0.001**
Multi-systemic inflammatory syndrome COVID-19 infection	46 (0.5%)	451 (0.3%)	**<0.001**
Post-COVID-19 status	33 (0.4%)	524 (0.3%)	0.529
Treatment			
Intensive care unit	2,826 (30.1%)	24,227 (14.5%)	**<0.001**
Mechanical ventilation	1,438 (15.3%)	10,704 (6.4%)	**<0.001**
Extracorporeal membrane oxygenation (ECMO)	257 (2.7%)	1,197 (0.7%)	**<0.001**
Dialysis	648 (6.9%)	4,927 (3.0%)	**<0.001**
Adverse events during hospitalization			
In-hospital death	1,585 (16.9%)	30,022 (18.0%)	**0.006**
Major adverse cardiac and cerebrovascular events (MACCE)	1,788 (19.1%)	33,236 (19.9%)	**0.039**
Cardiopulmonary resuscitation	288 (3.1%)	2,571 (1.5%)	**<0.001**
Venous thromboembolism	432 (4.6%)	4,555 (2.7%)	**<0.001**
Acute kidney failure	2,037 (21.7%)	20,038 (12.0%)	**<0.001**
Myocarditis	17 (0.2%)	209 (0.1%)	0.141
Myocardial infarction	174 (1.9%)	2,579 (1.5%)	**0.019**
Stroke (ischemic or hemorrhagic)	175 (1.9%)	3,021 (1.8%)	0.706
Intracerebral bleeding	49 (0.5%)	527 (0.3%)	**0.001**
Gastrointestinal bleeding	167 (1.8%)	2,781 (1.7%)	0.410
Transfusion of blood constituents	1,129 (12.0%)	12,745 (7.6%)	**<0.001**

**After using Bonferroni's correction method for multiple testing, p-values <0.00139 remain significant.*
**Significant P-values are marked in bold.*

known predictors of case-fatality rate during hospitalization. The results were presented as odds ratios (ORs) and 95% CI. Regarding the logistic regression models, only the p-values <0.05 (two-sided) were considered to be statistically significant.

All statistical analyses were carried out with the use of SPSS software (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. IBM Corp: Armonk, NY, USA).

RESULTS

Baseline Characteristics

Overall, 176,137 hospitalization cases with confirmed COVID-19 infection were reported in Germany during the year 2020. Among them, 9,383 (5.3%) were additionally coded with obesity.

Comparison of Obese vs. Non-Obese COVID-19 Inpatients

COVID-19 patients without obesity were in median 6 years older (72.0 [interquartile range (IQR) 56.0/82.0] vs. 66.0 [54.0/76.0] years, $p < 0.001$), while gender distribution was almost equal. Length of in-hospital stay was longer in obese than in non-obese COVID-19 patients (10.0 [5.0/19.0] vs. 8.0 [4.0/14.0], $p < 0.001$). Despite the younger age of obese COVID-19 patients, all investigated CVD risk factors and CVD were more prevalent in obese COVID-19 patients (**Table 1**). In addition, also chronic obstructive pulmonary disease, liver diseases, and CKD were more frequent in obese COVID-19 patients, and consequently, the Charlson comorbidity index score was higher in obese than

in non-obese COVID-19 patients (mean and SD: 4.44 ± 3.01 vs. 4.08 ± 2.92, p < 0.001). In contrast, cancer (5.2% vs. 4.2%, p < 0.001) was more prevalent in non-obese patients (**Table 1**).

The majority of obese and non-obese COVID-19 patients revealed pneumonia as a respiratory manifestation, whereby pneumonia (69.3% vs. 60.2%, p < 0.001) and also ARDS (15.6% vs. 6.1%, p < 0.001) occurred more often in obese than in non-obese COVID-19 patients (**Table 1**). In all ARDS severity categories, obese patients were more frequently detected (**Figure 1B**). Post-COVID-19 status was not more common in one of the groups. After Bonferroni's correction method was used for multiple testing, all of these reported differences between patient characteristics and adverse in-hospital events of both groups (COVID-19 cases with and without obesity) remained significant, since after Bonferroni's correction all p-values <0.00139 were still significant.

Treatment Differences of Obese vs. Non-Obese COVID-19 Inpatients

Obese COVID-19 patients were more often treated on ICUs (30.1% vs. 14.5%, p < 0.001) and needed more often MV (15.3% vs. 6.4%, p < 0.001) (**Table 1**). Extracorporeal membrane oxygenation (ECMO) was more frequently performed in obese patients (2.7% vs. 0.7%, p < 0.001), and the necessity of dialysis was also more than doubled in obese COVID-19 patients (**Table 1**).

Outcomes of Obese vs. Non-Obese COVID-19 Inpatients and Impact of Obesity on Adverse In-Hospital Events of COVID-19 Inpatients

Despite the unfavorable comorbidity profile of obese COVID-19 patients, the in-hospital case-fatality rate (16.9% vs. 18.0%, p = 0.006), the MACCE rate (19.1% vs. 19.9%, p = 0.039), and rate of myocardial infarction were lower than in non-obese patients, triggered by a large proportion of COVID-19 patients in older age decades of life (**Table 1**). While stroke and myocarditis were similar prevalent in both groups, VTE (4.6% vs. 2.7%, p < 0.001) and acute kidney failure (21.7% vs. 12.0%, p < 0.001) were more frequent in obese patients. Transfusion of blood constituents (12.0% vs. 7.6%, p < 0.001) and ICB events (0.5% vs. 0.3%, p = 0.001) were more often counted in obese patients (**Table 1**).

After adjustment for age, gender, and comorbidities, obesity was independently associated with increased in-hospital case fatality (OR 1.203 [95% CI 1.131–1.279], p < 0.001) and MACCE (OR 1.168 [95% CI 1.101–1.239], p < 0.001) rate (**Table 2** and **Figure 1A**), whereas univariate logistic regressions did not reveal the same associations due to clear differences in age, CVD risk factors, and comorbidities between the two groups (COVID-19 patients with and without obesity). For further in-depth analysis, we conducted an age-dependent comparison of COVID-19 patients with and without obesity in each decade of life. The in-hospital case-fatality rate was higher in obese than in non-obese COVID-19 patients in the 3rd to 8th decades of life. In younger patients, case fatality was similar between both groups, and in COVID-19 patients aged 80 years or older, case fatality was not negatively influenced by obesity (**Table 3** and **Figure 2**). The multivariate regression models demonstrated an independent association of obesity with increased case-fatality rate in COVID-19 patients aged between 20 and 69 years. Case-fatality rates of older patients were not significantly and independently influenced. The largest effect of obesity on case-fatality rate was seen in COVID-19 patients in the 3rd life decade with a 6.6-fold increased case-fatality rate (**Table 3** and **Figure 2**).

In addition, obesity affected the occurrence of pneumonia (OR 1.517 [95% CI 1.448–1.589], p < 0.001), ARDS (OR 2.605

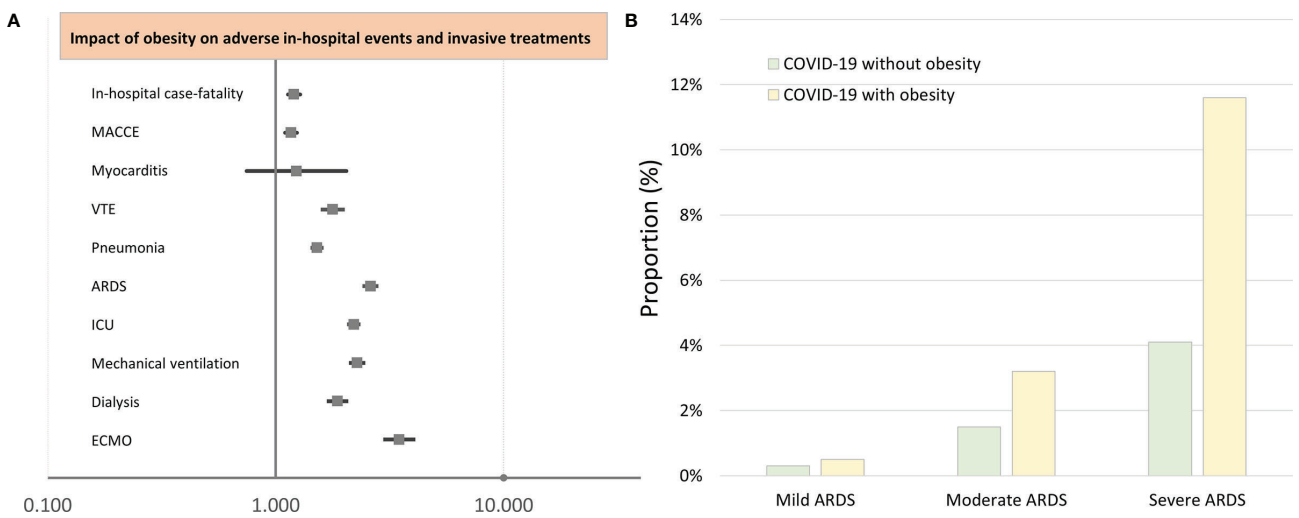

FIGURE 1 | Impact of obesity on adverse in-hospital events and interventional treatments of COVID-19 patients (multivariate logistic regression analysis). **(A)** Impact of obesity on adverse in-hospital events and interventional treatments of COVID-19 patients (multivariate logistic regression analysis). **(B)** Proportion of COVID-19 patients with and without obesity on ARDS. MACCE, major adverse cardiac and cerebrovascular events; VTE, venous thromboembolism; ARDS, acute respiratory distress syndrome; ICU, intensive care unit; ECMO, extracorporeal membrane oxygenation.

TABLE 2 | Impact of obesity on in-hospital death and adverse events during in-hospital stay in patients with COVID-19 (univariate and multivariate logistic regression models).

	Univariate regression model		Multivariate regression model	
	OR (95% CI)	p-Value	OR (95% CI)	p-Value
In-hospital death	0.926 (0.876–0.978)	**0.006**	1.203 (1.131–1.279)	**<0.001**
MACCE	0.946 (0.897–0.997)	**0.039**	1.168 (1.101–1.239)	**<0.001**
Pneumonia	1.493 (1.428–1.562)	**<0.001**	1.517 (1.448–1.589)	**<0.001**
ARDS	2.858 (2.694–3.033)	**<0.001**	2.605 (2.449–2.772)	**<0.001**
Venous thromboembolism	1.719 (1.554–1.901)	**<0.001**	1.780 (1.605–1.973)	**<0.001**
Acute renal failure	2.030 (1.929–2.137)	**<0.001**	1.955 (1.850–2.066)	**<0.001**
Myocardial infarction	1.203 (1.030–1.404)	**0.020**	0.991 (0.843–1.165)	0.915
Cardiopulmonary resuscitation	2.022 (1.787–2.288)	**<0.001**	1.695 (1.492–1.926)	**<0.001**
Stroke (ischemic or hemorrhagic)	1.030 (0.883–1.201)	0.706	1.013 (0.866–1.185)	0.868
Intracerebral bleeding	1.656 (1.235–2.221)	**0.001**	1.611 (1.194–2.172)	**0.002**
Gastrointestinal bleeding	1.068 (0.913–1.251)	0.410	1.093 (0.931–1.284)	0.277
Transfusion of blood constituents	1.653 (1.549–1.763)	**<0.001**	1.484 (1.387–1.589)	**<0.001**
Intensive care unit treatment	2.536 (2.421–2.655)	**<0.001**	2.201 (2.097–2.310)	**<0.001**
Mechanical ventilation	2.639 (2.486–2.800)	**<0.001**	2.277 (2.140–2.422)	**<0.001**
ECMO	3.895 (3.39–4.464)	**<0.001**	3.485 (3.023–4.017)	**<0.001**
Dialysis	2.437 (2.239–2.652)	**<0.001**	1.869 (1.708–2.045)	**<0.001**
Myocarditis	1.446 (0.882–2.372)	0.144	1.234 (0.746–2.040)	0.413
Post-COVID status	1.120 (0.787–1.593)	0.530	1.079 (0.755–1.543)	0.675

MACCE, major adverse cardiovascular and cerebrovascular events; ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation.
Significant P-values are marked in bold.

[95% CI 2.449–2.772], p < 0.001), and VTE (OR 1.780 [95% CI 1.605–1.973], p < 0.001) (**Table 2** and **Figure 1A**).

Obesity in COVID-19 patients is a risk factor for ICU treatment (OR 2.201 [95% CI 2.097–2.310], p < 0.001), MV (OR 2.277 [95% CI 2.140–2.422], p < 0.001), and the rescue treatment with ECMO (OR 3.485 [95% CI 3.023–4.017], p < 0.001) (**Table 2** and **Figure 1A**).

In addition, a higher rate of acute kidney failure (OR 1.955 [95% CI 1.850–2.066], p < 0.001) resulted in an increased necessity of dialysis treatment (OR 1.869 [95% CI 1.708–2.045], p < 0.001) in patients with obesity. COVID-19 patients presented with an increased risk for ICB (OR 1.611 [95% CI 1.194–2.172], p = 0.002) and had an elevated risk regarding transfusion of blood constituents (OR 1.484 [95% CI 1.387–1.589], p < 0.001) (**Table 2** and **Figure 1A**).

Impact of Obesity Classes on Outcomes and Treatment

The distribution of the obesity classes of the admitted patients with COVID-19 did not vary significantly over the observational period (**Figure 3A**). The highest proportions of severe obesity were found in the 4th to 7th decades of life (**Figure 3D**). The prevalence of pneumonia, ARDS, and VTE events is increased with increasing obesity classes (**Figures 3C, F**). In contrast, the proportion of COVID-19 inpatients who suffered from MACCE or died during the in-hospital stay was the highest in severe obesity and revealed the lowest mortality in the mild obesity class (**Figure 3B**). Remarkably, the use of MV and ECMO increased with the increase in obesity class (**Figure 3E**).

TABLE 3 | Impact of obesity on in-hospital death in patients with COVID-19 stratified for age decades (univariate and multivariate logistic regression models).

	Univariate regression model		Multivariate regression model	
	OR (95% CI)	p-Value	OR (95% CI)	p-Value
0–9 years	Not applicable	-	Not applicable	-
10–19 years	Not applicable	-	Not applicable	-
20–29 years	7.409 (2.947–18.626)	**<0.001**	6.581 (2.331–18.581)	**<0.001**
30–39 years	4.188 (2.222–7.894)	**<0.001**	3.566 (1.776–7.160)	**<0.001**
40–49 years	3.427 (2.449–4.795)	**<0.001**	2.821 (1.944–4.094)	**<0.001**
50–59 years	2.321 (1.944–2.771)	**<0.001**	1.753 (1.442–2.132)	**<0.001**
60–69 years	1.434 (1.267–1.622)	**0.020**	1.162 (1.017–1.327)	**0.027**
70–79 years	1.166 (1.052–1.294)	**0.004**	1.054 (0.944–1.176)	0.353
80–89 years	0.943 (0.845–1.053)	0.298	0.944 (0.843–1.059)	0.327
90–99 years	0.912 (0.668–1.246)	0.565	0.917 (0.667–1.261)	0.959

Significant P-values are marked in bold.

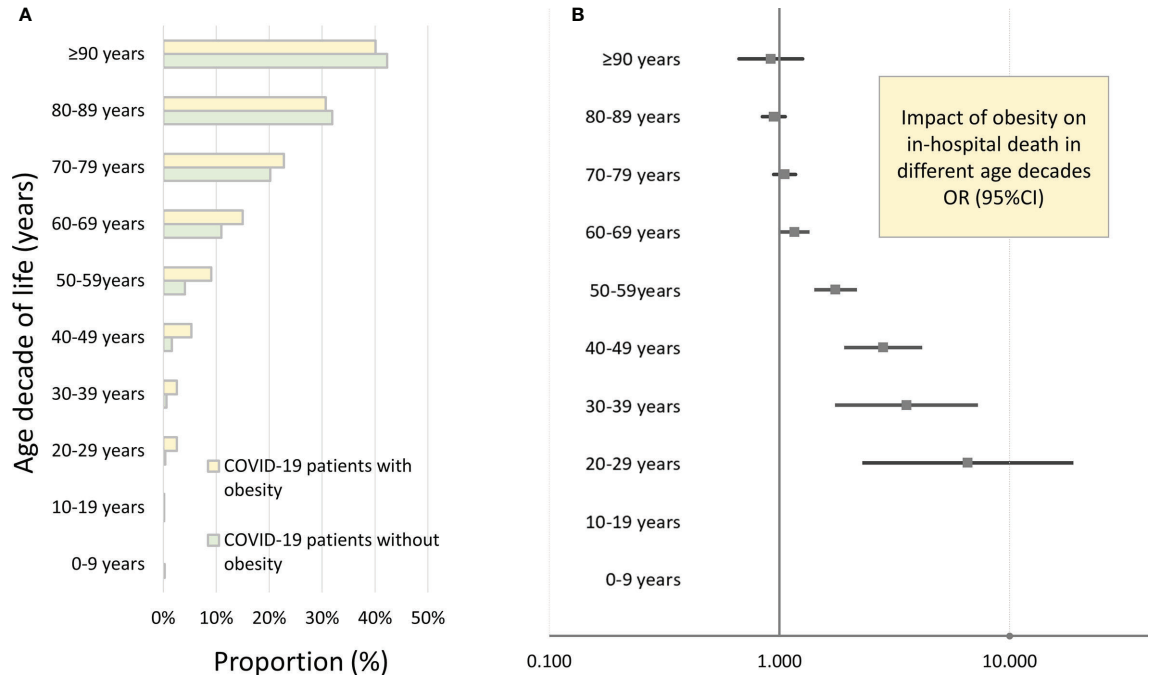

FIGURE 2 | Impact of obesity on in-hospital death of inpatients with COVID-19 infection in Germany 2020 stratified for age decades. **(A)** In-hospital case-fatality rates of COVID-19 patients in different age decades stratified for presence of obesity. **(B)** Independent impact of obesity on in-hospital case fatality of inpatients with COVID-19 infection stratified for age decades (results of the multivariate logistic regression model).

The adjusted multivariate logistic regression models showed that severe obesity was independently associated with case fatality of COVID-19 patients (OR 1.810 [95% CI 1.615–2.029], p < 0.001), whereas mild and moderate obesity affected the case fatality insignificantly (**Figure 4A**). Similarly, MACCE was independently influenced only by severe obesity (OR 1.616 [95% CI 1.447–1.805], p < 0.001), but not from mild and moderate obesity (**Figure 4B**). In contrast, the occurrence of pneumonia and VTE as well as the use of the treatments with MV and ECMO was affected by all obesity classes and the intensity of this impact of obesity on pneumonia, VTE, MV, and ECMO increased with the increase in obesity class (**Figures 4C–F**).

Temporal and Seasonal Trends

The highest monthly numbers of hospitalizations of COVID-19 patients with obesity were observed from October to December 2020 (**Figure 5A**). In November 2020, more than 3,000 obese COVID-19 patients were treated in German hospitals. During summer, the lowest obese COVID-19 patient numbers were detected (**Figure 5A**). The age-dependent analysis showed the highest total numbers of obese COVID-19 patients in the 7th and 8th age decades (**Figure 5B**).

The monthly case-fatality rates were increased in the months with higher numbers of admitted COVID-19 patients during March and April as well as between October and December (**Figure 5B**) but did not change significantly during the observational period when considering a trend over the whole year 2020 (β −0.135 [95% CI −0.304 to 0.034], p = 0.116). In contrast, the in-hospital case-fatality rate of obese COVID-19 patients increased exponentially with age (β 1.041 [95% CI 0.957 to 1.125], p < 0.001) (**Figure 5B**). Remarkably, the necessity of ICU treatment (β −0.909 [95% CI −1.045 to −0.882], p < 0.001) and MV (β −0.323 [95% CI −0.499 to −0.147], p < 0.001) decreased over the months of the year 2020 (**Figure 5A**).

The proportion of obese COVID-19 patients who were treated in ICUs and had to be ventilated was highest in the 5th to 8th life age decades (**Figure 5B**). Statistically, patient numbers of ICU treatment (β −0.120 [95% CI −0.191 to −0.050], p = 0.001) and MV (β −0.159 [95% CI −0.249 to −0.069], p = 0.001) decreased with increasing age decades (**Figure 5B**). In **Figure 5C**, the total numbers of obese COVID-19 patients treated in ICUs stratified for the different months are shown. The figure illustrates that the monthly proportions of ventilated patients who were admitted to ICUs were the highest in January and February 2020 and decreased afterward, although the total numbers of obese COVID-19 patients in ICUs were small in the first 2 months of 2020 compared to later months. This might be caused and may represent a learning curve regarding the ICU treatment modalities in German hospitals (**Figure 5C**). Although the total numbers of COVID-19 patients with obesity admitted to German ICU between 20th and 49th life-years were low in comparison to the age group between 50th and 79th life-years, the proportion of MV was substantially higher in the younger age group (**Figure 5D**).

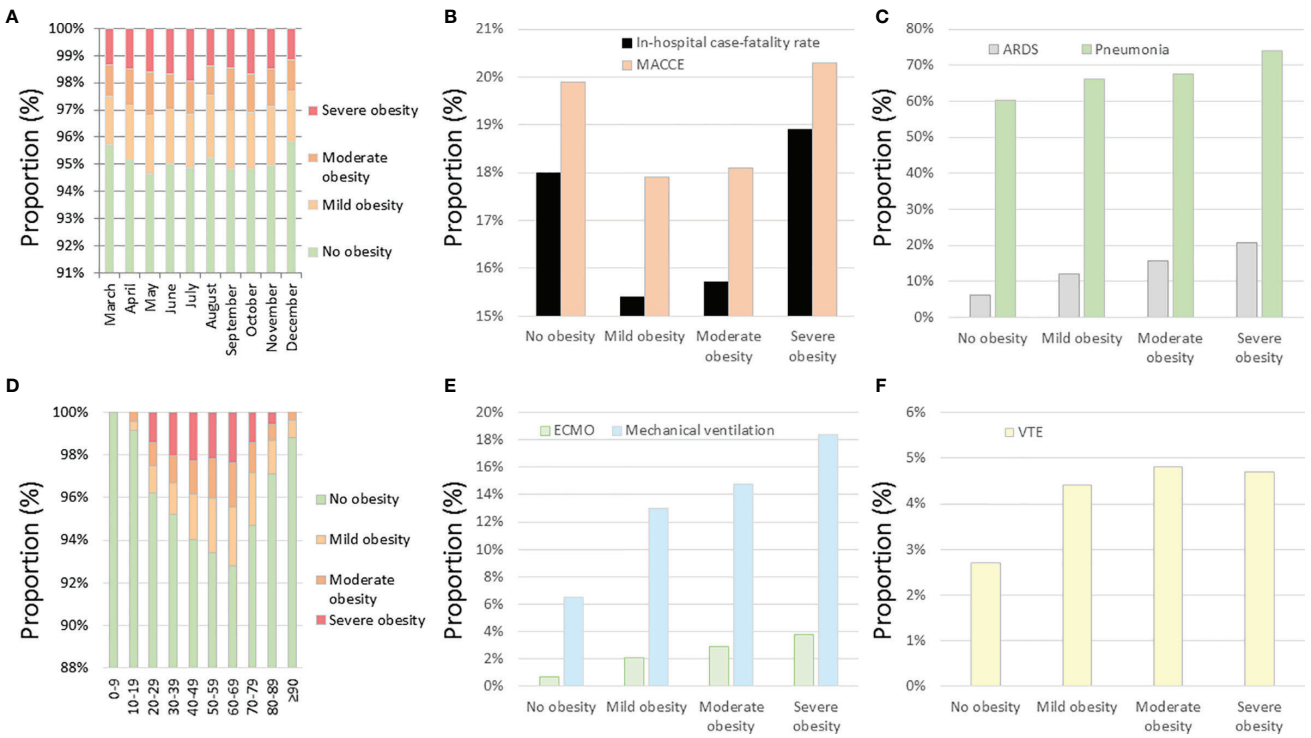

FIGURE 3 | Temporal trends regarding obesity classes and impact of obesity classes on outcomes and treatments of inpatients with COVID-19 infection in Germany 2020. **(A)** Temporal trends regarding obesity classes in inpatients with COVID-19 infection stratified for months. **(B)** Impact of obesity classes on in-hospital case fatality and MACCE in inpatients with COVID-19 infection. **(C)** Impact of obesity classes on ARDS and pneumonia in inpatients with COVID-19 infection. **(D)** Temporal trends regarding obesity classes in inpatients with COVID-19 infection stratified for age decades. **(E)** Impact of obesity classes on ECMO and mechanical ventilation in inpatients with COVID-19 infection. **(F)** Impact of obesity classes on VTE events in inpatients with COVID-19 infection. MACCE, major adverse cardiovascular and cerebrovascular events; ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; VTE, venous thromboembolism.

Last but not least, the monthly numbers of VTE events decreased over time (β −0.823 [95% CI −1.125 to −0.522], $p < 0.001$) (**Figure 5A**) but remained widely unchanged with age (β −0.128 [95% CI −0.283 to 0.027], $p = 0.105$) (**Figure 5B**).

DISCUSSION

One wave after another of the COVID-19 pandemic has been affecting the citizens and healthcare systems of the countries worldwide. At the end of January 2022, nearly 350 million COVID-19 cases and more than 5.5 million deaths linked with a COVID-19 infection were counted worldwide (10). Regarding risk stratification and better management of these patients with COVID-19 infections, it is of outstanding interest to identify risk factors of adverse outcomes and in-hospital death in hospitalized patients with COVID-19 to initiate adequate treatment, prevent poor outcomes, and save hospital resources to manage pandemic waves without overwhelming regional healthcare systems (2, 5). Several studies identified, among others, obesity is one of these risk factors for higher proneness to SARS-CoV-2 infection and a poorer outcome during COVID-19 infection (2, 10, 12, 14–17).

Thus, in the present study, we attempted to analyze the impact of obesity on adverse in-hospital events in all hospitalized COVID-19 patients in Germany during the year 2020.

The main results of the study can be summarized as follows:

i) COVID-19 patients with obesity were distinctly younger at admission; nevertheless, obese COVID-19 patients presented with an aggravated comorbidity profile.

ii) The majority of obese and non-obese COVID-19 patients presented with pneumonia as their respiratory manifestation, whereby pneumonia and ARDS occurred more frequently in obese than in non-obese COVID-19 patients.

iii) Obese COVID-19 patients were treated more often admitted to ICUs with a higher rate of organ support, such as MV, dialysis, and ECMO.

iv) Obesity was independently associated with increased in-hospital case fatality and MACCE rate as well as with pneumonia and VTE events. Particularly, severe obesity was associated with case fatality as well as MACCE.

v) An age-dependent impact of obesity on in-hospital case fatality was observed with the highest impact in the 3rd and

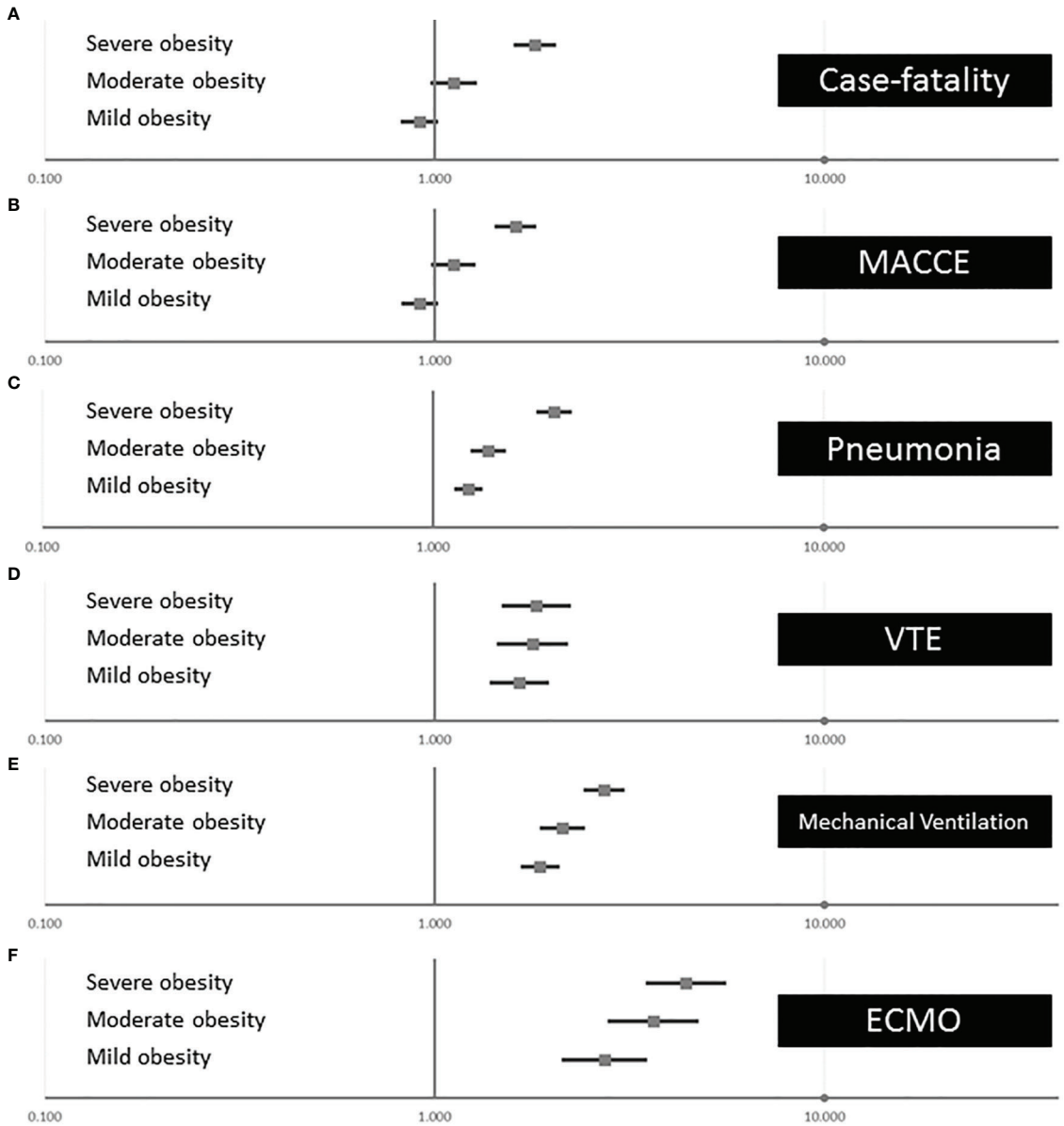

FIGURE 4 | Associations of obesity classes with outcomes and treatments of inpatients with COVID-19 infection in Germany 2020 (multivariate logistic regression models). **(A)** Independent association between the different obesity classes on in-hospital case fatality of inpatients with COVID-19. **(B)** Independent association between the different obesity classes on MACCE of inpatients with COVID-19. **(C)** Independent association between the different obesity classes on pneumonia of inpatients with COVID-19. **(D)** Independent association between the different obesity classes on VTE of inpatients with COVID-19. **(E)** Independent association between the different obesity classes on mechanical ventilation of inpatients with COVID-19. **(F)** Independent association between the different obesity classes on ECMO of inpatients with COVID-19. MACCE, major adverse cardiovascular and cerebrovascular events; VTE, venous thromboembolism; ECMO, extracorporeal membrane oxygenation.

4th decades of life, whereas obesity in older patients (≥8th decade of life) did not affect in-hospital case fatality independently.

In accordance with the literature (18, 28), our study results demonstrated that COVID-19 inpatients with obesity were younger than those without. Despite younger age, obese patients were affected with an unfavorable comorbidity profile, including CVD risk factors and CVD, and also lung diseases and CKD, similarly to other studies (13, 15, 16, 22, 28–31).

Our study results highlighted that the majority of COVID-19 patients suffered from pneumonia as their respiratory manifestation of COVID-19, whereby pneumonia and ARDS were more prevalent in obese than in non-obese COVID-19 patients. Regardless of the pathophysiological effects of acute

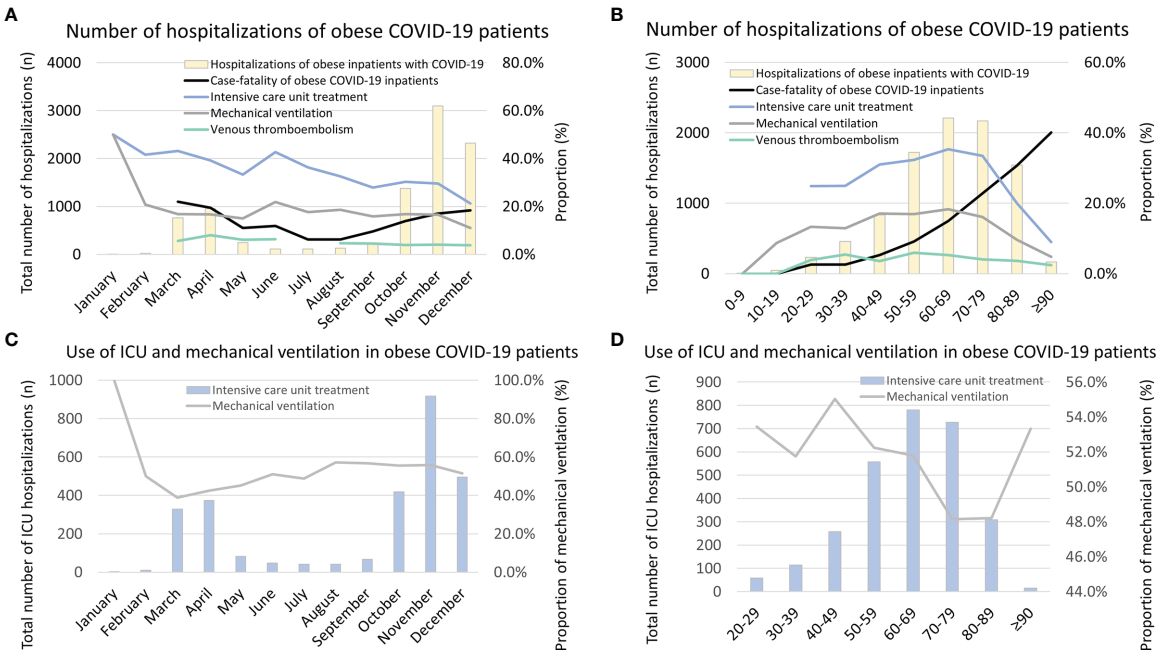

FIGURE 5 | Temporal trends regarding total numbers, case-fatality rate, VTE rate, treatment of ICU, and mechanical ventilation in obese inpatients with COVID-19 infection in Germany 2020. **(A)** Temporal trends regarding total numbers, case-fatality rate, VTE rate, treatment rates of ICU, and mechanical ventilation in obese inpatients with COVID-19 infection stratified for months. **(B)** Temporal trends regarding total numbers, case-fatality rate, VTE rate, treatment rates of ICU, and mechanical ventilation in obese inpatients with COVID-19 infection stratified for age decades. **(C)** Temporal trends regarding total numbers of ICU treatment, and among these, rate of mechanical ventilation in obese inpatients with COVID-19 infection is stratified for months. **(D)** Temporal trends regarding total numbers of ICU treatment, and among these, rate of mechanical ventilation in obese inpatients with COVID-19 infection is stratified for age decades. VTE, venous thromboembolism; ICU, intensive care unit.

respiratory failure (ARF) and ARDS, obese patients are characterized by multiple alterations in respiratory mechanics. The compliance of the respiratory system is influenced by the external compression due to the weight of fat tissue resulting in an impaired functional residual capacity (FRC) (32–34). The obesity hypoventilation syndrome is a well-known problem in severe obesity also outside COVID-19 infection and ICU treatment and is associated with an increase regarding the need for ventilator support and organ damage (35, 36).

Regarding the setting of respiratory parameters, the identification of optimal positive end-expiratory pressure (PEEP) in COVID-19 pneumonia and associated ARDS has especially been widely discussed since the beginning of the pandemic (37). Current consensus recommendations are provided on the basis of the ARDS network table to detect adequate PEEP (38). Since these recommendations for PEEP settings were derived from experiences in the standard population of patients predominantly with normal weight, it has to be suggested that obese patients might be ventilated with significantly higher PEEP values in order to overcome external compression of the respiratory system. Therefore, alternative approaches are needed to identify the optimal individualized PEEP in obese COVID-19 patients, such as electric impedance tomography or transpulmonary pressure measurement (39). In this context, too low PEEP values can result in negative end-expiratory trans-pulmonary pressure levels accompanied with elevated risk regarding the occurrence of atelectasis, impaired gas exchange, and cyclic lung collapse followed by pulmonary inflammation and ARF (40, 41).

Some other cornerstones in the up-to-date treatment of ARDS in COVID-19 patients, such as prone positioning, are also harder to achieve in obese patients. Prone positioning in obese patients requires more staff (nurses, respiratory therapists (RTs), and physicians) to provide it safely. Nevertheless, prone positioning could in severe obesity be harmful, and its implementation in the individual ICU treatment could sometimes be impossible if not provided by a skilled team (42–44).

In addition to the changes in respiratory mechanics, recent studies have indicated that the occurrence, disease severity of COVID-19 patients, and the attributed adverse outcomes of COVID-19 patients are directly associated with the weakened immune system in obese individuals by chronic inflammation due to adipose tissue and by dysregulation of pro-inflammatory cytokines (13, 15, 45). Therefore, it has to be hypothesized that acute inflammation arising from acute COVID-19 infection may amplify existing chronic inflammation secondary to obesity and might lead to a more severe disease status as well as poorer outcomes (15).

Our study results corroborate the aforementioned physiological effects of obesity, demonstrating that obese COVID-19 patients in Germany revealed more severe disease status and were treated more often in ICUs and with a higher rate of MV, dialysis, and ECMO. This more aggressive treatment approach might be attributed to

lower patient age and the higher number of obese COVID-19 patients who were treated at larger urban hospitals with more invasive capacities. However, it has been previously reported that obese patients have a higher demand for more aggressive treatments in the context of acute and critical care medicine including especially invasive treatment approaches (46–50).

Despite these strong efforts in therapy, obesity in COVID-19 was independently associated with increased in-hospital case-fatality rate and MACCE rate as well as VTE events in our study in accordance with others (10, 12, 14–17). Although the unadjusted comparison between obese and non-obese COVID-19 patients revealed that obese COVID-19 patients had a 1.1% lower in-hospital case-fatality rate (16.9% vs. 18.0%) in comparison to non-obese COVID-19 patients, the adjusted logistic regressions revealed a negative effect of obesity on the case-fatality rate. The multivariate logistic regression models (regarding the outcome in-hospital case fatality) demonstrated eminently an association of obesity in COVID-19 patients with increased in-hospital case fatality independently of age, sex, cancer, heart failure, coronary artery disease, peripheral artery disease, chronic obstructive pulmonary disease, essential arterial hypertension, hyperlipidemia, renal insufficiency (GFR < 60 ml/min/1,73 m^2), DM, and atrial fibrillation/flutter. For a more precise and in-depth comparison, we performed logistic regression models to analyze the impact of obesity on the case-fatality rate of COVID-19 patients in each decade of life. The age-dependent analysis demonstrated an independent association of obesity with increased case-fatality rate in the 3rd, 4th, 5th, 6th, and 7th decades of life in COVID-19 patients, while obesity did not affect case-fatality rates of older patients significantly and independently. Remarkably, the effect of obesity on the case-fatality rate was larger in COVID-19 patients in the 3rd and 4th decades of life. Since most hospitalized COVID-19 patients were older, it is not surprising that the univariate logistic regressions failed in the overall study sample without age-adjustment or age-dependent analysis to demonstrate an increased in-hospital case fatality in the unadjusted comparisons and was only evident in the adjusted and age-dependent analyses.

Gao et al. highlighted in accordance with our results that even below the threshold for obesity, a BMI higher than 23 kg/m^2 was associated with an increased risk of severe COVID-19 outcomes, particularly in patients younger than 40 years (13, 16). Also in line with these observations, the study of Mohammad et al. identified obesity as a major risk factor for adverse outcomes in patients with COVID-19 (15). In a large Swedish cohort of ICU patients with COVID-19, a high BMI was associated with an increased risk of death and prolonged length of in-hospital stay as well (18). Tartof et al. reported in a retrospective study that obesity plays an important role in risk for death from COVID-19, especially in male and younger patients (17). In addition, a large Korean study revealed a non-linear (U-shaped) relationship between BMI and fatal illness, meaning that especially patients with underweight as well as having a BMI ≥25 kg/m^2 had a higher risk of fatal COVID-19 disease (28). Also an analysis of the Premier Healthcare data of the United States (March–December 2020) showed that obesity was a risk factor for MV, hospitalization, and death predominantly among adults aged <65 years (51).

Based on nationally representative data on demographics and the cardiometabolic conditions of the patients, O'Hearn et al. estimated that nearly 2/3 (63.5%) of COVID-19 hospitalizations among the adult citizens of the United States were attributable to four cardiometabolic conditions: obesity, DM, arterial hypertension, and heart failure. Within this group, obesity (30.2%) and arterial hypertension (26.2%) were linked to most COVID-19 hospitalizations (52). The large epidemiology study of Popkin et al. reported an increase of COVID-19 patients' hospitalizations, ICU admissions, and deaths in nearly 400,000 COVID-19 patients with obesity worldwide (53). In contrast to some of the studies, our study results demonstrated that particularly severe obesity affected in-hospital case fatality and MACCE rate independently and significantly, while mild obesity and moderate obesity were not independently associated with these outcomes. In addition, as aforementioned, the impact of obesity was age-dependent.

In one previous publication of our research group, we observed a temporal trend regarding hospitalizations and in-hospital case-fatality rate of all hospitalized patients with COVID-19 infection in Germany 2020 (2). In line with the time trend of all admitted COVID-19 patients in Germany, the highest monthly numbers of hospitalizations of COVID-19 patients with obesity were observed during October to December 2020 and in the 7th and 8th age decades of life. Remarkably, the case-fatality rate was higher in the months with increased numbers of admitted COVID-19 patients, which might be interpreted as a surrogate of overloading of the healthcare system, and increased exponentially with age (2, 5, 8, 9).

Several pathophysiological mechanisms of obesity as a risk factor driving severe COVID-19 illness have been suggested (19): first, the adipose tissue has more angiotensin-converting enzyme-2 receptors, which is the site for the coronavirus entry into the cells, than does the lung tissue, so the excess adipose tissue could serve as a reservoir for the coronavirus (29, 30). Also an excess of abdominal fat and weight impairs adequate ventilation and increases the risk for infection (including expansion of the COVID-19 infection but also secondary infections) (19, 31), which might explain higher rates of pneumonia and ARDS of obese patients in our study. Certainly, central or abdominal obesity or visceral adipose tissue may carry a particularly "heavy" risk in COVID-19. Ventilating obese patients *via* mask ventilation or intubation is more difficult not least because of an increased thoracic mass accompanied by a need for higher positive end-expiratory and peak pressures to maintain proper oxygenation and an increased risk of barotrauma (such as alveolar injury/rupture and pneumothorax) (19, 31). Since our study detected a decrease regarding the necessity of ICU admissions and MV over the months of the year 2020, this could be interpreted as a learning curve of the treating physicians regarding the use of invasive treatments in obese COVID-19 patients. As mentioned, the effect of a weakened immune system in obese individuals by chronic inflammation due to adipose tissue and by dysregulation of pro-inflammatory cytokines might predispose obese COVID-19 patients to more severe infections (13, 15, 19, 45). Last but not least, social factors

may contribute to poor outcomes, including loneliness, and might be followed by a higher frequency of depressive syndromes (19). In addition, because the focus is on the healthcare system and the physicians working with the COVID-19 pandemic, other prevalent acute or chronic diseases that carry an increased risk for adverse outcomes in patients with COVID-19 infection and severe COVID-19 complications might be overlooked, be considered to be unimportant at this time, or be unnoticed (19). National lockdown measures with stay-at-home orders for longer periods favored sedentary lifestyle with distinctly reduced physical activity (PA) and exacerbated unhealthy dietary habits resulting in increased prevalence of obesity during the pandemic along with the psychological effects of social isolation (5, 8, 9, 19, 54). Nevertheless, the proportion of COVID-19 cases with severe obesity did not change over the months (**Figure 3A**), indicating only a slow shift regarding more severe obesity.

Obesity predisposes patients to develop a VTE event, which was reported by Karbhel et al., who demonstrated a strong association between increasing BMI and higher VTE rate (55). The authors outlined that the relative risk of unprovoked pulmonary embolism (PE) increased by approximately 8% per 1 kg/m^2 higher BMI and approached an approximately 6-fold elevated risk among individuals with a BMI ≥ 35 kg/m^2 (55, 56). This finding was supported by the results of the present study, revealing a 1.7-fold risk for VTE in obese vs. non-obese patients. VTE is a potentially life-threatening complication, and hospitalized COVID-19 patients frequently have macrovascular and microvascular thrombosis and inflammation, which are associated with a poor clinical outcome (57, 58). Interestingly, the number of VTE events in obese COVID-19 patients decreased over time but remained unchanged with age. This is an important finding, since the risk of VTE events increased in the general population, substantially with age (27, 59–61). Besides the challenges in dosing anticoagulants in critical ill overweight patients, it should be suggested that some VTE events might be overlooked since not all COVID-19 patients were examined by CT with angiography and PE might be fatal in COVID-19 patients before PE is diagnosed (62).

Based on our findings, we recommend that COVID-19 patients with obesity should be closely monitored when hospitalized (18). The awareness regarding VTE events is important in obese patients; these events or delays in the diagnosis of these life-threatening complications should not be overlooked (27, 59, 62). When clinicians develop healthcare plans for COVID-19 patients, they should consider the risk of poor outcomes, especially in patients with severe obesity (51). In addition, these considerations should be included in the promotion of COVID-19 prevention strategies and healthcare planning (51, 63, 64). Maintaining a healthy weight is therefore important not only to prevent chronic cardiometabolic diseases but also regarding better individual outcomes of COVID-19 patients (28, 63, 65, 66). Thus, public health efforts directed towards a healthy diet and an increase in PA are crucial in both children and adults (19, 63, 64, 66–70). A body of evidence suggests that the nutritional status of COVID-19 patients is directly associated with the severity of the SARS-CoV-2 disease (71–73). Although no single diet or food item has been proven to prevent COVID-19 infections, some key dietary components comprising vitamins C and D, omega-3 fatty acids, and zinc might have positive anti-inflammatory effects similar to the Mediterranean diet and might enhance the health of COVID-19 patients (71–73). In addition, the protective role of nutraceuticals such as quercetin and resveratrol in patients with obesity or cancer has to be considered and emphasized for regularization of the hypersecretion of interleukins and cytokines in order to improve the immune function and reduce the risk of ARDS and inflammation (73, 74). International efforts are needed to prevent obesity, particularly its progression to more severe degrees, and to improve PA, exercise, and fitness, as well as overall healthy living, for this and future pandemics (29, 31, 63–70).

Limitations

It is well known that obesity is an increasing problem worldwide (75, 76). The proportion of adults with prevalent obesity was estimated at 21.9% in male and 22.5% in female citizens of Germany (75). Thus, a rate of 5.3% obese COVID-19 patients suggests that there may have been an under-reporting and under-coding of obesity in the nationwide sample and, particularly, in those patients who died during the first hours after admission. Nevertheless, the rates in the nationwide sample of the United States and Korea were similar to ours (28, 77), despite a prevalence of obesity of 42% in adults in recent analyses of the United States (19, 78).

CONCLUSIONS

Obesity independently affected case fatality, MACCE, VTE, and other adverse in-hospital events of COVID-19 patients. Obesity should be taken into account regarding COVID-19 prevention strategies, risk stratification, and adequate healthcare planning. Maintaining a healthy weight is important not only to prevent chronic cardiometabolic diseases but also for better individual outcomes during COVID-19 infection.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHIC STATEMENT

Ethical review and approval were not required for the study on human participants in accordance with the local legislation and

institutional requirements. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

Conceptualization: KK and LH. Writing—original draft: KK. Writing—review and editing: KK, IS, VHS, VS, CE-K, CL, TM, and LH. Data curation: KK and LH. All authors discussed the results and contributed to the final manuscript.

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SYSTEMATIC REVIEW
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Association of Obesity With COVID-19 Severity and Mortality: An Updated Systemic Review, Meta-Analysis, and Meta-Regression

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Background: Obesity affects the course of critical illnesses. We aimed to estimate the association of obesity with the severity and mortality in coronavirus disease 2019 (COVID-19) patients.

Data Sources: A systematic search was conducted from the inception of the COVID-19 pandemic through to 13 October 2021, on databases including Medline (PubMed), Embase, Science Web, and Cochrane Central Controlled Trials Registry. Preprint servers such as BioRxiv, MedRxiv, ChemRxiv, and SSRN were also scanned.

Study Selection and Data Extraction: Full-length articles focusing on the association of obesity and outcome in COVID-19 patients were included. Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines were used for study selection and data extraction. Our Population of interest were COVID-19 positive patients, obesity is our Intervention/Exposure point, Comparators are Non-obese vs obese patients The chief outcome of the study was the severity of the confirmed COVID-19 positive hospitalized patients in terms of admission to the intensive care unit (ICU) or the requirement of invasive mechanical ventilation/intubation with obesity. All-cause mortality in COVID-19 positive hospitalized patients with obesity was the secondary outcome of the study.

Results: In total, 3,140,413 patients from 167 studies were included in the study. Obesity was associated with an increased risk of severe disease (RR=1.52, 95% CI 1.41-1.63,

p<0.001, I^2 = 97%). Similarly, high mortality was observed in obese patients (RR=1.09, 95% CI 1.02-1.16, p=0.006, I^2 = 97%). In multivariate meta-regression on severity, the covariate of the female gender, pulmonary disease, diabetes, older age, cardiovascular diseases, and hypertension was found to be significant and explained R^2 = 40% of the between-study heterogeneity for severity. The aforementioned covariates were found to be significant for mortality as well, and these covariates collectively explained R^2 = 50% of the between-study variability for mortality.

Conclusions: Our findings suggest that obesity is significantly associated with increased severity and higher mortality among COVID-19 patients. Therefore, the inclusion of obesity or its surrogate body mass index in prognostic scores and improvement of guidelines for patient care management is recommended.

Keywords: obesity, COVID – 19, systematic review & meta-analysis, meta-regression analysis, severity, mortality

INTRODUCTION

The entire world is enduring the effects of the global coronavirus disease 2019 (COVID-19) pandemic, which began in December 2019, when pneumonia of unknown origin was diagnosed in Hubei province, Wuhan, China (1, 2). It was later in January 2020 that the novel coronavirus strand was isolated and subsequently named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in February 2020 (3, 4). As of 28 December 2021 the Covid-19 pandemic has affected >281 million individuals and has led to >5.4 million global deaths (5). Even though many treatments have been proposed to combat COVID-19, there is currently no uniformly successful therapy (6–11). Although it is a widespread disease affecting multiple systems, obesity has been identified as one of the major comorbid factors in patients suffering from COVID-19 (12–21).

Overweight (BMI 25 kg/m^2-29.9 kg/m^2) and obesity (BMI 30 kg/m^2 or more) are major public health problems, especially during the COVID-19 pandemic, because of their association with increased morbidity and mortality (22, 23). Berrington de Gonzalez et al. (2010) studied the association between being overweight and obesity on overall mortality in 1.46 million white adults over a median follow-up period of 10 years. They found an approximately linear relationship in the hazard ratios for BMI. The hazard ratio for every 5-unit increment of BMI was 1.31 in the BMI range of 25 kg/m^2 to 49.9 kg/m^2 (24). According to the 2017-2018 National Health and Nutrition Examination Survey (NHANES), approximately 42.5% of U.S. adults aged 20 or over are obese and approximately 9% have class 3 obesity or severe obesity (BMI 40 kg/m^2or more) (25).

According to WHO, the prevalence of obesity has nearly tripled in the last four decades amounting to 13% of the entire world's adult population (26), which is a cause for concern during the pandemic. The interplay between obesity and other disease conditions has been established for a long time. The presence of these comorbid determinants is related to increased predisposition and severity of COVID-19 (27–30). Many studies have reported increased rates of hospitalization, mechanical ventilation, and mortality in patients with a higher BMI (31–35).

During the pandemic, due to worldwide lockdowns lasting several months, compromised work routine, increased calorie intake, lack of exercise options, and stress due to uncertainty, people are at an increased risk of becoming overweight and developing obesity (36). This could have an excessive toll on the management of COVID-19 disease. To mitigate the impact of heightened morbidity and mortality associated with COVID-19 infection in patients with obesity, it is vital to be cognizant of the implications of increased BMI and its dynamic interaction with other comorbid components. Hence, we evaluated obesity as a paramount risk factor for mortality and severity in COVID-19 infection, independent of potential confounders *via* systematic review and meta-regression.

METHODS

Data Sources and Searches

For documentation, we adopted the Preferred Systematic Analyses and Meta-Analysis Reporting Items recommendations (37). A systematic search was conducted from COVID-19 databases from the pandemic inception through October 13th, 2021 for full-length articles focusing on the association of increased BMI/Obesity [overweight is defined as a BMI between 25.0 and 29.9, and a BMI of 30 or higher is considered obese (38)] in COVID-19 using a pre-specified data extraction protocol including bibliographic information (year of publication, first author), study information (country, sample size), patient characteristics (age, baseline comorbidities, gender), treatment information and outcome data. The search strategy consisted of keywords "SARS-CoV-2", "COVID-19", "Coronavirus", "Obesity", "BMI", "Overweight" "Risk factors" across the three large COVID-19 databases (WHO COVID-19, CDC COVID-19, and LitCOVID PubMed) OVID-Medline Embase, Scopus, Web of Science, and Cochrane Central Controlled Trials Registry. Studies were included from all over the world. There were no language barriers during the literature search. Other literature sources such as the BioRxiv (preprints), MedRxiv (preprints), ChemRxiv (preprints), and SSRN (preprints) were searched as well. We screened the title and abstract of each study

identified in the literature search to include eligible articles where obesity or BMI was mentioned as a risk factor and overall comparative results or association with COVID-19 were provided in the abstract. Following this step, we conducted a full text review for final evaluation for study inclusion and data extraction. To discover further eligible studies, we manually searched the reference lists of the included studies, and previously published meta-analysis, systematic review, and the relevant literature. We also scanned the clinicaltrials.gov registry for completed, as well as in-progress randomized controlled trials (RCTs).

Study Selection

The inclusion criteria for the systematic review are as follows:

1. Studies reporting outcomes such as severity or mortality events of confirmed COVID-19 positive patients, at least one functional endpoint of COVID-19 positive hospitalized patients where body mass index (BMI) values or comparison of obese vs non-obese were provided.

2. Full text and peer-reviewed articles (Case-studies and case series, randomized controlled trials) were included.

3. Studies published only in the English language were included.

Exclusion Criteria

1.Studies published in a language other than English were not considered.

2. Studies with insufficient information were excluded. Case reports, reviews, or nonhuman studies were excluded.

3. Studies focused on patients aged under 18 years old were also excluded.

Data Extraction and Quality Assessment

The authors (HK and SSR) downloaded all articles from electronic search to EndNote X9 (39) and duplicates were eliminated. Based on the preset eligibility criteria, each study was reviewed by at least two authors (AT, GSS, HK, NJ, YC, RS, SK, KI, and SSR) independently and verified with internal author-reviewer, and disagreements were discussed amongst all author-reviewers and resolved *via* a consensus. The cases included obese Covid-19 positive hospitalized patients and the controls included the non-obese Covid-19 positive hospitalized patients.

Unadjusted and adjusted impact measurements were also extracted where appropriate. From each study, various details including first author name, study type, hospitalized total covid-19 positive patients, the definition of COVID-19 severity, definition of obesity, total obese & non-obese COVID-19 positive patients, patients with high severity and mortality, median age, gender (female sex proportion), proportions of hypertension, pulmonary disease, cardiovascular disease, diabetes, dyslipidemia, liver disease were recorded (**Supplementary Table 1**). The included data was checked for accuracy by all authors. Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were followed (**Figure 1** and **Supplemental Table 2**).

Risk of Bias Assessment

The NIH study quality assessment Tool was used for measuring the risk of bias in case-control studies and cohort studies (40). The NIH quality assessment tools were based on quality assessment methods, concepts, and other tools developed by researchers in the Agency for Healthcare Research and Quality (AHRQ), Cochrane Collaboration, USPSTF, Scottish Intercollegiate Guidelines Network, and National Health Service Centre for Reviews and Dissemination, consulting epidemiologists and evidence-based medicine experts, with adaptations by methodologists and NHLBI staff (40). Three authors (AT, KI, SA, and SSR) evaluated the likelihood of bias independently, and any conflict was resolved by consensus (**Supplementary Tables 3A–C**).

Data Synthesis and Analysis

All-cause severity in hospitalized COVID-19 patients with high BMI/obesity was the primary outcome. The severity criteria were defined as the need for ICU admission or the need for mechanical ventilation for the admitted COVID-19 positive patients. If both severities were given in the article, then the category with a higher number of reported events was selected as the severity for COVID-19. The severity rate was evaluated in comparison to the control group (non-obese COVID-19 hospitalized patients). While all-cause mortality in COVID-19 hospitalized patients with high BMI/obesity was the secondary outcome.

The meta-analysis specifically included case-control and cohort studies comparing the effects of high BMI/obesity in COVID-19 hospitalized patients comparing them to the non-obese COVID-19 hospitalized patients. All outcomes were analyzed using the Mantel-Haenszel method for dichotomous data to estimate pooled risk ratio (RR) utilizing the Review Manager (RevMan)- Version 5.4, The Cochrane Collaboration, 2020. Meta-analysis was performed first for studies reporting severity of patients in both groups followed by that for studies reporting severity of disease assuming independence of results for studies that reported both. Due to anticipated heterogeneity, summary statistics were calculated using a random-effects model. This model accounts for variability between studies as well as within studies. Statistical heterogeneity was assessed using Q value and I^2 statistics.

To explore the differences between studies that might be expected to influence the effect size, we performed random effects (maximum likelihood method) univariate and multivariate meta-regression analyses. The potential sources of variability hypothesized were the gender of the study sample, the proportion of subjects with diabetes, pulmonary disease, dyslipidemia, cardiovascular disease, and hypertension. Covariates were selected for further modeling if they significantly ($P < 0.05$) modified the association between mortality or severity in the COVID-19 hospitalized patients with high BMI/Obesity. Two models were created, one for severity and the other for mortality of disease as primary and secondary outcomes, respectively. Subsequently, preselected covariates were included in a manual backward and stepwise multiple meta-regression analysis with $P = 0.05$ as a cutoff point for removal. $P < 0.05$. ($P < 0.10$ for heterogeneity) was considered statistically significant. All meta-analysis and meta-regression tests were 2-tailed. The meta-regression was performed with the Comprehensive Meta-Analysis software package (Biostat, Englewood, NJ, USA)14 (41).

We conducted sensitivity analysis with BMI categories (BMI <18 kg/m^2, BMI 18 kg/m^2-25 kg/m^2, BMI 25

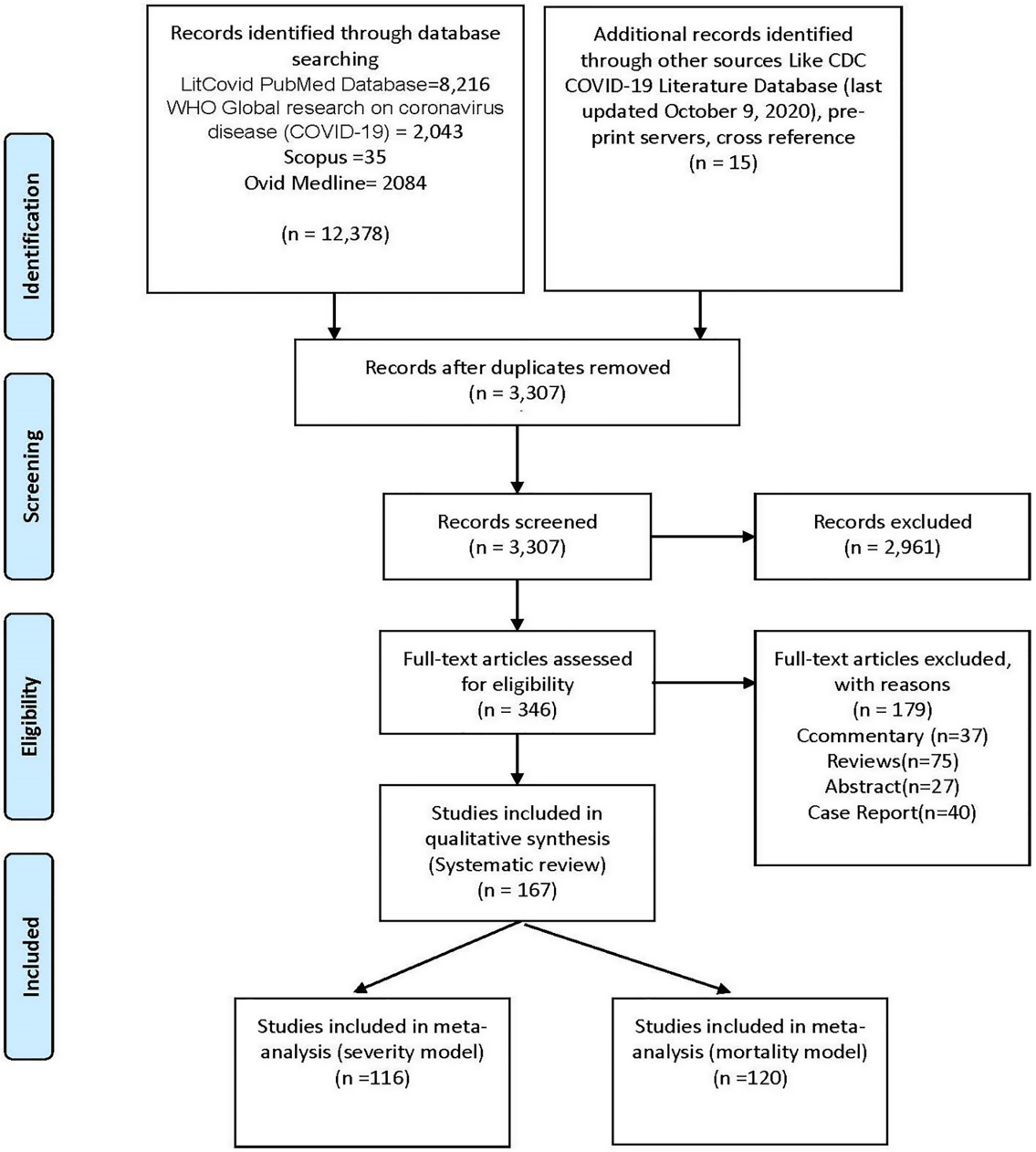

FIGURE 1 | Prisma flow diagram.

kg/m^2-29.9 kg/m^2, BMI >30 kg/m^2, and BMI>40 kg/m^2) to decrease inherent selection bias in observational studies (42).

RESULTS

Study Characteristics of Included Studies

A total of 167 studies, consisting of 3,140,413 COVID-19 patients were included in the meta-analysis. The median age for included patients was 62 (56.4-65.5) with an average of 44.3% female participants (**Supplementary Table 1**). Of the comorbidities considered, 28.1% were diabetics, 22.8% had cardiovascular diseases. For the primary endpoint, i.e. disease severity, a total of 116 studies with predefined severity events with obese vs non-obese were included in the meta-analysis (31, 33, 43–156). These had a combined sample size of 1,685,283 with 117,839 patients reaching the endpoint of high disease severity (**Supplementary Table 1**). Similarly, a total of 120 studies (33, 43–45, 47, 51, 52, 54–59, 61, 62, 64–67, 69, 71, 73–75, 78, 80, 82, 86, 89–91, 93, 96, 99, 100, 104, 106–108, 112–115, 117–120, 122,

124, 125, 127–134, 136, 138, 139, 141–143, 147, 149, 150, 152, 153, 157–207) were included for mortality meta-analysis as a secondary outcome. These had a combined sample size of 1,935,503 with 277,780 patients reaching the endpoint of mortality.

Meta-Analysis for Severity Outcome

Findings from the meta-analysis showed that being obese was correlated with increased severity of COVID-19 positive hospitalized patients in comparison to non-obese patients (RR=1.52, 95% CI 1.41-1.63, p<0.001). Heterogeneity was high with I^2 = 97% (**Figure 2**).

Meta-Analysis for Mortality Outcome

Meta-analysis findings showed that obesity was associated with an increased risk of mortality in obese patients from COVID 19 infections in comparison to the non-obese patient population (RR=1.09, 95% CI 1.02-1.16, p=0.006). Heterogeneity was high with I^2 = 97% (**Figure 3**).

Multivariate Meta-Regression Model for Severity Outcome

Multivariate meta-regression was performed to explain variations in the association between COVID-19 severity and obesity. We found that age, female gender, the proportion of pulmonary disease, diabetes, cardiovascular diseases, and hypertension covariates to be significant, and this explained R^2 = 40% of the between-study heterogeneity in severity. **Figure 4A** shows the resulting equation and individual covariate effect graphs.

Multivariate Meta-Regression Model for Mortality Outcome

Multivariate meta-regression was performed to explain variations in the association between mortality and obesity, and revealed that age, female gender, the proportion of pulmonary disease, diabetes, hypertension, and cardiovascular diseases were significant together. Overall, these covariates together explained R^2 = 50% of the between-study heterogeneity in mortality. **Figure 4B** shows the resulting equation and individual covariate effect graphs.

Sensitivity Analysis

We did not find any statistical significance for risk of mortality with COVID-19 when analyzed by BMI categories during sensitivity analysis (**Supplementary Figures 1A–C**). However, we observed that underweight status (BMI<18 kg/m^2) is associated with increased risk of mortality in COVID-19 (RR 1.50, 95% CI 1.36-1.65, p=<0.001; I^2 = 46%) (**Supplementary Figure 1D**) but not statistically significant to severity of COVID-19 (RR 1.04, 95% CI 0.85-1.28, p=0.69; I^2 = 83%) (**Supplementary Figure 1E**) as compared to normal BMI category of 18-24.99 kg/m^2. Normal weight is protective to COVID-19 disease severity compare to overweight (BMI 25-29.9 kg/m^2) (RR 0.75, 95% CI 0.69-0.82, p=<0.001; I^2 = 88%), Class 1 and Class 2 obesity (BMI of 30-39.99 kg/m^2) (RR 0.67, 95% CI 0.60-0.74, p=<0.001; I^2 = 94%) and Class 3 obesity (BMI >40 kg/m^2) (RR 0.77, 95% CI 0.68-0.88, p=<0.001; I^2 = 89%).

Publication Bias

Visual inspection of the standard error plots for the severity analysis also (**Supplementary Figure 2A**) suggests symmetry without an underrepresentation of studies of any precision. However, in Egger's regression test the null hypothesis of no small study effects was rejected at p<0.05 (estimated bias coefficient = -0.27 ± 0.16SE).

Similarly, visual inspection of the standard error plots for the mortality analysis (**Supplementary Figure 2B**) suggests symmetry without an underrepresentation of studies of any precision. Corroborating inspection findings, Egger's regression test, the null hypothesis of no small study effects, was rejected at p<0.05 (estimated bias coefficient = -0.20 ± 0.15SE).

DISCUSSION

Summary of Result

In our study, we found that obesity has a strong association with increased severity and mortality of COVID-19 infection. Our results suggest that obese individuals are 1.5 times more likely to experience severe outcomes and 1.09 times more likely to die when compared to non-obese individuals with COVID-19 disease. Our meta-regression severity model suggested that 40% of the heterogeneity could be explained by age, gender, diabetes, hypertension, pulmonary and cardiovascular diseases. The mortality meta-regression model suggested that 50% of the heterogeneity could be explained by age, gender, diabetes, hypertension, pulmonary and cardiovascular diseases. Through these regression models, we were able to address the major amount of heterogeneity seen in our meta-analysis.

Comparison With Existing Literature

Various meta-analyses were conducted to evaluate the association of obesity with mortality and severity in critically ill patients (208–210). The results were not universal, despite a wide variety of observations. In a total of 62,045 critically ill patients, Akinnusi et al. compared the ICU mortality between obese and non-obese patients and found no dissimilarities (208). Hogue et al. (n=22) conducted a meta-analysis of 88,051 patients and found that obesity did not impact ICU mortality (209). However, Oliveros and Villamor et al. found that ICU mortality was increased only in underweight patients and reduced in overweight and obese patients (210). In another study, Zhao et al. observed that having a high BMI is related to a longer duration on mechanical ventilation but lower mortality (211). We also found four meta-analyses (studies n=6, 17, 40, 76) (212–215) that explored the association of obesity and worse outcomes in COVID-19 and found a similar association. On the contrary, one study (216) refuted the possibility of this association. Owing to their small sample population (Studies n=2), it is likely that they were underpowered to tease out the true difference or association (216). With a much larger sample size (n=167) our study provides more robust evidence to establish this association.

Over the last year, five meta-regression studies evaluating the direct relationship between obesity and COVID-19 have been

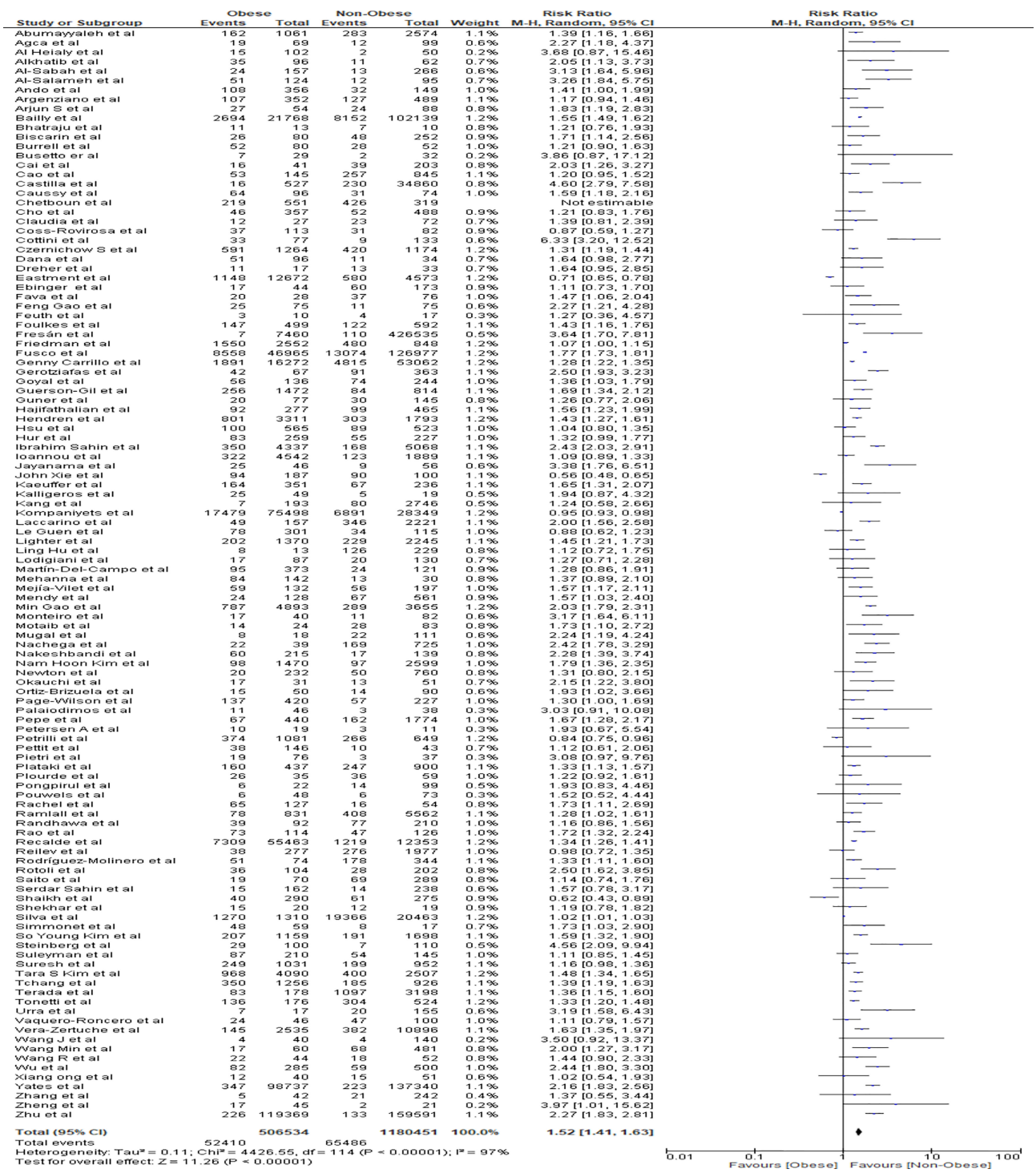

FIGURE 2 | Forest plot for severity analysis.

published. Yang et al. (studies n=41) concluded that in COVID-19 patients obesity is associated with increased mortality, increased rates of hospitalization, ICU admissions, and the need for mechanical ventilation. However, they found no confounding factors causing heterogeneity regarding hospitalization, ICU admission, and in-hospital mortality of COVID-19 patients (217). In another such study, Mesas et al. (studies n=60) described that obesity was linked to increased

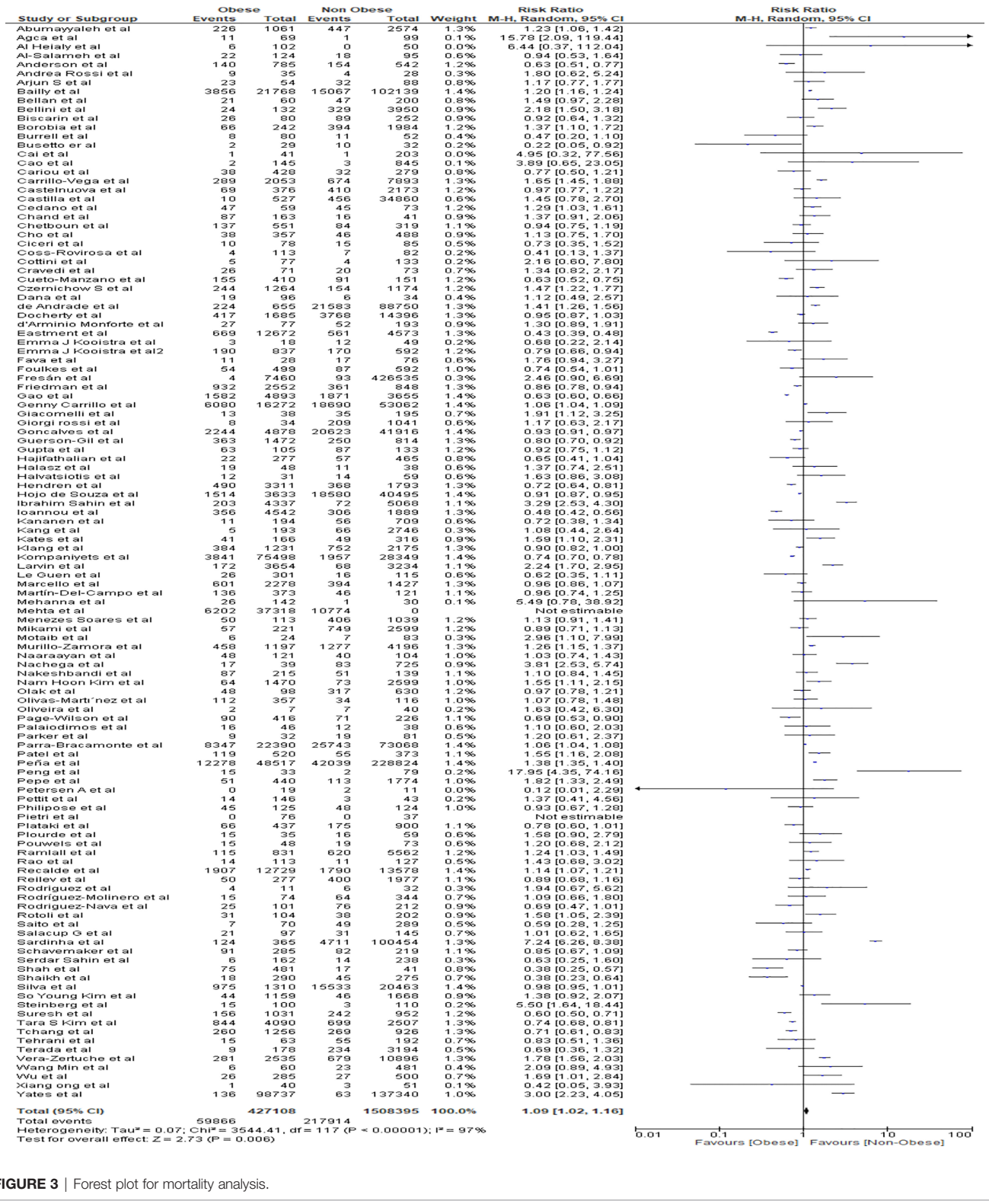

FIGURE 3 | Forest plot for mortality analysis.

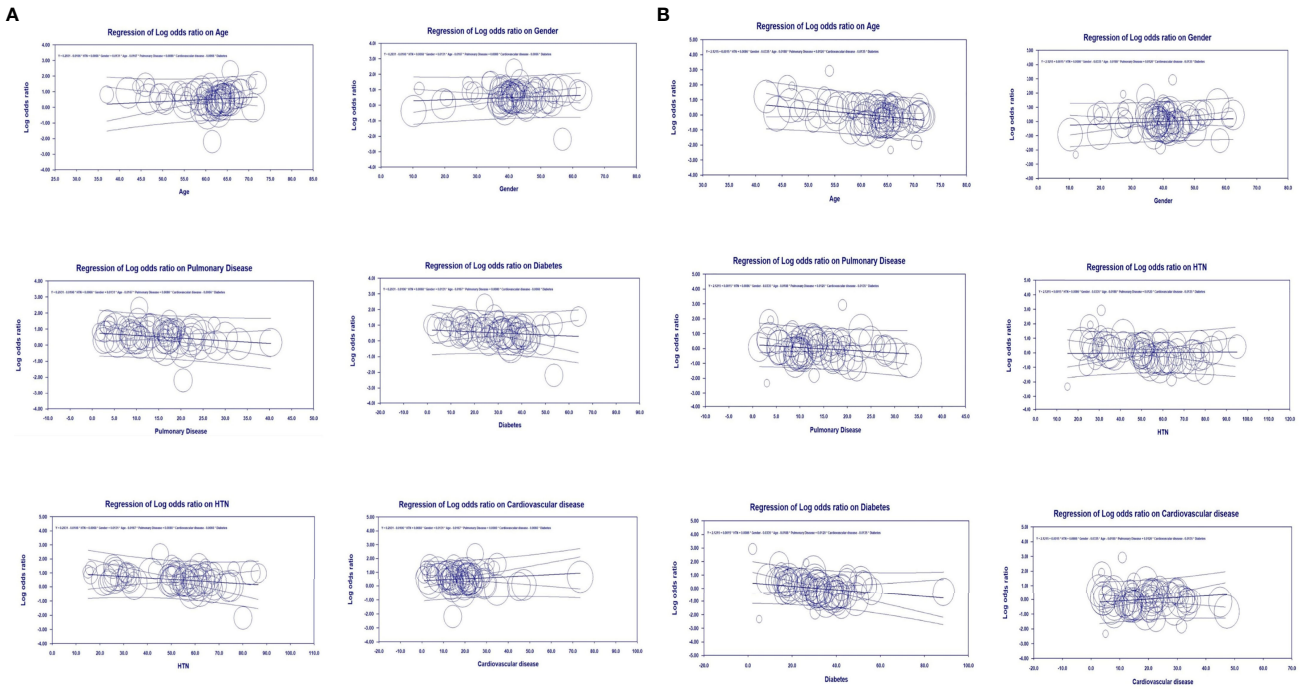

FIGURE 4 | Meta-regression analyses, **(A)** Severity meta-regression analysis, **(B)** Mortality meta-regression analysis.

mortality only in studies with fewer chronic or critical patients and reported the mean age of patients as the most important source of heterogeneity, followed by sex and health condition (218). Soereto et al. (studies n=16) reported that patients with higher BMI were at increased risk of developing 'poor outcomes' - defined as mortality, ICU admission, ARDS incidence, severe COVID-19, need for mechanical ventilation, and hospitalization. In their meta-regression, the heterogeneity in poor outcomes was explained by age, type 2 diabetes mellitus, hypertension, and gender (219). Cai Z. et al (220) also published meta-analysis results involving 46 studies and a population size of 625,153 patients. They also found similar results as our meta-analysis, wherein patients with obesity have a higher risk of hospitalization, ICU admission, and mechanical ventilation. We have improved upon that and analyzed 167 studies involving more than 3.14 million patients and achieved similar results. Another meta-analysis and regression study by Poly TN et al (213) included 17 studies and reiterated that patients with class III obesity are at more risk than patients with class II or class I obesity. Du et al (148) and Chu et al (149) (studies n=16 and 22, respectively) found that the association between obesity and COVID-19 severity and mortality was significantly influenced by age, but not by gender or other comorbidities. Our meta-regression identified the likely confounders to be age, gender, and co-morbidities. Through this model, we were able to explain high heterogeneity with the highest number of confounders, which other meta-regressions in recent literature were not able to reach and many did not define high heterogeneity in their analysis (217–219, 221, 222). Thus, we established the remarkable, strong association that obesity plays in worsening these outcomes in patients with COVID-19 infection.

In the sensitivity analyses, we were only able to find statistically significant results for increased mortality in BMI<18 kg/m^2 as compared to BMI 18 kg/m^2-25 kg/m^2, however, such significance was not noted in any other BMI categories with severity and mortality in COVID-19. This could be due to BMI being a crude estimate of adiposity, and that it may not be sensitive enough to tease out the real differences. However, in their study, Anderson et al (157) found that patients with obesity have a greater chance of intubation or mortality, with people with class 3 obesity having the greatest risk compared to overweight patients.

Pathophysiological Connection of Obesity and COVID-19 Infection

Obesity is known to be associated with many comorbid conditions (223), including hypertension, atherogenic dyslipidemia, cardiovascular disease, insulin resistance or type 2 diabetes, and altered cortisol metabolism, etc (224). Various biological mechanisms contribute towards increased risk of severity or mortality upon COVID-19 infection in obese patients. First, ectopic fat exacerbates the inflammation caused by COVID-19 by the upregulation of proinflammatory cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), angiotensin II (ATII), and prothrombotics (225–227). Second, obese patients are found to have decreased levels of

anti-inflammatory adipokine, adiponectin, which is linked to an increased level of ATII (228, 229). Obesity is associated with overexpression of ACE2 receptors which may aid infection and serve as viral reservoir (230). Further, coronavirus reduces the activity of ACE2 inhibitors, which again leads to an increase in the ATII level (231, 232). Higher levels of ATII lead to progression of lung injury among COVID-19 patients by triggering the NADH/NADPH oxidase system and promoting fibrosis, contraction, and vasoconstriction (233, 234). Moreover, it is associated with endothelial dysfunction (235), the key pathogenic event in COVID-19 leading to mortality and morbidity (236, 237). Furthermore, an increased expression of inflammatory adipokine molecules enhances the production of cytokines TNF-α and IL-6, which are associated with alveolar damage that leads to higher severity and mortality (238). Obesity or increased adiposity plays a key role in endothelial dysfunction by activating several cascades of pathological events, namely activation of renin-angiotensin system (239), activation of procoagulant/hypercoagulation pathway (240), activation of proinflammatory mediators (241), insulin resistance (242), oxidative stress (243), platelet dysfunction (244), and immune dysregulation (245). In the study by Danzinger et al (246) obesity was found to be associated with increased incidence of acute kidney injury and an increase in short- and long-term mortality. These events are summarized in **Supplementary Figure 3**.

Public Health Implication

The COVID-19 pandemic has created a multitude of concerns globally, and public health providers are working towards minimizing the damaging effects of COVID-19. There is no direct and effective treatment available to control the infection, thus, global morbidity and mortality increase day by day (5). COVID19 shows a wide spectrum of symptoms; many individuals recover without many health complications. However, some infected patients had severe symptoms which required hospitalization, care in intensive care units (ICU), prolonged symptom management, still many succumbed to death (247). Elderly patients were more vulnerable to severe outcomes because they have had multiple diseases and associated risks. A significant number of studies reported that elderly patients and patients with diabetes, stroke, CKD, and COPD are associated with poor outcomes (248, 249). Obesity, especially, class 3 obesity, was associated with an increased rate of mortality among patients infected with COVID-19. Similarly, during the previous H1N1 pandemic, patients with obesity observed prolonged hospitalization, mechanical ventilation, and increased mortality when it was calculated as an independent risk factor (250, 251).

Several population-based cohort studies reported that obesity is linked to increased comorbidities like diabetes, hypertension, and heart disease. Importantly, the mortality rate among patients with obesity proportionally increased with BMI (22, 252). Moreover, obesity makes patients' conditions worse if patients develop infections by downregulating the inflammatory cascade. Hyperactivation of inflammatory pathways alter the level of cytokines, adiponectin, and leptin and distort both macro- and micro-vascular responses (22, 252, 253). Obesity is also associated with lung function impairment, which involves altering mechanics and airway resistance and decreasing the gas exchange (254, 255). The findings of our study suggest that health care providers and physicians should pay attention to the obesity status of COVID-19 patients because this group of patients is at high risk of worse consequences. The conclusions of our study as well as of others, highlight the need for vigilance, and an earlier start to treatment in obese patients with COVID-19 infection (256, 257) as obese patients had higher hospitalization, ICU care, a requirement of mechanical ventilation with poor prognosis, and worse outcomes.

Effect of COVID-19 on Obesity and Prevention/Treatment Strategies for Patients With Obesity

COVID-19 plays a role in the emergence of obesity in this regard. The public health response to the COVID-19 pandemic is mostly based on restricting human contact and isolation, which affects people's behavior, and is linked to an increased risk of mental disease (258) and adds to increased incidence of obesity (259). Maintaining a healthy body weight requires regular physical activity, which was cut down during the isolation required during the COVID-19 pandemic (260). People tend to overeat as a result of increased anxiety and monotony, resulting in the consumption of additional energy/calories and an intense desire for food (261). Similarly, quarantine during the COVID-19 outbreak has led to an economic burden, and in some cases, this might mean people having to choose cheaper, less healthy meals. These foods are processed and associated with more fat, carbohydrates, and higher calorie intake (262), which is more likely to cause weight gain than a balanced healthy diet (263).

Obesity must be avoided at all costs. Increased physical activity and calorie restriction are typically used to lose weight. For weight maintenance, it is recommended that people exercise for more than 300 minutes each week (264). People use a range of weight-loss tactics to achieve this, such as consuming fewer calories, daily exercise, intermittent fasting, and using weight-loss medications or diuretics (265). Decreasing calorie consumption is by far the most popular method for weight reduction (266, 267). Metformin usage was reported to be strongly linked with a decrease in COVID-19 mortality in one study (268). This discovery might be explained by a number of factors. Metformin usage was reported to be strongly linked with a decrease in COVID-19 mortality in another recent study (269). This discovery might be explained by a number of factors (268). First, metformin inhibits SARS-CoV-2 from attaching to the receptor (270). Second, metformin suppresses SARS-CoV-2 infectivity and COVID-19 mortality by inhibiting the mTOR signaling pathway (268). Finally, metformin has been shown to reduce inflammatory responses (271). Metformin also lowers the risk of negative outcomes in COVID-19 individuals by lowering their BMI and body weight (272).

Strengths and Limitations

The prime strength of this study is the large sample size. With an exhaustive search strategy, we compiled 167 studies conducted globally. We also added the most recent studies to our meta-

analysis and meta-regression model including those that reported contradictory information. This enabled us to arrive at a more definitive conclusion about the risk associations. To define the heterogeneity in the meta-analysis, we also conducted a meta-regression analysis. For moderators, we used the most probable confounders based on the available evidence. This enabled us to delineate the impact of obesity as an independent risk factor for mortality and severity in COVID-19.

We included five studies from preprint databases (78, 102, 109, 146, 200) that may not be comparable to peer-reviewed articles in terms of their quality of methodology. However, given the time-sensitive nature of this pandemic, the benefit of early dissemination of critical information and its inclusion in various analyses outweighs the risk from minor methodological flaws. The second factor was the heterogeneity in the studies in terms of the study design and methodology, patient sample, and treatment received. There was a lack of uniformity in the type of outcomes evaluated for severity and their definitions in different studies. For the same reason, it was not possible to deduce the effect of obesity on individual outcomes. The third limitation is that the analysis was undertaken for hospitalized patients only, meaning we cannot generalize our results for patients treated in outpatient clinics or at home. Analyzing outpatient data may help us gain a complete picture of the impact of obesity on overall COVID-19 outcomes. The fourth limitation is that our analysis did not compare the outcomes with respect to visceral obesity and only BMI was used. However, it was beyond the scope of this analysis because of the lack of those details in most included studies. We suggest that prospective studies should obtain and report this information about their sample population. Lastly, it is possible that some confounders, which could have otherwise accounted for the residual heterogeneity, were not evaluated in the meta-regression analysis due to limited information.

Conclusion

Our findings suggest that obesity significantly increases the risk of severity and mortality in hospitalized COVID-19 patients. Therefore, the inclusion of obesity or surrogate body mass index in prognostic scores and streamlining the management strategy and treatment guidelines to account for the impact of obesity would be vital to improving patient outcomes in hospitalized COVID-19 patients. Our findings also serve as a call for the scientific community to delve further into its pathophysiology and identify potential pharmacological targets, since COVID-19 is an ever-evolving disease. Finally, this information must be disseminated to the general public to intensify the primary prevention of obesity.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/**Supplementary Material**.

AUTHOR CONTRIBUTIONS

Authors RS and SSR contributed equally to defining the study outline and manuscript writing and are co-primary authors. Data review and collection were performed by AT, GSS, HK, KI, NJ, RS, SK, AP, YC, and SSR; statistical analysis was undertaken by AB, SK, and VB; risk of bias was done by AT, SA, KI, NS, and SSR. Study design and the distribution of articles for critical review were performed by IM, VP, RK, and VB. All authors approved the final version of the published study. RS, SSR, VB, and VP are the guarantors of the published work, and take responsibility for the integrity of the work as a whole, from inception to the published article. All authors contributed to the article and approved the submitted version.

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The first version of this manuscript was submitted to medRxiv preprint server. Data from this study were submitted as an abstract format for the upcoming SCCM 51st Critical Care Congress in San Juan, Puerto Rico, and received Bronze Snapshot Awards.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2022.780872/full#supplementary-material

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Impact of Obesity on Vaccination to SARS-CoV-2

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To combat the immense toll on global public health induced by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), new vaccines were developed. While these vaccines have protected the populations who received them from severe SARS-CoV-2 infection, the effectiveness and durability of these vaccines in individuals with obesity are not fully understood. Our uncertainty of the ability of these novel vaccines to induce protective immunity in humans with obesity stems from historical data that revealed obesity-associated immune defects to influenza vaccines. This review analyzes the efficacy of SARS-CoV-2 vaccines in humans with obesity. According to the vaccine safety and efficacy information for the Pfizer, Moderna, and Johnson & Johnson formulations, these vaccines showed a similar efficacy in both individuals with and without obesity. However, clinical trials that assess BMI and central obesity showed that induced antibody titers are lower in individuals with obesity when compared to healthy weight subjects, highlighting a potential early waning of vaccine-induced antibodies linked to obesity rates. Thus, the desired protective effects of SARS-CoV-2 vaccination were potentially diminished in humans with obesity when compared to the healthy weight population, but further studies outlining functional implications of the link between obesity and lower antibody titers need to be conducted to understand the full impact of this immune phenomenon. Further, additional research must be completed to truly understand the immune responses mounted against SARS-CoV-2 in patients with obesity, and whether these responses differ from those elicited by previously studied influenza viruses.

Keywords: COVID- 19, Moderna vaccine, Pfizer, Johnson & Johnson, SARS – CoV – 2, obesity, BMI - body mass index

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INTRODUCTION

In November 2019, a new, highly infectious RNA virus in the *Coronaviridae* family, termed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged. SARS-CoV-2 infections became uncontrolled worldwide and caused a widespread illness coined coronavirus-2019 disease (COVID-19) (1). SARS-CoV-2 has infected and killed millions of individuals worldwide with numbers still rising, leaving the world suspended in a pandemic state (1, 2). The severity of this viral disease and its associated negative outcomes correlate with multiple risk factors, including age (1) and presence of other diseases (3), with obesity being a major risk factor for COVID-19 and subsequent death (1–5).

As COVID-19 continues to pose a public health threat and new, more infectious variants arise, the importance of vaccinations and booster vaccines have become more apparent (6). However, based upon previous research studying the vaccine responses to Influenza A (H1N1) in populations with high obesity rates, we predict that SARS-CoV-2 vaccine responses will wane more rapidly in individuals with obesity. Thus, patients of obesity, who are at a higher risk of severe viral infection and death by COVID-19, might not have the same duration of vaccine-conferred protection as individuals without obesity (7, 8). Further compounding the importance of studying the impact of obesity on vaccine-induced immune responses, studies done over the course of 2021 after SARS-CoV-2 vaccinations became widely available to the public indicated that obesity may be linked to breakthrough infections (9–16).

THE ETIOLOGIES AND CONSEQUENCES OF THE OBESITY PANDEMIC

The SARS-CoV-2 pandemic is not the only current pandemic; the prevalence of obesity has tripled from 1975 to 2016 worldwide (2). Almost 2 billion people worldwide are either overweight or obese, and the global prevalence of obesity in the younger population has increased by 47% between 1980 and 2013 (17). Currently in the United States, about one third of adults and 17% of children are obese or overweight (18).

Obesity is characterized by abnormal or excessive fat accumulation that causes pathophysiology, threatening overall health (19). One standard to measure obesity is body mass index (BMI), where individuals with a BMI of > 30kg/m^2 are classified as obese, while another is by using central obesity in which waist circumference is ≥ 80 cm for women and ≥94 cm for men (16, 19). Obesity is a multifactorial disease that is commonly caused by excess dietary intake relative to energy expenditure (2, 20). The complex etiology of obesity is not limited to overeating and sedentary lifestyles (21). This disease can develop from a mixture of genetic, physiologic, psychologic, environmental, political, and social factors. Commonly used medications including corticosteroids and some anti-depressants, endocrine disruptors, lack of sleep and microbiome diversity have all been implicated in obesity (20, 22, 23). The combination of inexpensive, high caloric, fat-laden foods and decreased physical activity over the last few decades are often listed as significant contributors to the prevalence of obesity (20). In addition, the cessation of smoking may be a contributor to the obesity pandemic, as weight gain is a common consequence of smoking cessation (20, 24). As the etiological factors that lead to obesity are multifactorial and often difficult to counteract, efforts on improving treatments and vaccines for individuals with obesity are essential.

Obesity is associated with increased all-cause mortality and the risk of developing other complications, such as cardiovascular disease, hypertension, several types of cancer, diabetes mellitus, gallbladder disease, kidney disease, osteoarthritis, and stroke (2, 17). Additionally, obesity is shown to increase the risk of acquiring respiratory tract infections, like SARS-CoV-2 and influenza A virus and can impede pulmonary function through decreased expiratory reserve volume, functional capacity, and lung compliance (4, 25). In the obese state, pulmonary function is compromised due to higher abdominal fat which can also decrease diaphragm excursion (4). Treatment of obesity and its related sequelae requires approximately 21% of the United States health care expenditure, which poses an economic burden on top of a public health concern (26). Thus, the pandemic state of obesity, coupled with its related illnesses and risks, makes having appropriate medical tools to counteract rising obesity rates — the treatment, prevention, and surveillance — a public health necessity (18, 27). As such, it is imperative that scientific efforts and funding are geared toward obesity research.

THE EFFECTS OF OBESITY ON THE IMMUNE SYSTEM

Underlying the association between poor vaccine responses and obesity is the effect of obesity on the immune system. Obesity is associated with immune cell-mediated inflammation (7, 28), and the influence of this inflammation on immune responses is only now beginning to be understood. Expansion of adipose tissue is linked to increased inflammation (29). While adipose tissue in individuals with a healthy weight predominately contains regulatory and suppressive cytokines including IL-4, IL-10, IL-13, and IL-33, adipose tissue in individuals who are obesity is associated inflammatory cytokines including IL-1β, IL-6, IL-12, IL-18, TNF-α, and IFN-γ (30–32). Adipokines and cytokines direct the immune responses to pathogens and the presence or absence of adipokines and cytokines during vaccination can alter adaptive immune response development leading to differences in the protective efficacy following vaccination.

Previous studies have also reported an association between leptin and altered influenza vaccine responses (33, 34). Leptin, an adipokine (cell-signaling hormone) that regulates appetite and controls energy metabolism (35), is found throughout the immune system on innate immune cells (macrophages, dendritic cells, and mast cells) and on adaptive immune cells (B and T cells). Leptin plays a major role in the chronic inflammation found in patients with obesity (35). Leptin's effect on neutrophils is especially important in COVID-19 progression in the obese state: increased leptin levels, characterized by increased neutrophilic lung inflammation, causes more severe lung injury (1). Higher leptin in obesity also correlates with a decreased levels of T_{reg} cells, resulting in more pro-inflammatory than anti-inflammatory cytokine expression, and an increased activation of neutrophils (1). Leptin has also been shown to direct T cell proliferation and reactivity by activating the JAK/STAT pathway, thereby enhancing immune inflammation (36, 37). However, based on some studies in humans and animals, it is thought that the hyperleptinemia state in patients with obesity may eventually induce leptin resistance (35, 38, 39). Leptin sensitivity and

resistance remain active areas of research and the clinical criteria for defining leptin resistance and its diagnostic use have not yet been established.

As previously described, the expansion of adipose tissue in the obese state is known to contribute to chronic, low-grade inflammation due to adipocyte hypoxia and resulting immune cell infiltration (21, 40). Chronic inflammation not only directly increases the risk for cardiovascular disease (CVD) and diabetes, but also causes upregulation of proteins and cytokines (like p38 MAPK and TNF-α), which can cause tissue damage (1, 21, 40) and result in a positive feedback loop that further promotes inflammation. This chronic immune stimulation can weaken the humoral responses and cell-mediated immunity, specifically lowering T cell response magnitude and increasing the time it takes for such responses to be mounted (7, 8). For example, individuals with obesity show suppressed T cell activation and differentiation in response to influenza infection when compared to individuals of healthy weights. Also, decreases in T cell production of effector molecules like IFN-γ and granzyme B is associated with obesity (7, 28). Further, obesity can induce B cell defects, including a lower frequency of regulatory B cells (with phenotypes $CD19^{+}$ $CD27^{+}$ $CD38^{High}$, $CD19^{+}$ $CD24^{High}$ $CD38^{High}$, and $CD19^{+}$ $CD24^{High}$ $CD38^{High}$ $IL\text{-}10^{+}$), in response to infection (41, 42). This obesity-induced immune suppression, particularly regarding B cell impairment, makes it unsurprising that individuals with obesity have inadequate seroconversion rates following vaccination. This is shown with decreased antibody titers in response to vaccination to hepatitis B, tetanus, and rabies (43). In addition to decreased antibody titers following vaccination, antibody responses also wane rapidly in individuals with obesity compared to people of healthy weights (44). Furthermore, the influenza vaccine is not as effective in individuals with obesity compared to individuals of healthy weights, potentially in part due to decreased antibody titers, decreased CD8+ T-cell activation, and decreased production of functional proteins IFN-ɣ and granzyme B (44, 45).

Data gathered from previous vaccine trials have shown that development of personalized vaccines might be necessary to surmount the immune suppression induced by obesity (7). Identifying the effects of obesity on immune responses mounted post-influenza infection or vaccination have provided key insights on how to improve vaccine design so vaccination can better protect populations with high obesity rates from severe viral disease and confer lifelong protection that does not rapidly wane.

EFFECTS OF OBESITY ON SARS-COV-2 INFECTION AND SEVERITY

First identified during the 2009 influenza A (H1N1) pandemic, obesity is a major risk factor for severe respiratory viral infection and increased mortality of infected individuals (19, 46). Obesity is associated with increased hospitalizations, intensive care unit (ICU) admissions, intubations, invasive mechanical ventilations (IMV), and viral exposures when compared to patients of healthy weight (19, 47–49). The exacerbation of COVID-19 disease progression in the population with obesity is thought to be linked to higher viral load and slower antiviral responses seen in COVID-19 patients with obesity (19).

Similar to the H1N1 pandemic, enhanced viral disease severity among COVID-19 patients with obesity have been noted amidst the SARS-CoV-2 pandemic. First, hospital admissions, stays, and recovery time of COVID-19 patients with obesity are longer than those of individuals of healthy weights (19, 50). Specifically, patients with obesity took 19 ± 8 days to achieve a negative nasopharyngeal swab for SARS-CoV-2 resolution compared to individuals of healthy weights who took 13 ± 7 days (50). Furthermore, among ICU COVID-19 patients, a higher BMI was reported in comparison with non-ICU patients (19). Interestingly, in a study conducted in Italy among 1591 ICU patients, 68% had at least one comorbidity, including hypertension, CVD, and diabetes, which are all obesity-related illnesses (51). Similarly, IMV indications were positively correlated with elevated BMI, and were greatest in COVID patients with a BMI ≥ 35 kg/m^2 (19). Obesity also increased the risk of pneumonia in COVID-19 patients compared to individuals without obesity (52). In addition, acute respiratory distress syndrome (ARDS), embodied by respiratory failure and hypoxemia, is a severe consequence of COVID-19, and reports highlight that obesity increases the ARDS risk and incidence in COVID-19 patients compared to COVID-19 patients of healthy weights (19). Due to the severe effects of COVID-19 infections in individuals with obesity and their diminished immune responses contributing to viral disease progression, targeted treatments are necessary to avoid long-term health effects and death in this patient population. Similar to data from influenza infections, SARS-CoV-2 patient outcome statistics again highlight the importance of formulating personalized vaccines or modifying vaccine schedules on a per patient basis.

SARS-COV-2 VACCINE TRIALS AND OBESITY

To combat the SARS-CoV-2 pandemic, multiple vaccine platforms were adapted for rapid Phase I, II and III clinical trials with limited or emergency use. Four vaccines are currently approved for use and being used worldwide from the following manufacturers: Moderna, Johnson & Johnson (J&J, Jansen Ad26), AstraZeneca and Pfizer-BioNTech (Pfizer, BNT162b2 mRNA). Along with the Pfizer-BioNTech vaccine, the Moderna vaccine was granted full FDA approval. During the clinical trial phases, Pfizer, Moderna, and J&J collected data on vaccine efficacy (VE) in individuals with obesity against the ancestral SARS-CoV-2 strain and alpha variant of concern; however, AstraZeneca has not provided data about VE in subjects with obesity. Thus, the remainder of our review will focus on the three vaccine platforms currently used in the United States that assessed VE in the context of obesity: Moderna, J&J and Pfizer.

Pfizer BioNTech BNT162b2

The Pfizer BNT162b2 formulation is an mRNA vaccine encoding the full-length spike (S) protein (53, 54). The phase III trial for this vaccine included a sample size of about 43,000 people and was a randomized, placebo-controlled trial (53). In this trial, participants received 2 doses (21 days apart) of either the vaccine or a placebo (53). Independent of weight, the VE was 95% in people without a previous COVID-19 infection who received the vaccine compared to the ones who received the placebo (53).

In this phase III trial, 13,218 subjects were classified as having obesity based on a BMI ≥ 30 kg/m^2 (53). The vaccinated group had 6,556 participants with obesity, and the placebo group had 6,662 participants with obesity (53). Based on results from this trial, obesity did not impact VE (53). Specifically, this study looked seven days after the second dose where VE was 95.4% in individuals with obesity versus 94.8% VE in subjects without obesity (53). When these data were stratified for age, no significant differences in VE were noted; VE in younger adults with obesity (ages:16-64) was ~95%, whereas in older adults with obesity (age >65), VE was 100% (53). While these data are promising, VE tests were completed only seven days after the second dose; VE studies were not conducted at later time points post-vaccination. Similarities in the vaccine responses early after vaccination between either individuals with obesity or of healthy weights have previously been seen in studies of the seasonal influenza vaccine (44). However, in such studies, virus specific antibody responses wane significantly in individuals with obesity after one year as compared to antibody titers of individuals of healthy weights (44).

The impact of obesity on the durability of vaccine-conferred protection is critical to understand as multiple studies have shown that a booster or third dose of a SARS-CoV-2 vaccine helps provide protection as immunity against this virus wanes (55–58). In at least one limited study consisting of 1,060 subjects, antibody levels to SARS-CoV-2 following the Pfizer BNT162b2 mRNA vaccination were measured at baseline, 21 days post first dose, 30-40 days post second dose and 90-100 days post second dose and compared between subjects with obesity versus those without. Consistent with studies conducted following seasonal influenza virus vaccination, early antibody titers were essentially equivalent between individuals with obesity versus those without, but by one month post second dose, antibody titers reported for subjects with obesity were significantly lower than those noted for subjects of healthy weight. Similarly, antibody titers of individuals with obesity were further significantly reduced at three months post-second dose when compared to levels reported for individuals of healthy weights (59). However, these studies only report a waning of the antibody response and did not address the implications of decreased antibody titers in individuals with obesity. Further studies using functional assays need to be conducted to determine if lower antibody titers correlate with functional defects in the ability for individuals with obesity.

In concordance with the previously described study, a study done by Watanabe et al. enrolled 22 adult subjects experiencing central obesity and at least one obesity-associated comorbidity, such as hypertension. This study was conducted to examine the impact of obesity on immune responses elicited by the Pfizer BNT162b2 mRNA vaccine (60). Prior to entering the study, these subjects were not vaccinated against SARS-CoV-2 and upon enrollment into the study, patients were placed on dietary intervention, with energy requirements calculated by adjusting for the physical activity level of each individual (60). Patients were vaccinated against SARS-CoV-2, and data generated following both doses in the vaccine schedule highlighted that BMI was inversely correlated with both cell-mediated and humoral immune responses (60). Interestingly, while following the dietary restrictions established upon enrollment into this study, patients lost ~10% of their body weight (accompanied by metabolic improvements), and this weight loss positively correlated with improved cell-mediated responses following vaccination (60). This study provides a unique perspective on vaccination in individuals plagued by obesity as it highlights that losing weight, or improving metabolic health, may counteract the immune defects that occur during priming in the obese state, showing that these cellular changes can be reversed.

Moderna mRNA-1273

The Moderna SARS-CoV-2 vaccine also utilizes an mRNA platform, coined mRNA-1273. This vaccine encodes a stabilized pre-fusion form of the S protein, a desirable vaccine design due to stabilized pre-fusion viral glycoproteins being highly immunogenic (54, 61). A randomized, placebo-controlled trial was conducted with a sample size of 30,351 participants (61). These participants were adults (age >18). Similar to the Pfizer trial, two doses were given to participants, but they were administered 28 days apart instead of 21 (61). The overall efficacy of this vaccine was 94.1%, but when VE was measured separately only among the vaccinated individuals with obesity (901 subjects), VE only dropped slightly from 94.1% to 91.2%. However, 11 cases of COVID-19 were reported in the vaccinated group, one of which was severe and did occur in a subject with obesity (61). On the other hand, 185 COVID-19 cases were reported in the placebo group. Of the 185 cases, 30 cases were severe, and one case led to death (61). Similarly, these data were further broken down to examine infection rates about placebo subjects with obesity. Of the 30 severe COVID-19 cases reported among the placebo group, 11 of them were diagnosed in subjects with obesity. Thus, overall, mRNA-1273 VE appeared to be similar between subjects with obesity or those of healthy weights, although reported viral disease severity did trend higher in the subjects with obesity.

However, similar to the Pfizer BioNTech BNT162b2 phase three trial, the primary endpoint for this study was 15 days after the second vaccine dose was given. While the VE reported in this clinical trial appears promising for individuals with obesity, as noted above, prior research suggests that it is essential to look at the long-term durability of VE to conclude if obesity impacts SARS-CoV-2 vaccine-conferred protection. Further studies should be conducted to examine the durability of vaccine specific responses in humans with obesity to determine if administering booster vaccinations earlier might could sustain long-term immunity to viral pathogens.

Janssen/Johnson & Johnson Ad26.CoV2.S

J&J developed a replication-incompetent adenovirus serotype 26 vectored vaccine (Ad26.CoV2.S) and similarly conducted a randomized, double blind, placebo-controlled trial. The sample size of this trial was 39,321 individuals (62). In this vaccine schedule, only one dose is administered to each subject. Fourteen days post-vaccination, VE was reported as 67.4%. By 28 days post-vaccination, VE was noted to be 66.2%.

In this trial, 28.5% of the cohort were classified as having obesity based on BMI > 30kg/m^2. VE in this group was 66.8% 2 weeks post-vaccination and 65.9% 28 days post-vaccination. No deaths were reported among subjects with obesity in the vaccinated group, but 6 out of 7 fatalities in the placebo group were subjects with obesity (62). Based on this phase three trial, the reported VE was consistent in individuals with obesity compared to subjects of healthy weights as reported for the Pfizer BioNTech and Moderna formulations, but viral disease severity did trend higher in the unvaccinated subjects with obesity. Again, although VE reported in this trial appears equivalent among subjects with obesity versus those without, tracking vaccine-specific immune responses as time progresses post-vaccination could illuminate implications for obesity on durability of VE.

CURRENT RESEARCH MAY ILLUSTRATE EFFECTS OF OBESITY ON VACCINATION AGAINST SARS-COV-2

Although information provided from the SARS-CoV-2 vaccine trials did not appear to show differences in terms of VE between individuals with obesity versus those of healthy weights, several longitudinal studies have highlighted some immune defects in populations with high obesity rates. One longitudinal study measured the effects of central obesity on Pfizer/BioNTech vaccination in 86 healthcare workers in Italy (16). This study showed that central obesity was associated with lower antibody titers following vaccination, but this phenomenon occurred independently from BMI (16). In a study looking at the antibody titers of individuals who were overweight, obese or of healthy weight between the first and second dose of the Pfizer/BioNTech vaccine, Pellini et al. noted that a single vaccination activated the humoral immune response in individuals of healthy weights, but some subjects with obesity or who were reported as being overweight (age >47 and BMI >25 kg/m^2) did not have a change in their IgG antibody levels (41). The authors concluded that IgG antibody titers in populations classified as having healthy weights or being young in age were higher than antibody responses in populations classified as being overweight or older in age, but more research has to be done regarding its direct correlation to protection against severe viral disease (41). While both studies noted a difference in antibody responses following vaccination, the results differ as to the association with BMI and central obesity. The current randomized, controlled trials assessed different measures of obesity, but both showed that obesity can be associated with a lower antibody titer following vaccination to COVID-19. These studies suggest that variabilities in how vaccine efficacy is measured, the time elapsed post vaccination, and the specific vaccine formulation administered can lead to confounding results. However, these studies, as well as the phase three trial discussed above, reveal that vaccination of the individuals with obesity against SARS-CoV-2 is effective, at least for conferring short-term protection. While the duration of the effectiveness may be shortened, there is a window of time where protection is observed. As the SARS-CoV-2 pandemic is ongoing, follow up studies comparing vaccine-induced immune responses among individuals with obesity versus those of healthy weights are essential studies to conduct.

DISCUSSION

Data from the phase III SARS-CoV-2 vaccine trials and subsequent clinical trials conducted to measure immune responses primed in the obese state after inoculation produced results that contradict each other, likely due to the physiological complexity of obesity. Overall, the vaccine trials of the three SARS-CoV-2 vaccines administered in the US show that they are efficacious in individuals with obesity; however, statistical analyses were not completed on these data to validate the outcomes. Moreover, other clinical trial cohorts report decreased antibody titers and weakened immune responses following SARS-CoV-2 vaccination in individuals who are overweight or obese. The current research is limited, and the contradiction sparks a need for further studies to be conducted. The clinical trials that measured central obesity did not find an association to BMI and a decreased immune response. This finding does not match with Pellini et al. (41) and their study on BMI, in which a high BMI was associated with lower antibody titers. Watanabe et al. explain that BMI is not an appropriate way of measuring obesity, highlighting that central obesity presents a more accurate measure of the severity of obesity and its sequalae in those with high waist circumferences, a phenomenon that has shifted the field of obesity to now focus on classifying individuals as having metabolic syndrome. Thus, different measures of obesity might indicate a varying response than what is seen in the vaccine trials, as the vaccine trials used BMI to assess efficacy of the vaccine in individuals with obesity, and it is possible that a different measure of obesity might yield a different result. Hence, more research is necessary to resolve these scientific questions.

Additionally, the study methods differed in a way that might lead to significant differences in vaccine efficacy results, such as measuring antibody titers at varying time points or using different antibody measuring kits. Moreover, the sample sizes in the clinical trials measuring the effects of obesity on vaccine responses in individuals with obesity were small compared to samples sizes utilized in vaccine trials and not entirely representative of the general population of individuals with obesity. For example, Watanabe et al. and Pellini et al. (41, 60) recruited study participants who were healthcare workers, a group that generally has more access to health care to help with any current or future obesity-related illnesses, in contrast to

the general population which may not have immediate or affordable health care access. Further, although some pre-existing medical conditions were noted for the subjects analyzed in these studies, information regarding their medication use to treat such conditions was not disclosed, potentially skewing the data generated.

Even with the present research presented, many questions remain unanswered, such as how immune responses change depending on the age demographic. The clinical trials discussed throughout this review focused on adults, but with an increasing population of children becoming overweight and obese, studies must be expanded to include subjects of varying ages to determine whether vaccines are efficacious in conferring protection against severe viral diseases in children with obesity. It is also difficult to assess how people with obesity-related comorbidities benefit from the current vaccines, especially regarding lifelong, durable protection. Furthermore, if vaccine efficacy is similar in individuals with obesity to those individuals of healthy weights during a close time frame to when the vaccine is administered, how durable vaccine efficacy is in individuals with obesity is unknown and could pose threats to public health as time post vaccination increases. It is possible that additional vaccine boosters will be necessary for individuals with obesity to achieve protective and durable vaccine-induced immunity.

CONCLUSION

We believe that more research needs to be done to assess the impact of obesity on vaccination to SARS-CoV-2. The currently reported research is contradictory, and numerous questions remain unanswered. We believe more work needs to be done to assess long-term efficacy of the available vaccines to SARS-CoV-2, what the best scheduling for boosters is, and how different patterns of fat distribution could be affecting immune responses to vaccination. However, it is clear that obesity hinders immune responses to vaccines and infections. As obesity rates are projected to continually rise globally, it is important to gear medical treatments towards populations with high obesity incidences and to increase awareness about non-dietary causes of obesity. Furthermore, more data needs to be gathered concerning the growing number of young individuals with obesity and if they will be protected from severe viral disease by SARS-CoV-2 vaccines. With these future research efforts in mind, we are confident that vaccine development can improve to induce long-lasting, protective immune responses in patients with obesity.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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Obesity and clinical outcomes in COVID-19 patients without comorbidities, a *post-hoc* analysis from ORCHID trial

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Objective: Large body of studies described individuals with obesity experiencing a worse prognosis in COVID-19. However, the effects of obesity on the prognosis of COVID-19 in patients without comorbidities have not been studied. Therefore, the current study aimed to provide evidence of the relationship between obesity and clinical outcomes in COVID-19 patients without comorbidities.

Methods: A total of 116 hospitalized COVID-19 patients without comorbidities from the ORCHID study (Patients with COVID-19 from the Outcomes Related to COVID-19 Treated with Hydroxychloroquine among Inpatients with Symptomatic Disease) were included. Obesity is defined as a BMI of ≥30 kg/m^2. A Cox regression analysis was used to estimate the hazard ratio (*HR*) for discharge and death after 28 days.

Results: The percentage of obesity in COVID-19 patients without comorbidities was 54.3% (63/116). Discharge at 28 days occurred in 56/63 (84.2%) obese and 51/53 (92.2%) non-obese COVID-19 patients without comorbidities. Four (3.4%) COVID-19 patients without any comorbidities died within 28 days, among whom 2/63 (3.2%) were obese and 2/53 (3.8%) were non-obese. Multivariate Cox regression analyses showed that obesity was independently associated with a decreased rate of 28-day discharge (adjusted *HR*: 0.55, 95% *CI*: 0.35–0.83) but was not significantly associated with 28-day death (adjusted *HR*: 0.94, 95% *CI*: 0.18–7.06) in COVID-19 patients without any comorbidities.

Conclusions: Obesity was independently linked to prolonged hospital length of stay in COVID-19 without any comorbidity. Larger prospective trials are required to assess the role of obesity in COVID-19 related deaths.

KEYWORDS

obesity, COVID-19, comorbidities, death, discharge

Introduction

Obesity, traditionally defined as an excess of body fat causing prejudice to health usually with body mass index (BMI) of >30 kg/m^2, is a serious global epidemic (1). As of late December 2021, there have been over 2 billion cases of COVID-19 and more than 5 million deaths reported worldwide. Both previous and our studies (2–4) showed a significant positive association between BMI and adverse outcomes in patients with COVID-19. Notably, in the COVID-9 pandemic, almost 94% of patients with COVID-19 co-exist with at least one comorbidity, and these comorbidities were higher in severe COVID-19 cases (5–7). These co-existing comorbidities, such as hypertension and diabetes, have been proven to be the strongest predictors of adverse outcomes in COVID-19 patients. Therefore, the effect of obesity on adverse outcomes in patients might be overestimated, even with full adjustment of those confounding factors in statistical processing. Despite the extensive work done on prognostic factors of COVID-19 and, considering that obesity often presents with other patient factors, limited data exist to investigate obesity in isolation of other co-morbidities in relation to COVID-19 prognosis. Given this background, we conducted this second analysis from the ORCHID (Patients with COVID-19 from the Outcomes Related to COVID-19 Treated with Hydroxychloroquine among Inpatients with Symptomatic Disease) trial, which is a multicenter, blinded, randomized clinical trial in the US that compared hydroxychloroquine with placebo during the clinical course of hospitalized patients with COVID-19, to examine the effect of obesity on prognosis in COVID-19 patients without comorbidities.

Materials and methods

This research conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (8).

Data source

The detailed design and the main results of the ORCHID study have been previously reported (9). In brief, ORCHID is a multicenter, blinded, randomized clinical trial across 43 hospitals in the US that compared hydroxychloroquine with placebo during the clinical course of hospitalized patients with COVID-19. The trial included 479 hospitalized patients with COVID-19 confirmed with laboratory-confirmed SARS-CoV-2 positivity between 2 April 2020 and 19 June 2020. The Prevention and Early Treatment of Acute Lung Injury (PETAL) Clinical Trials Network Clinical Coordinating Center reviewed all the information to ensure the data quality. The ORCHID study was approved by the central institutional review board at the Vanderbilt University Medical Center. Informed consent for participation was obtained from all patients or their legally authorized representatives. The main results of the ORCHID study showed that COVID-19 patients treated with hydroxychloroquine, compared with placebo, did not significantly their improve clinical status on day 14 (9). Notably, the investigators of the RCTs were not involved in this study. This article was prepared using research materials obtained from the National Institutes of Heart, Lung, and Blood Institute.

We first excluded 35 patients with missing BMI (body mass index) values. Secondly, 349 patients with known pre-existing comorbidities at baseline were excluded (in detail described in Supplemental Table S1). Finally, 116 patients were included in the analysis.

Study aim

Our present study provides evidence of the relationship between obesity and clinical outcomes in COVID-19 patients without comorbidities.

Exposure

According to the recommendations of Body Mass Index (BMI) being classifications adopted by the World Health Organization (WHO) (1), obesity is defined as BMI ≥30 kg/m^2. BMI was calculated as weight (kg) divided by height $(m)^2$.

Clinical follow-up

Patients were followed up for discharge and death following the trial randomization, and patient follow up included the use of in-hospital records and follow-up telephone interviews for discharged patients at 14 and 28 days after the trial randomization.

Outcomes

The primary outcomes were a 28-day hospital discharge and a 28-day death. The detailed definitions of these outcomes were based on the previous descriptions (9).

Statistical analysis

Baseline characteristics for continuous variables with normal distributions or nonnormal distributions were expressed as the means with standard deviations or medians with interquartile ranges, respectively. Categorical variables are expressed as frequencies and percentages. Comparisons between the groups were examined using unpaired Student's t-tests (normal distribution) or the Wilcoxon–Mann–Whitney tests (nonnormal distribution) for continuous variance. Categorical variables with normal distribution or nonnormal distribution were compared using the χ^2 tests or the Kruskal–Wallis test, respectively. Cox proportional hazards models were used to calculate the adjusted risk estimates (also known as hazard ratios [*HR*] and their confidence intervals [*CIs*]). Multivariate regression analysis was performed, and the confounding factor adjustment strategy was considered along with sample size, cases, and meaningful clinical confounding. Due to the limited sample size and cases, several principal confounding factors (age, sex, in-hospital use of corticosteroids, and SOFA score) were selected in this analysis.

Results

Baseline characteristics

One hundred and sixteen patients with COVID-19 without comorbidities were included in this study. Table 1 shows the baseline characteristics of this cohort. Overall, the mean age of the cohort was 46.4 years, and 31% were females. The percentage of obese COVID-19 patients was 54.3% (63/116). There was no significant difference in age, sex, and other baseline characteristics stratified by obesity.

Association between obesity and death and hospital discharge

Discharge at 28 days occurred in 56/63 (88.9%) obese COVID-19 patients without comorbidities and in 51/53 (96.2%) non-obese COVID-19 patients without comorbidities. Figure 1 shows the age-adjusted incidence of 28-day discharge across obesity and non-obesity groups, with a lower rate of 28-day discharge among obese patients (p <0.001). The association between obesity and outcomes by Cox regression is summarized in Table 2. Consistently, obesity was independently associated with a decreased rate of 28-day discharge after adjusting for age, sex, in-hospital use of corticosteroids, and SOFA score (adjusted *HR*: 0.55, *95% CI*: 0.35–0.83).

Four (3.4%) COVID-19 patients without any comorbidities died within 28 days, among whom 2/63 (3.2%) were obese, and 2/53 (3.8%) were non-obese. There was no significant difference in the age-adjusted 28-day death rate between obesity and non-obesity in COVID-19 patients without any comorbidities (P = 0.95). Further univariable and age-adjusted analyses showed similar results (adjusted *HR*: 0.94, *95% CI*: 0.18–7.06). Using sensitivity analysis by changing the 28-day death as in-hospital death or a composite of ECMO or in-hospital mortality, the results were similar to the primary analyses (data not shown).

Discussion

To the best of our knowledge, this is the first study to explore the impact of obesity on COVID-19 patients without comorbidities. In this multicenter cohort study, we included 116 COVID-19 patients without any comorbidities from the US and found that obesity is associated with a decreased rate of 28-day discharge in COVID-19 patients without comorbidities as it had no significant effect on 28-day death.

Among patients with COVID-19, the prognosis could be worsened by co-existing disease burdens such as hypertension and cardiovascular diseases. Previous evidence showed that obese patients with COVID-19 have a worse prognosis, including respiratory and multiple organ failure and higher mortality (10) Nevertheless, most of the prior studies were based on patients with COVID-19 coexisting with comorbidities. Since obese patients often have these chronic conditions, this might be the most crucial reason for the increased risk of obesity in COVID-19 (11). Although the effect of comorbidities was adjusted, questions remain regarding the association and magnitude of the association between obesity and adverse outcomes in patients with COVID-19 without commodities. Our study excluded COVID-19 patients with any comorbidities and found that obese individuals are less likely to be discharged within 28 days than non-obese patients. However, our study did not find a significant association between obesity and the risk of 28-day death. Notably, we should explain these results with caution. First, we all know, the prevalence of comorbidities in children is much lower than that in adults. Multiple studies (12), according to a lower COVID-19 infection, severe cases, and cases in young adults or children, were observed. However, regarding death, the results were not consistent across children and young adults. In a small

TABLE 1 Baseline characteristics of hospitalized patients with COVID-19 without comorbidities storified by obesity.

	Overall (n = 116)	Non-obesity (BMI <30 kg/m^{2}n = 53)	Obesity (BMI ≥30 kg/m^{2}n = 63)	*P*-value
Demography				
Age, years	46.36 (14.45)	46.81 (15.28)	45.98 (13.83)	0.76
Sex, male (%)	80 (69.0)	39 (73.6)	41 (65.1)	0.432
BMI, kg/m^2	32.1 (7.1)	26.72 (2.0)	36 (6.3)	<0.001
Obesity I (%)	32 (27.6)	0 (0)	32 (50.1)	
Home medication				
Corticosteroids (%)	8 (6.9)	5 (9.4)	3 (4.8)	0.534
Symptoms of acute respiratory infection				
Cough (%)	70 (60.3)	31 (58.5)	39 (61.9)	0.854
Fever (%)	73 (62.9)	32 (60.4)	41 (65.1)	0.742
Shortness of breath (%)	81 (69.8)	36 (67.9)	45 (71.4)	0.836
Sore throat (%)	9 (7.8)	2 (3.8)	7 (11.1)	0.261
Total SOFA score (mean (SD))	2.94 (3.13)	2.70 (3.04)	3.14 (3.21)	0.448
Measurements				
Systolic blood pressure, mmHg	109 [99, 119]	109 [96, 117]	109.50 [105, 121]	0.189
Lowest SpO2, %	92 [90, 94]	92 [90, 95]	91.50 [90, 94]	0.246
Highest respiratory rate, breaths per minute	27.20 (8.33)	26.79 (9)	27.56 (7.76)	0.627
Hemoglobin, g/dl	13.45 [12.60, 14.72]	13.45 [12.62, 14.28]	13.55 [12.62, 14.97]	0.309
Sodium, mEq/L	136 [134, 138]	136 [134, 138]	136 [134.25, 138]	0.858
Potassium, mEq/L	3.80 [3.50, 4.10]	3.80 [3.50, 4.12]	3.80 [3.50, 4.10]	0.83
BUN, mg/dl	12 [9, 16]	12 [9, 17]	12 [9, 14]	0.57
AST, U/L	51.50 [38, 76.75]	50 [38, 80]	53 [37, 75]	0.809
ALT, U/L	47 [28, 72]	43.50 [33, 73.75]	48.50 [27.75, 63]	0.656
ALP, IU/L	76 [54, 90]	73 [55, 91.50]	76 [53, 89.75]	0.936
Bilateral opacities/infiltrates (%)	83 (74.8)	35 (68.6)	48 (80.0)	0.248
Pre-medication up to randomization				
Hydroxychloroquine (%)	3 (2.6)	2 (3.8)	1 (1.6)	0.879
Remdesivir (%)	7 (6.0)	3 (5.7)	4 (6.3)	1
Corticosteroids (%)	5 (4.3)	3 (5.7)	2 (3.2)	0.843
Tocilizumab (%)	3 (2.6)	3 (5.7)	0 (0.0)	0.185
Azithromycin (%)	37 (31.9)	15 (28.3)	22 (34.9)	0.574
Medication between randomization and hospital discharge				
Corticosteroids (%)	22 (19.0)	10 (18.9)	12 (19.0)	0.998
Tocilizumab (%)	11 (9.5)	3 (5.7)	8 (12.7)	0.332
Immunomodulating medication (%)	2 (1.7)	1 (1.9)	1 (1.6)	0.957

M(IQR) for nonnormally distributed data, M ± SD for normally distributed data, and n (%) for categoric variables.
SOFA, Sequential Organ Failure Assessment; BUN, blood urea nitrogen; ALT, alamine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; BMI, body mass index.

case-control study by Zhang et al. (13), obesity predisposes to higher death in young adults. In a large study from the UK, the relative risk of severe COVID-19 due to increasing BMI was found, particularly in people younger than 40 years old (14). A multi-center cohort study also found obesity, diabetes, and hypertension increase the risk of COVID-19-related mortality in young and middle-aged patients (15). In contrast, a cohort study of 795 children did not find increased mortality, although the length of hospital stays or severity was found (16). Secondly, since the mortality of this cohort was relatively low (3.4%), our study may be underpowered to detect such a difference; the *post hoc* power calculation showed that this study had a power of 4% to detect the difference observed (17). Finally, results from a UK national cohort found graded I obesity and severe obesity significantly increased the risk of mortality, rather than graded I obesity (30–34.9 kg/m^2) (18). Notably, more than half of the patients in our cohort were grade I obese, which have diluted the statistical power. Therefore, based on current evidence, we cannot draw any final conclusion on the association of obesity with death in patients without comorbidities.

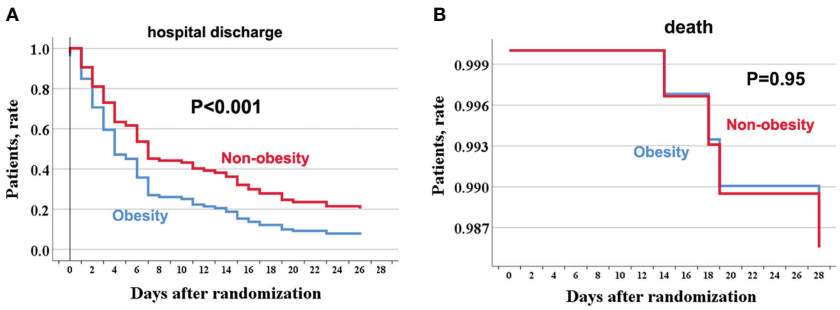

FIGURE 1
The age-adjusted incidence rate of hospital discharge and death through 28 days among obese and no-obese hospitalized patients with COVID-19 without comorbidities. hospitalization **(A)**; death **(B)**. For hospital discharge, all patients were followed up to discharge or 28 days after randomization in ORCHID. A patient was considered discharged from the hospital once discharged from the index hospitalization; rehospitalizations were not considered in this analysis. COVID-19, Corona Virus Disease 2019; ORCHID, Outcomes Related to COVID-19 Treated With Hydroxychloroquine Among Inpatients With Symptomatic Disease.

The potential mechanisms for the effect of obesity on COVID-19 length of hospital stay or severity have been extensively studied. Firstly, findings from the post mortem showed that pulmonary involvement was the dominant pathological feature. Increasing evidence indicates that obesity could result in altered lung physiology, including reduced lung volumes, abnormal ventilation, and perfusion distribution, decreased compliance, and respiratory muscle inefficiency (19–21). These changes subsequently induce ventilation–perfusion abnormalities and further reduce the ventilatory reserve, which makes the obese more prone to respiratory failure or even multiple organ failure after the infection of COVID-19 (22). Secondly, the weight gain and adipose tissue dysfunction in obesity could induce hyperinsulinemia/insulin resistance (23), metabolic tissue stress, resulting in chronic inflammation and further leading to the release of chemotactic mediators (24), which promote inflammatory leukocyte infiltration and secretion of pro-inflammatory cytokines (25), as well as complement system hyperactivation (26). These changes might ultimately develop a condition described as "cytokine storm," the proposed mechanism that appears to drive severe COVID-19 infections (27). Finally, information on echocardiography in this study is not available. However, the hospitalized COVID-19 patients with obesity, even without comorbidities, may be associated with subtle myocardial dysfunction, which leads to worse clinical outcomes (28, 29).

Strength and limitations

To the best of our knowledge, this is the first study exploring the association between obesity and clinical outcomes of COVID-19 in patients without comorbidities. However, the small sample size inevitably becomes the main limitation of our study. Studies with a larger sample size are needed to confirm our results. Secondly, our study is based on the US population, which limits the generation in other countries. Third, though being a typical measurement of obesity, BMI itself has various deficiencies, including its indirection of measuring body fat and of reflecting body fat distribution, as well as the changes in muscle mass (30). This might lead to a misinterpretation of the relationship between obesity and mortality. Other measurements, such as waist circumference, need to be further assessed. Thirdly, other confounding factors in COVID-19, such as race (31), physical activity (32), and fitness, are missing in our study.

TABLE 2 Association between obesity and 28-day hospital discharge, and 28-day death in patients with COVID-19 without comorbidities.

	28-day discharge*	*P*-value	28-day death#	*P*-value
Cases/N	50/116		4/116	
Crude HR (95% CI)	0.72 (0.61–0.85)	**<0.001**	1.14 (0.16–8.07)	0.90
Adjusted HR (95% CI)	0.55 (0.35–0.83)	**<0.001**	0.94 (0.18–7.06)	0.95

*Adjusted for age, sex, in-hospital use of corticosteroid, and SOFA score.
#Adjusted for age.
SOFA, Sequential Organ Failure Assessment; HR, hazard ratio.

Conclusion

Obesity is linked to prolonged hospital length of stay in COVID-19 without comorbidities. The role of obesity on COVID-19 related deaths should be studied by larger prospective trials.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by ORCHID trial. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YS and XL were responsible for the entire project and revised the draft. PY, ZL, JZ, PX, and XT performed the data extraction, statistical analysis, interpreted the data, and drafted the first version of the manuscript. JM and MX revised the manuscript. All authors participated in the interpretation of the results, prepared the final version of the manuscript, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2022.936976/full#supplementary-material

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Causal associations between body fat accumulation and COVID-19 severity: A Mendelian randomization study

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Previous studies reported associations between obesity measured by body mass index (BMI) and coronavirus disease 2019 (COVID-19). However, BMI is calculated only with height and weight and cannot distinguish between body fat mass and fat-free mass. Thus, it is not clear if one or both of these measures are mediating the relationship between obesity and COVID-19. Here, we used Mendelian randomization (MR) to compare the independent causal relationships of body fat mass and fat-free mass with COVID-19 severity. We identified single nucleotide polymorphisms associated with body fat mass and fat-free mass in 454,137 and 454,850 individuals of European ancestry from the UK Biobank, respectively. We then performed two-sample MR to ascertain their effects on severe COVID-19 (cases: 4,792; controls: 1,054,664) from the COVID-19 Host Genetics Initiative. We found that an increase in body fat mass by one standard deviation was associated with severe COVID-19 (odds ratio $(OR)_{body\ fat\ mass}$ = 1.61, 95% confidence interval [CI]: 1.28–2.04, $P = 5.51 \times 10^{-5}$; $OR_{body\ fat\text{-}free\ mass}$ = 1.31, 95% CI: 0.99–1.74, $P = 5.77 \times 10^{-2}$). Considering that body fat mass and fat-free mass were genetically correlated with each other (r = 0.64), we further evaluated independent causal effects of body fat mass and fat-free mass using multivariable MR and revealed that only body fat mass was independently associated with severe COVID-19 ($OR_{body\ fat\ mass}$ = 2.91, 95% CI: 1.71–4.96, $P = 8.85 \times 10^{-5}$ and $OR_{body\ fat\text{-}free\ mass}$ = 1.02, 95%CI: 0.61–1.67, P = 0.945). In summary, this study demonstrates the causal effects of body fat accumulation on COVID-19 severity and indicates that the biological pathways influencing the relationship between COVID-19 and obesity are likely mediated through body fat mass.

KEYWORDS

COVID-19, body fat accumulation, body composition, Mendelian randomization, genetics

Introduction

More than 500 million individuals have been infected by the coronavirus disease-19 (COVID-19) with 6 millions of deaths worldwide to date (1). The severity of COVID-19 varies considerably among individuals, and identifying modifiable risk factors associated with COVID-19 severity is essential for optimizing public health policies, allocating resources, and assisting clinical decisions.

A major risk factor for COVID-19 appears to be obesity. A community-based cohort study involving 6.9 million individuals in England showed a positive association between body mass index (BMI) and COVID-19 severity (2), which was replicated in other independent observational studies (3–5). However, the key limitation of BMI is that it is a crude proxy of obesity because it is calculated only with height and weight and does not consider body composition (i.e., body fat mass and body fat-free mass) (6). Therefore, direct measures of body composition assessed by dual-energy X-ray absorptiometry or bioelectrical impedance analysis might better elucidate the association of body fat accumulation with COVID-19 outcomes. In this regard, two recent studies utilized the direct measures of body composition to evaluate the effect of obesity on COVID-19 (7, 8). However, individuals with increased body fat mass are also more likely to have increased body fat-free mass because there is a positive correlation between body fat mass and body fat-free mass (9). Thus, we have to specifically study the independent effects of body fat mass and body fat-free mass to disentangle the causal effects of obesity on COVID-19.

Regarding a means of exploring the associations between risk factors and outcomes of the interest, observational studies can evaluate correlations but not causations; in fact, interpreting the results of observational studies as a causal relationship relies on untestable and usually implausible assumptions, including the absence of unmeasured confounders and reverse causation (10). Given these limitations inherent to traditional observational epidemiology studies, Mendelian randomization (MR) has emerged as a way to mitigate against such shortcomings through its use of genetic variants as instrumental variables to infer a causal relationship between exposures and outcomes (11, 12). Using MR, we can estimate the causal effects of genetically predicted levels of adiposity-related exposures on COVID-19 outcomes, in contrast to typical observational studies that evaluate only associations. Because genetic alleles are randomly assigned at conception, which is generally well before the onset of the disease, the risk of reverse causation is substantially decreased. Taking advantage of MR analysis, previous studies evaluated causal associations of anthropometric traits of obesity and some direct measures of body composition, such as body fat percentage (7, 13–15). However, none has taken into account the correlation of body fat and fat-free mass and evaluated the independent causal associations of body fat mass and body fat-free mass with COVID-19 outcomes.

In this study, we conducted a two-sample MR to assess independent causal associations of body fat mass and body fat-free mass with COVID-19 severity outcomes using data from the UK Biobank and the COVID-19 Host Genetics Initiative.

Methods

Instrumental variables for body fat mass, body fat-free mass, body fat percentage, and BMI

Instrumental variables were defined as independent genome-wide significant single-nucleotide polymorphisms (SNPs) ($P < 5 \times 10^{-8}$) for exposure traits. Independence of SNPs was defined as not in linkage disequilibrium with other SNPs ($r^2 < 0.001$ within a 10,000 kilobase [kb] window). The exposures used in this study were body fat mass, body fat-free mass, body fat percentage, and BMI. Body fat percentage and BMI were included as supplementary analyses. To select SNPs used as instrumental variables, we obtained the genome-wide association study (GWAS) results of body fat mass, body fat-free mass, body fat percentage, and BMI from individuals with European ancestry in the UK Biobank (Figure 1), using the OpenGWAS and MR-Base platform of the MRC Integrative Epidemiology Unit at the University of Bristol (16). Accession IDs were as follows: body fat mass (ukb-b-19393), body fat-free mass (ukb-b-13354), body fat percentage (ukb-b-8909), and BMI (ukb-b-19953). A full description of the study design, participants and quality control procedures were described in detail previously (17). Briefly, GWAS was performed using 12,370,749 SNPs on 463,005 individuals by BOLT-LMM (18) with the following quality control criteria: Imputation quality (INFO) score > 0.3 for SNPs with a MAF > 3%; INFO score > 0.6 for SNPs with a MAF between 1–3%; INFO score > 0.8 for SNPs with a MAF between 0.5–1%; INFO score > 0.9 for SNPs with a MAF between 0.1–0.5%; SNPs with a MAF below 0.1% were excluded; individuals who were outliers in heterozygosity and missing rates, and individuals with sex-mismatch (i.e. different genetic sex and reported sex) or sex-chromosome aneuploidy were excluded. The fat mass and fat-free mass of the UK Biobank participants were evaluated by performing bioelectrical impedance analysis using the Tanita BC418MA body composition analyzer (Tanita, Tokyo, Japan). We restricted the analyses to individuals of European ancestry to maximize the statistical power, given that the majority of UK Biobank participants were of European ancestry. To select instrumental variables, SNPs were clumped using PLINK (v1.90) according to a linkage disequilibrium threshold of $r^2 < 0.001$ with a clumping window of 10,000 kb using the 1000G European reference panel (16, 19) in order to select an independent SNP with the lowest *P*-value in each linkage disequilibrium block. When a selected SNP was not present in the results of the GWAS of COVID-19

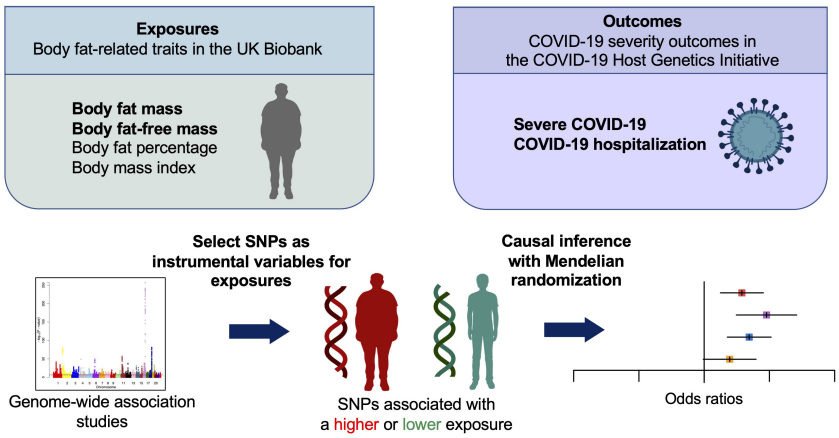

FIGURE 1
Schematic representation of the Mendelian randomization study. SNPs, single nucleotide polymorphisms.

severity outcomes, we instead used a proxy SNP that was in linkage disequilibrium with the selected SNP, with an r^2 of ≥0.8 and minor allele frequency of ≤0.3 using 1000G European reference panel as described before (12). We calculated *F*-statistics for the exposure traits and a genetic correlation between body fat mass and body fat-free mass using LDAK (v5.1) (19).

Severe COVID-19 and COVID-19 hospitalization outcomes

For proxy outcomes of COVID-19 severity, we adopted the outcomes of the COVID-19 Host Genetics Initiative, an international consortium working collaboratively to share data and ideas, recruit patients, and disseminate scientific findings. The outcomes were severe COVID-19 and COVID-19 hospitalization (20). For definitions of COVID-19 outcomes, the severe COVID-19 group was defined as individuals whose death was due to COVID-19, or those requiring hospitalization and respiratory support due to symptoms related to laboratory-confirmed SARS-CoV-2 infection. The COVID-19 hospitalization group was defined as individuals requiring hospitalization due to symptoms associated with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. For the definitions of controls in the GWAS data, ancestry-matched controls were sourced from participating population-based cohorts. Controls included individuals whose status of exposure to SARS-CoV-2 was either negative according to electronic health records/questionnaires or unknown (20). We used the largest GWAS summary statistics of the COVID-19 Host Genetics Initiative for severe COVID-19 and COVID-19 hospitalization outcomes in individuals of European-ancestry, excluding those from the UK Biobank. The datasets corresponding to each outcome were as follows: severe COVID-19 (cases: 4,792; controls: 1,054,664; dataset ID: COVID19_HGI_A2_ALL_eur_leave_ukbb_23andme_20210107 from data release 5) and COVID-19 hospitalization (cases: 14,652; controls: 1,114,836; and dataset ID: COVID19_HGI_B2_ALL_eur_leave_ukbb_23andme_20210622 from data release 6). We note that the COVID-19 Host Genetics Initiative's data release 6 did not include ancestry-specific GWAS for the severe COVID-19 outcome and also that the latest data release 7 did not include GWAS in European-ancestry individuals excluding those from the UK biobank. Hence, we used data release 5 for the severe COVID-19 outcome and data release 6 for the COVID-19 hospitalization outcome to minimize bias due to sample overlap or genetic confounding due to population stratification.

Mendelian randomization

We performed univariable MR using the inverse variance weighted method (hereinafter referred to as univariable MR) to evaluate the relationship of body fat mass, body fat-free mass, body fat percentage, and BMI with severe COVID-19 and COVID-19 hospitalization. Univariable MR is a weighted linear regression model in which the effect of genetic variants i ($i = 1 \ldots n$) on an outcome $\hat{\beta}_{Y_i}$ is regressed on the effect of the same genetic variant i on the exposure $\hat{\beta}_{X_i}$ weighted by the inverse of the squared standard error $(se(\hat{\beta}_{Y_i})^{-2})$. The estimated total effect (θ) of the exposure on the outcome can be formulated as follows:

$$\hat{\beta}_{Y_i} = \theta\hat{\beta}_{X_i} + \varepsilon_i, \varepsilon_i \sim \mathcal{N}\left(0,\ se\left(\hat{\beta}_{Y_i}\right)^{-2}\right)$$

The instrumental variable assumptions are as follows: (I) Relevance–genetic variant is associated with the exposure. (II) independence–genetic variant does not share the unmeasured cause or confounder with the outcome. (III) exclusion restriction–genetic variant does not influence the outcome except through the exposure (11, 12). These assumptions are illustrated by a canonical diagram in Figure 2.

Multivariable MR was performed using the inverse variance weighted method (hereinafter referred to as multivariable MR). This is an extension of univariable MR, in which the effects of genetic variant i ($i = 1 \ldots n$) on the outcome ($\hat{\beta}_{Y_i}$) are regressed on the effect of genetic variant i on two exposures of X_1(fat mass) and X_2(fat-free mass). In multivariable MR, genetic variants used as instrumental variables are associated with one or both of the exposures (21).

The causal associations were evaluated using odds ratios (ORs), which are expressed according to a standard deviation (SD) increase in genetically predicted body fat mass (kg), or body fat-free mass (kg), body fat percentage (%), and BMI (kg/m^2).

Results with a $P < 0.0125$ were considered statistically significant ($P = 0.05/4$; Bonferroni-corrected significance threshold according to the number of exposures). We note that such a correction is likely overly conservative, given that the exposures are non-independent. MR analyses were performed using TwoSampleMR (v0.5.6) in R (v4.02). This study was conducted in accordance with the STROBE-MR guideline (6, 7). STROBE-MR checklist is provided in Supplementary Material.

Sensitivity analysis

We performed the MR-Egger intercept test, Cochran's Q test, and the MR-PRESSO global test (22, 23) to detect horizontal pleiotropy, which occurs when instrumental variables influence outcomes through pathways independent of the exposure. MR-Egger relaxes the exclusion restriction assumption and is valid under the Instrument Strength Independent of Direct Effect (InSIDE) assumption that associations of the genetic variants with the exposure trait are independent of direct effects of the genetic variants on the outcome. Deviation of the MR-Egger intercept from zero indicates horizontal pleiotropy. The results of Cochran's Q test were used to evaluate the heterogeneity of genetic variants used as instrumental variables. Results of Cochran's Q test were presented with I^2 index, based on which the heterogeneity of genetic variants was defined categorically with I^2 index as low (I^2 index ≤ 25%), moderate (25% < I^2index ≤ 50%), and high (I^2 index > 50%). Additionally, we performed the MR-PRESSO global test, which can detect horizontally pleiotropic outlier SNPs. A significant result indicates the presence of pleiotropic outlier SNPs and this method then generates ORs after removing and correcting for these outliers (outlier-corrected ORs). MR-PRESSO can also be used to evaluate the distortion of the causal estimates before and after the removal of pleiotropic outlier SNPs following the MR-PRESSO distortion test. MR-PRESSO requires at least 50% of the genetic variants to be valid instruments with no horizontal pleiotropy and also relies on the InSIDE assumption. We also performed leave-one-out analyses for all exposure-outcome

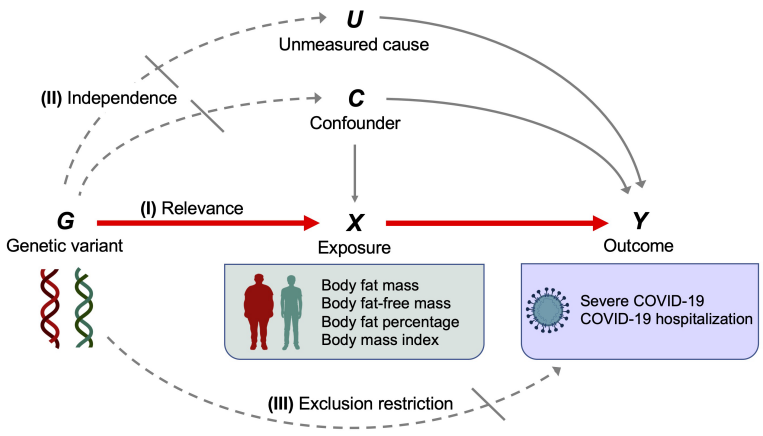

FIGURE 2
Canonical diagram illustrating the instrumental variable assumptions made in the Mendelian randomization analyses. Genetic variant *G* is used as an instrumental variable for exposure *X* (body fat mass, body fat–free mass, body fat percentage, or body mass index) to evaluate the causal effect of *X* on the outcome *Y* (severe COVID–19 or COVID–19 hospitalization). Instrumental variable assumptions include the following: (I) Relevance–genetic variant *G* is associated with exposure *X*. (II) independence–genetic variant *G* does not share the unmeasured cause or the confounder with the outcome *Y*. (III) exclusion restriction–genetic variant *G* does not influence the outcome *Y* except through the exposure *X*. Red solid arrows represent causal effects, gray solid arrows represent causal effects of the unmeasured cause or confounder that do not violate the instrumental variable assumptions, dashed arrows represent causal effects that are specifically prohibited by the instrumental variable assumptions.

associations, which repeated univariable weighted MR excluding each SNP to assess whether the overall estimate is driven by a single SNP. We also generated scatter plots and funnel plots to inspect for horizontal pleiotropy.

Results with a $P < 0.05$ were considered to indicate the presence of horizontal pleiotropy for the MR-Egger intercept test, Cochran's Q test, MR-PRESSO global test, and MR-PRESSO distortion test. Sensitivity analyses were performed with TwoSampleMR (v.0.5.6) and MR-PRESSO (v1.0).

Ethics statements

The UK Biobank and COVID-19 Host Genetics Initiatives obtained ethics approval from the relevant institutional ethics committees. We used publicly available summary statistics of GWAS results of UK Biobank and COVID-19 Host Genetics Initiative and did not use individual-level data.

Results

Instrumental variables for the exposure traits

The characteristics of the exposure traits (body fat mass, body fat-free mass, body fat percentage, and BMI) are presented in Table 1. The mean ± SD of body fat mass was 24.9 ± 9.6 kg, body fat-free mass was 53.2 ± 11.5 kg, body fat percentage was 31.4 ± 8.5%, and BMI was 27.4 ± 4.8 kg/m^2 (Table 1). For body fat mass, body fat-free mass, body fat percentage, and BMI, 417, 530 377, and 439 independent genome-wide significant SNPs were identified as instrumental variables from the GWAS results of the UK Biobank, respectively. *F*-statistics for these exposure traits were 502.2, 607.4, 496.9, and 507.6, respectively. The SNPs used as instrumental variables are presented in Supplementary Table 1.

Severe COVID-19 outcome

For the severe COVID-19 outcome, univariable MR showed that the genetically predicted increase per SD in body fat mass, body fat percentage, and BMI was associated with an increased risk of severe COVID-19 ($OR_{body\ fat\ mass}$ = 1.61, 95% CI 1.28–2.04, $P = 5.51 \times 10^{-5}$; and $OR_{body\ fat\text{-}free\ mass}$ =1.31, 95% CI: 0.99–1.74, $P = 5.77 \times 10^{-2}$; $OR_{body\ fat\ percentage}$ = 1.94, 95% confidence interval [CI]: 1.41–2.67; $P = 5.07 \times 10^{-5}$; OR_{BMI} = 1.49, 95% CI: 1.19–1.87, $P = 5.57 \times 10^{-4}$) (Figure 3). Further, as instrumental variables for body fat mass and body fat-free mass were not independent of each other ($r = 0.64$ for the genetic correlation of the two traits) (Figure 4), we performed multivariable MR to elucidate the independent causal effects of body fat mass and body fat-free mass on the severe COVID-19 outcome, which showed that only body fat mass was independently associated with the severe COVID 19 outcome (body fat mass: $OR_{body\ fat\ mass}$ = 2.91, 95% CI: 1.71–4.96, $P = 8.85 \times 10^{-5}$, and $OR_{body\ fat\text{-}free\ mass}$ = 1.02, 95% CI: 0.61–1.67, $P = 0.945$) (Figure 5).

COVID-19 hospitalization outcome

For the COVID-19 hospitalization outcome, univariable MR showed that a genetically predicted increase per SD in body fat mass, body fat-free mass, body fat percentage, and BMI and was associated with an increased risk of COVID-19 hospitalization ($OR_{body\ fat\ mass}$ = 1.32, 95%CI: 1.20–1.46, $P = 2.52 \times 10^{-8}$; $OR_{body\ fat\text{-}free\ mass}$ = 1.27 95%CI: 1.13–1.42, $P = 4.44 \times 10^{-5}$; $OR_{body\ fat\ percentage}$ = 1.44, 95%CI: 1.26–1.66, $P = 1.22 \times 10^{-7}$; OR_{BMI} = 1.31, 95%CI: 1.19–1.44, $P = 3.46 \times 10^{-8}$) (Figure 3). In multivariable MR, only body fat mass was independently associated with COVID-19 hospitalization ($OR_{body\ fat\ mass}$ = 2.38, 95%CI: 1.56–3.61, $P = 5.29 \times 10^{-5}$; $OR_{body\ fat\text{-}free\ mass}$ = 0.82, 95%CI: 0.56–1.19, $P = 0.293$), consistent with the findings for severe COVID-19 (Figure 5).

TABLE 1 Dataset descriptions.

Data source	Dataset details	Phenotype	Sample size of each dataset	Mean ± SD
UK Biobank	• GWAS in individuals of European ancestry. • Body fat and body fat–free mass were measured using bioelectrical impedance analysis.	Body fat mass	454,137	24.9 ± 9.6 kg
		Body fat–free mass	454,850	53.2 ± 11.5 kg
		Body fat percentage	454,633	31.4 ± 8.5%
		Body mass index	461,460	27.4 ± 4.8 kg/m^2
COVID–19 Host Genetics Initiative	• Meta–analysis of GWAS in individuals of European ancestry excluding those from UK biobank	Severe COVID–19	Cases: 4,792 Controls: 1,054,664	–
		COVID–19 hospitalization	Cases: 14,652 Controls: 1,114,836	–

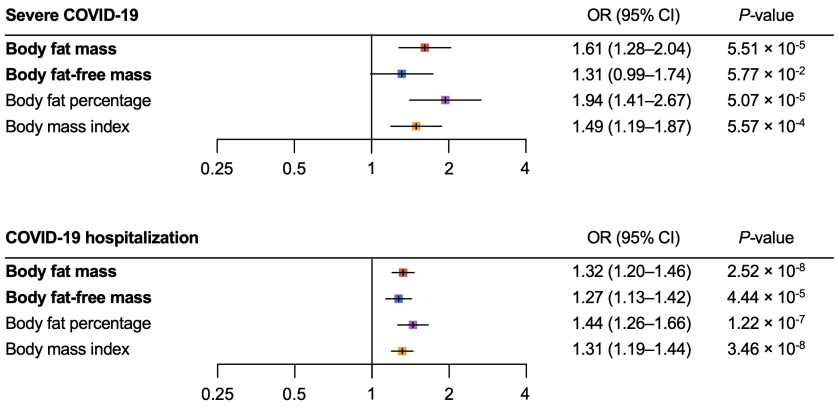

FIGURE 3
Univariable Mendelian randomization analysis for the severe COVID–19 and COVID–19 hospitalization outcomes. MR, Mendelian randomization.

Sensitivity analysis

We performed MR-Egger, Cochran's Q test and MR-PRESSO for sensitivity analysis (Table 2). In the MR-Egger, the 95%CI results of the MR-Egger intercept (Egger intercept) contained the null hypothesis value zero for all exposure-outcome relationships, suggesting no evidence of horizontal pleiotropy. Heterogeneity estimates of instrumental variables were low according to the I^2 index (I^2 index were ≤ 25% for all exposure traits). The leave-one-out analyses showed that causal estimates were robust to exclusion of single SNPs (Supplementary Tables 2–5). Visual inspection of the scatter plots and funnel plots did not suggest biased estimates or pleiotropy (Figure 6 and Supplementary Figure 1). However, MR-PRESSO detected some pleiotropic outlier SNPs in instrumental variables body fat mass, body fat percentage, and BMI with the COVID-19 hospitalization outcome (*P*-value for global test < 0.05). Nevertheless, results with MR-PRESSO after removal and correction for these pleiotropic outlier SNPs were directionally consistent with those from univariable MR, supporting the robustness of the findings with univariable MR. In addition, the MR-PRESSO distortion test detected no significant distortion in the causal estimates before and after the removal of outlier pleiotropic SNPs (Table 2).

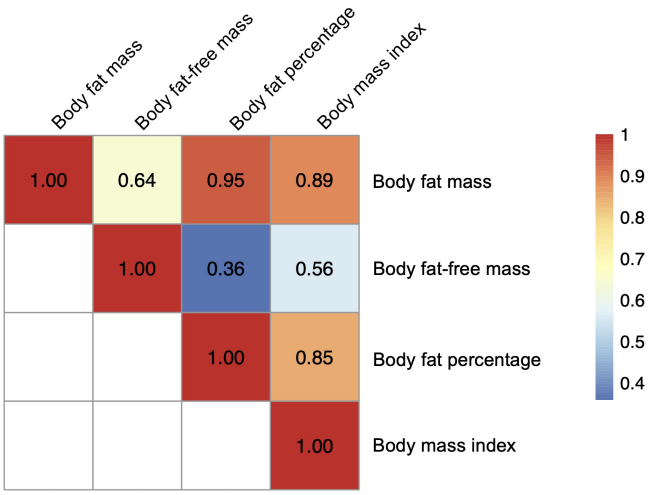

FIGURE 4
Heatmap for genetic correlation coefficients between the body fat–related traits. Genetic correlations among the four exposures (body fat mass, body fat–free mass, body fat percentage, and body mass index) were analyzed with LDAK using the results of corresponding genome–wide association studies.

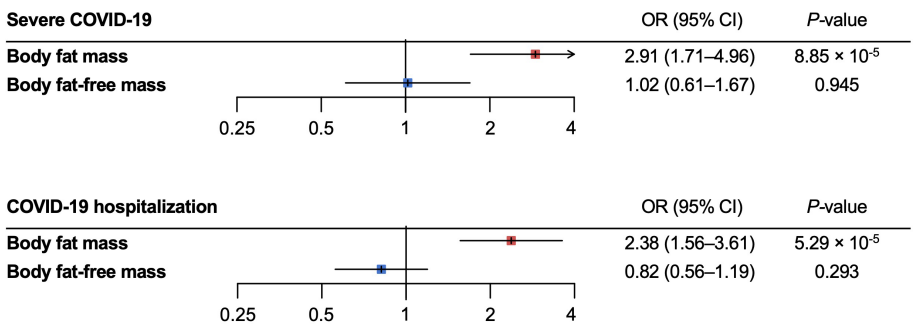

FIGURE 5
Multivariable Mendelian randomization analysis for the severe COVID–19 and COVID–19 hospitalization outcomes. MR, Mendelian randomization.

Discussion

In this study, we used two-sample MR to disentangle the independent effects of body fat mass and body fat-free mass and showed that body fat mass, but not body fat-free mass, is independently associated with severe COVID-19 outcomes. First, we performed univariable weighted MR and found that increased body fat mass, along with BMI and body fat percentage, were associated with an increased risk of severe COVID-19 and COVID-19 hospitalization. We further used

TABLE 2 Sensitivity analysis results.

Exposures	Outcomes	Sensitivity analysis methods								
		MR–Egger				Cochran's Q test I^2 index	MR–PRESSO			
		Egger slope (95% CI)	*P*–value (Egger slope)	Egger intercept (95% CI)	*P*–value (Egger intercept)		Global test *P*–value	Outlier–corrected OR (95% CI)	Outlier–corrected *P*–value	Distortion test *P*–value
Body fat mass	Severe COVID–19	1.63 (0.84–3.15)	0.147	–0.0002 (–0.012–0.012)	0.975	4.0	0.273	No outlier	—	—
Body fat–free mass		0.74 (0.38–1.45)	0.378	0.009 (–0.001–0.018)	0.066	5.0	0.551	No outlier	—	—
Body fat percentage		1.79 (0.62–5.14)	0.282	0.001 (–0.013–0.016)	0.874	9.7	0.108	No outlier	—	—
Body mass index		1.24 (0.65–2.37)	0.523	0.004 (–0.008–0.015)	0.542	1.8	0.417	No outlier	—	—
Body fat mass	COVID–19 hospitalization	1.53 (1.17–2.00)	2.31×10^{-3}	–0.003 (–0.008–0.002)	0.264	17.3	0.004	1.3351 (1.3348–1.3353)	3.98×10^{-3}	0.881
Body fat–free mass		1.12 (0.85–1.46)	0.433	0.002 (–0.002–0.006)	0.302	12.3	0.174	No outlier	—	—
Body fat percentage		1.80 (1.17–2.76)	8.04×10^{-3}	–0.003 (–0.009–0.003)	0.297	18.4	0.003	1.4498 (1.4493–1.4503)	1.60×10^{-7}	0.810
Body mass index		1.27 (0.99–1.64)	6.34×10^{-2}	0.001 (–0.004–0.005)	0.812	19.5	0.001	1.3085 (1.3082–1.3088)	7.09×10^{-9}	0.864

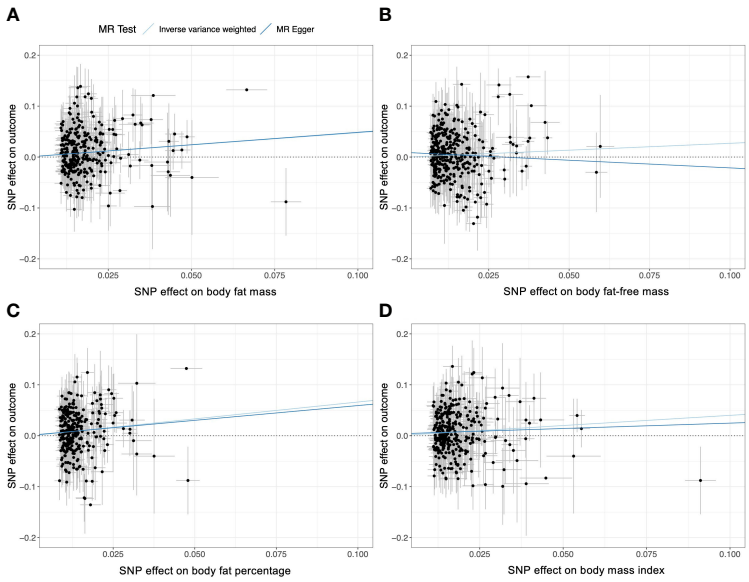

FIGURE 6
Scatter plots of the univariable weighted MR analyses for **(A)** body fat mass, **(B)** body fat–free mass, **(C)** body fat percentage, and **(D)** body fat mass. Each dot represent a genetic instrumental variable. Two lines represent causal estimate (β_{IV}) by the inverse variance weighted method (light blue) and the MR–Egger method (blue). Error bars represent 95%CIs. MR, Mendelian randomization.

multivariable MR to disentangle the independent causal effects of body fat mass and body fat-free mass on these outcomes and revealed that only body fat mass was independently associated with the outcomes.

During the COVID-19 pandemic, obesity has emerged as a major risk factor for COVID-19 outcomes. Multiple observational and MR studies suggested that obese individuals present an increased risk of severe diseases, hospitalization, and death due to COVID-19 (2–4, 24). However, observational studies are prone to confounding bias and reverse causation and do not estimate the causal effects of exposures on outcomes. To tackle this problem, recent studies have used MR to estimate the causal effect of obesity on the risk of COVID-19. For instance, the landmark paper from the COVID-19 Host Genetics Initiative showed that BMI was causally associated with an increased risk of COVID-19 hospitalization (20). This was supported by multiple MR studies and our analysis, which included BMI as the supplementary exposure. Other studies also assessed multiple anthropometric traits, including waist circumference, hip circumference, waist-to-hip ratio, and trunk fat ratio as well as BMI to evaluate the effect of adiposity on the risk of COVID-19 (7, 8, 13, 14, 25–31). These MR studies consistently estimated that increases in BMI, waist circumference, and hip circumference are causal for COVID-19 severity (7, 13, 14, 26, 28). On the other hand, the waist–to–hip ratio was not associated with COVID–19 severity (7, 28), contradicting observational studies. These discrepancies may be explained by confounding factors involved in observational studies but also by the limited ability of anthropometric traits to act as proxies for body composition (i.e., body fat mass and fat–free mass). It should also be noted that BMI is a function only of weight and height and an indirect measurement of obesity. Thus, it may not necessarily reflect body composition, which can be directly measured with bioelectrical impedance analysis or dual–energy X–ray absorptiometry (DXA). For example, individuals with similar BMI may have very different body composition, if there are large changes in lean body mass. This highlights the importance of directly measuring adiposity. In this regard, two recent MR studies used GWAS of direct measurements of obesity (i.e., body fat mass, fat–free mass, and body fat percentage) and found that they influence the risk of COVID–19, which was replicated by our univariable MR analyses (7, 8). However, analyses using body composition measurements still have limitations such as the high correlation between body fat mass and body fat–free mass, which was highlighted by our genetic correlation analysis (r = 0.64). To the best of our knowledge, the present study is the first to disentangle the independent causal effects of body fat mass and body fat–free mass on COVID–19 severity.

Our multivariable MR showed that one SD increase in body fat mass (9.6 kg) is causally associated with 2.91–fold and 2.38 fold–increase in the risk of severe COVID–19 and COVID–19 hospitalization, respectively, highlighting the burden of body fat accumulation on COVID–19 severity. On the contrary, body fat–free mass were not independently associated with increased

risk of severe COVID–19 or hospitalization. We used multivariable MR since most instrumental variables of adiposity affect both fat mass and fat–free mass, although some variants more strongly and proportionally influence fat mass, whereas others influence fat–free mass more strongly. Therefore, multivariable MR can test the differential causal effects of fat mass and fat–free mass. Using this approach, recent MR studies showed differential associations between body fat mass and body fat–free mass with various disorders (9, 32–34). The present findings extend this knowledge to COVID–19. Results from multivariable MR showed that body fat mass but not body fat–free mass was independently associated with severe COVID–19 and COVID–19 hospitalization. The association between body fat mass and COVID–19 severity was strengthened in multivariable MR relative to findings using univariable MR, whereas the effects of body fat–free mass on COVID–19 severity was markedly attenuated in multivariable MR, thereby illustrating the independent causal effects of body fat mass on COVID–19 severity.

The underlying mechanism of these associations remains to be clarified. Obesity is a metabolic disease characterized by systemic changes in metabolism, including insulin resistance, glucose intolerance, dyslipidemia, changes in adipokines (e.g., increased leptin and decreased adiponectin levels), chronic inflammation, and altered immune response, all of which could collectively increase the risk of COVID–19 severity (35–37). In addition, recent studies suggests that adipose tissue is a potential organ for direct infection with SARS–CoV2 in obese individuals (35). The infection of adipose tissue can cause systemic metabolic dysregulation including hyperglycemia, which is known as another risk factor for COVID–19 severity (36). Moreover, obesity causes respiratory dysfunction, including impaired respiratory physiology, increased airway resistance, impaired gas exchange, low lung volume, and low muscle strength, which can also increase the risk of COVID–19 severity. Furthermore, the physical characteristics of obese individuals render intubation and laryngoscopy difficult, which could also aggravate outcomes (37). Further studies are needed to explore the pathways linking adiposity to increased risk of COVID–19 severity.

This study has several strengths. We used an MR design, which minimized bias from reverse causation and confounders, thereby enabling us to test for causal effects, provided compliance with MR assumptions. In this MR study, we used the data from the UK Biobank for the exposure traits (F–statistics > 10 for all exposure traits) and COVID–19 Host Genetics Initiative for the outcomes, both of which have large sample sizes, thus increasing the statistical power of the analysis. Furthermore, as proxy measures of body composition, we not only considered BMI, which is a common indirect measure, but also direct measures, including body fat mass, body fat–free mass, and body fat percentage and revealed associations of these traits with COVD–19 severity.

Our study also has important limitations. First, MR analysis relies on several key assumptions, the violation of which compromises causal inference: relevance, independence, and exclusion restriction (Figure 2). To test for possible violations of these assumptions, we performed multiple sensitivity analyses. The MR–Egger intercept test did not detect horizontal pleiotropy. Although heterogeneity of effects were detected for certain SNPs when analyzing COVID–19 hospitalization, the removal of outlier SNPs *via* MR–PRESSO still showed results consistent with those from MR inverse variance weighted method. We believe that these sensitivity analyses demonstrate the robustness and validity of the present findings. However, we acknowledge that horizontal pleiotropy is difficult to exclude entirely. Second, regarding exposure traits, we used measures derived from the bioelectrical impedance analysis (i.e., body fat percentage, body fat mass, and body fat–free mass) instead of DXA–derived measures to maximize statistical power. Although the UK Biobank collected DXA–derived measures for body fat mass and body fat–free mass, the sample size was markedly smaller for these measurements (n = 5,170). Moreover, although DXA–derived measures are generally more accurate than impedance–derived measures, high correlations between the two were reported for fat mass (r = 0.96) and fat–free mass (r = 0.86) in the UK Biobank dataset (9). Hence, we believe impedance–derived measures can serve as clinically–relevant exposure traits in the present analysis. Third, we only used summary–level data and did not use individual–level data. Therefore, we could not evaluate the nonlinear relationship between exposures and outcomes. However, it should be noted that MR using summary statistics can still test for the presence of causal effects of exposures on outcomes, even if the exposure–outcome relationship is nonlinear (38). Additionally, a recent prospective cohort study of 6.9 million individuals in the UK suggested that BMI and COVID–19 severity have a linear relationship within a BMI range ≥23 kg/m^2 (2). Notably, the BMI of a majority of the individuals in the UK Biobank population included in the present analysis fell within this range (≥23 kg/m^2). Fourth, we restricted our analysis to individuals of European ancestry given that majority of participants in the UK Biobank were of European ancestry. Future studies are warranted to evaluate the generalizability of our findings to other populations. Lastly, we did not evaluate other clinically established risk factors such as diabetes, respiratory, heart, kidney, liver, autoimmune disorders, older age, smoking, and lower socioeconomic status (39). When considering risk factors for COVID–19 severity, we have to take into account phenotypic and genetic correlations. This was highlighted by a recent study showing that the causal effect of diabetes on COVID–19 severity is mediated by BMI (40). Another study also showed that the effect of BMI on severe COVID–19 is partially mediated by socioeconomic status measured by household income (26). Furthermore, obesity is

associated with other risk factors for severe COVID–19, including, but not limited to, chronic obstructive lung disease, heart failure, chronic kidney disease, liver cirrhosis, and autoimmune disorders (41–45). The interconnected nature of these risk factors highlights the importance of disentangling the independent causal effect of each risk factor, which requires further investigation.

In summary, the present MR study provides evidence that indicates a causal relationship between body fat accumulation and COVID–19 severity. Because excess fat can be reduced by following an appropriate diet and exercising, it might represent an important modifiable risk factor. Thus, body weight reduction considering direct measurements of body fat (i.e., body fat mass and body fat percentage) can be an effective strategy to reduce the risk of COVID–19 severity.

Data availability statement

All GWAS summary statistics used in this study are publicly available. The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

Author contributions

SY conceptualized and analyzed the data. SY, HM, and JBR wrote the original draft of the manuscript. JBR and NY supervised the study. All authors discussed the results and contributed to the final manuscript.

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Conflict of interest

JBR institution has received investigator–initiated grant funding from Eli Lilly, GlaxoSmithKline and Biogen for projects unrelated to this research. He is the founder of 5 Prime Sciences (www.5primesciences.com), which provides research services for biotech, pharma and venture capital companies for projects unrelated to this research. NI received research funds from Terumo Corp., Drawbridge, Inc., and Asken Inc. NI received speaker honoraria from Kowa Co., Ltd., MSD K.K, Astellas Pharma Inc., Novo Nordisk Pharma Ltd., Ono Pharmaceutical Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., Takeda Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corp., Sumitomo Dainippon Pharma Co., Ltd., Sanofi K.K., Eli Lilly Japan K.K., received scholarship grant from Kissei Pharmaceutical Co., Ltd., Sanofi K.K., Daiichi–Sankyo Co., Ltd., Mitsubishi Tanabe Pharma Corp., Takeda Pharmaceutical Co., Ltd., Japan Tobacco Inc., Kyowa Kirin Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., Astellas Pharma Inc., MSD K.K., Ono Pharmaceutical Co., Ltd., Sanwa Kagaku Kenkyusho Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., Novo Nordisk Pharma Ltd., Novartis Pharma K.K., and Life Scan Japan K.K. NI is an advisory board member of Novo Nordisk. These agencies did not play any role in study design, the collection, analysis, or interpretation of data, the writing of the report, or the decision to submit this paper for publication.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2022.899625/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Funnel plots of the univariable weighted MR for **(A)** body fat mass, **(B)** body fat–free mass, **(C)** body fat percentage, and **(D)** body fat mass. Each dot represent a genetic instrumental variable. Two lines represent causal estimate (β_{IV}) by the inverse variance weighted method (light blue) and the MR–Egger method (blue). SE_{IV} represents standard error for each genetic instrumental variable. Error bars represent 95%CIs. MR, Mendelian randomization, IV, genetic instrumental variable.

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Nationwide changes in physical activity, nutrient intake, and obesity in South Korea during the COVID-19 pandemic era

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Background: This study aimed to examine changes in obesity rates and obesity-related factors during the COVID-19 pandemic compared to a previous period.

Methods: An ecological time-series study was designed using the Korean National Health and Nutritional Examination Survey (KNHANES) database from 2014 to 2020. The expected values of obesity rate, physical activity rate, and nutrient intake for 2020 were estimated. The differences between the predicted and actual values for 2020 were also examined. In addition, a multiple logistic regression model was used to examine the changes in obesity and physical activity rates in 2020 compared to 2019.

Results: The actual obesity rates in 2020 were higher, and the walking and aerobic physical activity rates were lower than the predicted values for the same year. However, the actual resistance training rates in 2020 were higher and the total energy intake was lower than the predicted values for 2020. In the multiple logistic regression model, the odds ratios for obesity, aerobic physical activity, and walking among men in 2020 were 1.29 (95% CI: 1.08 to 1.55), 0.86 (0.74 to 1.01), and 0.84 (0.73 to 0.97), respectively, compared to those in 2019. However, there were no significant differences between the values for women in 2020 and 2019.

Conclusions: This study suggests that the male obesity rate in Korea has significantly increased during the COVID-19 epidemic, mainly due to a decrease in physical activity.

KEYWORDS

COVID-19, obesity, exercise, physical activity, nutrients, diet

Introduction

Coronavirus disease 2019 (COVID-19), an infection caused by SARS-CoV-2, was first identified in Wuhan City in December 2019 and subsequently spread worldwide. The World Health Organization declared a public health emergency of international concern in January 2020 and raised it to the pandemic level in March 2020 (1). COVID-19 has not only led to the loss of many lives but has also had a great impact on our lifestyle. Many countries implemented lockdowns or social distancing measures to prevent the spread of COVID-19 (2).

Moderate- to vigorous-intensity physical activity not only reduces the risk of cardiovascular disease mortality but also reduces cancer mortality and all-cause mortality (3). In addition, physical activity above the recommended level was associated with a reduction in the risk of death due to COVID-19 as well as the severity of COVID-19 (4). However, several studies have reported that the recent emerging COVID-19 pandemic has led to a decrease in physical activity levels, mainly due to lockdown or social distancing (2, 5, 6). In addition, physical inactivity and restricted access to healthy and necessary nutrients due to COVID-19 measures are expected to negatively affect dietary habits and obesity (7). As expected, a study conducted in the UK in 2020 reported that participants experienced negative changes in eating and physical activity behaviors and barriers to weight management during the lockdown during the COVID-19 pandemic compared to their lifestyle before the lockdown (8). In Poland, it has been reported that the frequency of meals, the proportion of people snacking, and the incidence of weight gain significantly increased during the lockdown due to COVID-19 in 2020 compared to those before the lockdown (9).

However, most previous studies were not representative sampling studies for the entire country or population. In addition, changes in physical activity, nutrient intake, and body weight during lockdowns or the COVID-19 pandemic did not accurately reflect real nationwide changes because they used mobile devices or self-questionnaires. In addition, there were controversial study findings regarding whether physical activity or nutrient intake really had deteriorated during the COVID-19 pandemic (10, 11).

South Korea is geographically close to China, with many personal contacts, including travel and trade. Therefore, the early COVID-19 outbreak could not be avoided. More than 6,600 patients diagnosed with COVID-19 were reported in Dae-Gu City and the Gyeongsangbuk-do region around March 2020, in the early stage of the COVID-19 pandemic (12). However, unlike other countries, South Korea did not implement a lockdown and only maintained non-pharmaceutical interventions (NPI) such as social distancing, hand washing, and wearing a facial mask (13).

Therefore, although South Korea did not implement a compulsory lockdown, we hypothesized that the COVID-19 epidemic affected physical activity, nutrient intake, and the prevalence of obesity resulting from a decrease in outdoor activity due to social distancing and the fear of COVID-19 in South Korea. To test this hypothesis, we used a nationwide representative health survey database and compared it with physical activity rates, nutrient intake, and obesity rates with past trends.

Materials and methods

Data source

We used information from the Korean National Health and Nutritional Examination Survey (KNHANES) database from 2014 to 2020 to determine changes in physical activity and prevalence rates of obesity in South Korea. The KNHANES dataset is a representative cross-sectional survey of the entire Korean population conducted by the Korean Center for Disease Control and Prevention (KCDC) from 1998 to 2020 (14). The purpose of this nationwide survey was to estimate national representative and reliable statistics such as health behaviors, prevalence of chronic diseases, and food and nutritional intake at a national health level. The study participants were sampled using a stratified cluster random sampling method to represent the entire Korean population. The protocol and method for this survey were quality-controlled by external experts and the KCDC, the details of which have been previously reported (14, 15). Our study included only adults aged over 20 years old, and the numbers of participants in 2019 and 2020 were 6,542 and 6,072, respectively. The KNHANES dataset is freely available to all researchers. The observational study protocol was reviewed and approved by the Institutional Review Board of Kyung Hee University (KHSIRB-22-114(RA)).

Measurement of physical activity

Physical activity was measured using the Global Physical Activity Questionnaire (GPAQ) in KNHANES from 2014 to 2020 (16). In the KNHANES, the GPAQ consisted of physical activity in three different domains: activity at work, activity from transportation, and leisure time activity. We converted the metabolic equivalent (MET) minutes per week for physical activity in each domain. We then added all METs and classified physical activity into the following six subdomains: vigorous work, moderate work, travel, vigorous recreation, moderate recreation, and sitting (17). Finally, people who met the following conditions were classified as engaging in aerobic physical activity during work, transport, and leisure time: moderate-intensity physical activity for 150 min or more per week, high-intensity physical activity for 75 min or more per

week, or moderate- to- vigorous-intensity physical activity for at least 600 MET minutes or more (18).

The resistance exercise rate (%) was defined as the proportion of those who performed resistance training, such as push-ups, sit-ups, and dumbbells, more than 2 days per week (18). The walking rate (%) was defined as the proportion of walking for more than 30 min for more than 5 days per week (19). Sedentary time was defined as the average time spent lying down or sitting per day.

Definition of obesity

Obesity was defined as a body mass index (BMI) ≥25 kg/m^2 according to the Asian-Pacific cutoff points and the 2018 guidelines from the Korean Society for the Study of Obesity (20). Height and weight were measured while the subjects wore a medical gown. Height (m) was measured using a Seca 225 (Seca, Germany). When measuring height after inhaling, the heel, buttocks, back, and head were all in contact with a vertical plate. Body weight (kg) was measured using a GL-6000-20 (G-Tech, Korea). When measuring the weight, participants took off their shoes, and the weight was read to one decimal point while the participant inhaled.

Other covariates

Total energy intake (kcal/day) and saturated fat intake (g/day) were calculated through a 24-h recall food intake survey for each individual (21). Income level was calculated as the individual income quartile, and education levels were classified as elementary school education, middle school education, high school education, university education, or higher education.

Statistical analysis

All analyses were performed using a complex survey design by sex. Age standardization was applied to adjust for different age structures by year, using the mid-2005 Korean population as the standard population. For age standardization, the direct standardization method was used by applying the prevalence rates by age groups in 5-year intervals (0–4/5–9/…/80–84/85+) for each year to the 2005 mid-year Korean standard population.

To obtain the expected value for 2020, joinpoint regression was applied to prevalence rates such as obesity and physical activity rates (22), and linear regression analysis was applied to continuous variables like total energy intake (kcal), sedentary time (h), and BMI (kg/m^2) to estimate the predicted value for 2020. Subsequently, the age-adjusted differences between the actual values measured in the KNHANES in 2020 and the predicted values estimated by linear regression and joinpoint regression models were calculated. In addition, we compared the age-adjusted differences between the actual values measured in the KNHANES in 2019 and those measured in 2020. Linear regression models were used to test the differences in continuous variables between 2019 and 2020 after adjusting for age groups, and logistic regression models were used to test the differences in categorical variables between 2019 and 2020 after adjusting for age groups.

Finally, multiple logistic regression models for complex survey designs were used to estimate the odds ratio (OR) and 95% confidence intervals (CIs) of the obesity, walking, and aerobic physical activity rates for 2020, compared to 2019 after adjusting for age, income level, and education level. Statistical significance was set at p <0.05. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and Stata version 17.0 (StataCorp, TX, USA).

Results

Difference in physical activity, nutrient intake, and obesity between the expected value and the observed value of 2020

The expected values for 2020 were predicted using the joinpoint regression model for proportion and the linear regression model for continuous variables, and the expected values for 2020 were compared with the observed values for 2020, which were measured in the KNHANES survey (Table 1 and Figures 1, 2). The observed obesity rate in 2020 (36.22%) was higher than the expected value (31.82%), and the difference was markedly larger among men (+4.84% vs. +3.27% for women) (Figure 1). The observed sedentary time was lower than the expected value.

Regarding physical activity, the observed walking rate was lower than expected for both men and women (Figure 2), and the observed aerobic physical activity rate was lower than expected in men but higher than expected in women (Figure 3). The observed resistance exercise rate increased more than expected in both men and women. The total energy intake and saturated fat intake were lower than the expected values.

Change in physical activity, nutrient intake, and obesity in 2020 compared to 2019

In addition to examining the actual change between 2019 and 2020, we compared the observed values in 2019 and 2020 using the KNHANES database (Table 2). The actual obesity rates increased in 2020 for men (51.18%) but not for women (25.61%)

TABLE 1 Age-adjusted difference between expected and observed values for physical activity, nutrient intake, and obesity in 2020.

Variables	Observed value for 2020	Expected value for 2020	Difference between expected and observed values in 2020
	Age-adjusted mean value or (%) (s.e.)	Age-adjusted mean value or (%)	Age-adjusted mean value or (%)
Total			
Sedentary time (h)	8.68 h (0.08)	8.79 h	−0.11 h
Walking (%)	39.31% (1.02)	45.03%	−5.72%*
Aerobic physical activity (%)	45.33% (0.92)	46.80%	−1.46%
Resistance exercise (%)	24.70% (0.77)	23.59%	+1.11%
Total energy intake (kcal)	1,935.17 kcal (18.84)	1,958.17 kcal	−23.00 kcal
Saturated fat intake (g)	16.79 g (0.03)	17.11 g	−0.31 g*
Obesity (BMI ≥ 25kg/m^2) (%)	36.22% (0.94)	31.82%	+4.39%*
BMI (kg/m^2)	24.18 kg/m^2 (0.08)	23.88 kg/m^2	0.30 kg/m^2*
Men			
Sedentary time (h)	8.72 h (0.11)	8.85 h	−0.13 h
Walking (%)	39.88% (1.29)	46.02%	−6.14%*
Aerobic physical activity (%)	47.87% (1.30)	54.09%	−6.22%*
Resistance exercise (%)	31.81% (1.17)	36.33%	+4.53%*
Total energy intake (kcal)	2,264.93 kcal (29.30)	2,309.91 kcal	−44.98 kcal
Saturated fat intake (g)	19.19 g (0.47)	19.76 g	−0.57 g
Obesity (BMI ≥ 25 kg/m^2) (%)	51.18% (1.64)	46.34%	+4.84%*
BMI (kg/m^2)	25.18 kg/m^2 (0.10)	24.68 kg/m^2	+0.50 kg/m^2*
Women			
Sedentary time (h)	8.64 h (0.09)	8.73 h	−0.08 h
Walking (%)	38.67% (1.46)	43.91%	−5.24%*
Aerobic physical activity (%)	42.76% (1.20)	41.38%	+1.38%
Resistance exercise (%)	17.34% (0.86)	14.48%	+2.87%*
Total energy intake (kcal)	1,609.64 kcal (19.56)	1,613.89 kcal	−4.25 kcal
Saturated fat intake (g)	14.41 g (0.30)	14.50 g	−0.09 g
Obesity (BMI ≥ 25kg/m^2) (%)	25.61% (1.11)	22.34%	+3.27%*
BMI (kg/m^2)	23.08 kg/m^2 (0.11)	22.99 kg/m^2	+0.09 kg/m^2

The observed value for 2020 was actually estimated from the KNHANES database of 2020. Expected value for 2020 year was predicted value using the KNHANES database from 2014 to 2019 fitted by joinpoint regression model and linear regression model (percentage: joinpoint regression model, continuous variables: linear regression model). Differences between expected and observed in 2020 were calculated as follows: (Observed value for 2020 − Expected value for 2020). Walking rate was defined as the proportion of doing walk more than 30 min for more than 5 days per week. Aerobic physical activity was defined as doing moderate-intensity aerobic physical activity for 150 min or more per week or doing vigorous-intensity aerobic physical activity for 75 min or more per week. Resistance exercise rate was defined as the proportion of doing resistance training such as push-ups, sit-ups, and dumbbells, more than 2 days per week. s.e., standard error.

*The expected value is outside the range of 1.96× standard error of the observed value for 2020.

compared to those in 2019 [difference; men: +6.25% (p = 0.005), women: +2.25% (p = 0.24)]. The change in actual sedentary time did not show a significant difference between 2019 and 2020.

The walking rate in 2020 was significantly lower than that in 2019 for men (difference: −4.33%, p = 0.002). Although the change in aerobic physical activities was not significant, the aerobic physical activity rate in 2020 was lower than that in 2019 in men and higher than that in 2019 in women. However, the resistance exercise rate for women in 2020 was significantly higher than that in 2019 (difference: +2.75%, p = 0.03). There were no statistically significant changes in the total energy intake and saturated fat intake between 2019 and 2020.

Multiple logistic regression model for obesity and aerobic physical activity in 2020 compared to 2019

After adjusting for age, income level, and education level, a multiple logistic regression analysis was performed by sex to estimate the ORs of obesity rate, aerobic physical activity rate, and walking rate in 2020 compared to 2019 (Table 3). For men, compared to 2019, the OR for obesity rates in 2020 was 1.29 times (95% CI: 1.08–1.55) higher even after adjusting for age, income, and education level. In addition, the OR for walking rates among men in 2020 was 0.84 times (95% CI: 0.73–0.97)

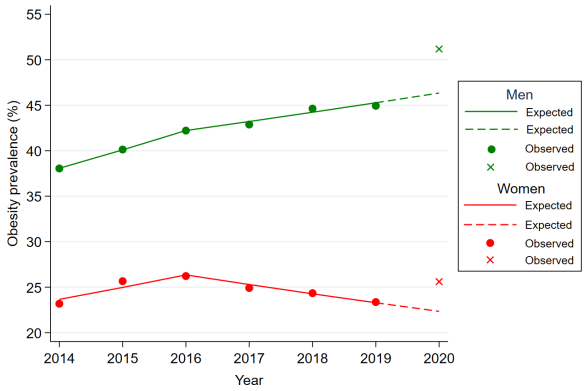

FIGURE 1
Difference between expected and observed obesity rates for men and women in 2020 year. Footnotes: Age-adjusted obesity rates were used to illustrate for expected and observed obesity rates. The circled dot and the X-point represent the observed obesity rates for each year in KNHANES data from 2014 to 2020 year. The solid represent the expected obesity rates fitted by the Joinpoint regression model using the KNHANES data from 2014 to 2019 year. The dashed line is the predicted value of the obesity rate in 2020 year using the regression equation (y=b1*x + b0) of the Jointpoint regression fitted for the year 2014-2019.

lower than that in 2019, after adjusting for all covariates. Although it was not statistically significant in men, the OR for aerobic physical activity rate in 2020 was 0.86 (95% CI: 0.74–1.01) compared to that in 2019. However, there were no statistically significant increases or decreases in the ORs for obesity rate, aerobic physical activity rate, and walking rate in 2020 compared to those in 2019 for women.

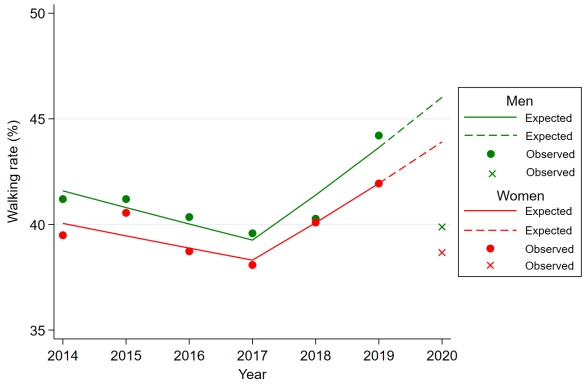

FIGURE 2
Difference between expected and observed walking rates for men and women in 2020 year. Footnotes: Age-adjusted walking rates were used to illustrate for expected and observed obesity rates. The circled dot and the X-point represent the observed walking rates for each year in KNHANES data from 2014 to 2020 year. The solid represent the expected walking rates fitted by the Joinpoint regression model using the KNHANES data from 2014 to 2019 year. The dashed line is the predicted value of the walking rate in 2020 year using the regression equation (y=b1*x + b0) of the Jointpoint regression fitted for the year 2014-2019.

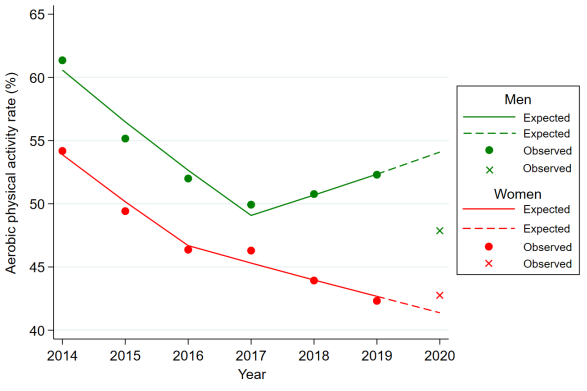

FIGURE 3
Difference between expected and observed aerobic physical activity rates for men and women in 2020 year. Footnotes: Age-adjusted aerobic physical activity rates were used to illustrate for expected and observed obesity rates. The circled dot and the X-point represent the observed aerobic physical activity rates for each year in KNHANES data from 2014 to 2020 year. The solid represent the expected aerobic physical activity rates fitted by the Joinpoint regression model using the KNHANES data from 2014 to 2019 year. The dashed line is the predicted value of the aerobic physical activity rate in 2020 year using the regression equation (y=b1*x + b0) of the Jointpoint regression fitted for the year 2014-2019.

Discussion

This study examined the changes in obesity and obesity-related factors, such as physical activity and nutrient intake, during the COVID-19 epidemic (2020). Our findings showed that the obesity rate during the COVID-19 epidemic had significantly increased compared to the expected obesity rate of 2019, especially in men. This increase in the obesity rate was accompanied by a decrease in physical activity, especially aerobic physical activity and walking rate.

The increase in obesity rates accompanied by a decrease in physical activity during the COVID-19 epidemic was not limited to Korea but has been reported in several countries around the world. The US Behavioral Risk Factor Surveillance System also reported that the obesity rate in March 2020 had increased significantly by 1.1% compared to that in 2019 (23). In addition, it was reported that weight and BMI increased in 32 countries during the first lockdown period compared to those before the lockdown period (24). Obesity rates in Latin America have also increased simultaneously with the COVID-19 epidemic (25). Furthermore, a meta-analysis of eight

TABLE 2 Difference in age-standardized rates for physical activity, nutrient intake, and obesity between 2019 and 2020.

Variables	Observed value for 2020	Observed value for 2019	Difference between observed value in 2019 and observed value in 2020	*p*-value*
	Age-adjusted mean value or (%)	Age-adjusted mean value or (%)	Age-adjusted mean value or (%)	
Total				
Sedentary time (h)	8.68 h (0.08)	8.58 h (0.08)	+0.11 h	0.68
Walking (%)	39.31% (1.02)	43.09% (1.02)	−3.78%	0.03*
Aerobic physical activity (%)	45.33% (0.92)	47.49% (0.97)	−2.15%	0.19
Resistance exercise (%)	24.70% (0.77)	23.62% (0.81)	+1.08%	0.35
Total energy intake (kcal)	1,935.17 kcal (18.84)	1,977.67 kcal (19.00)	−42.50 kcal	0.15
Saturated fat intake (g)	16.79 g (0.03)	16.57 g (0.27)	+0.23 g	0.37
Obesity (BMI ≥ 25) (%)	36.22% (0.94)	32.94% (1.01)	+3.28%	0.02*
BMI (kg/m^2)	24.18 kg/m^2 (0.08)	23.76 kg/m^2 (0.07)	+0.42 kg/m^2	<0.001*
Men				
Sedentary time (h)	8.72 h (0.11)	8.65 h (0.10)	+0.08 h	0.90
Walking (%)	39.88% (1.29)	44.21% (1.36)	−4.33%	0.02*
Aerobic physical activity (%)	47.87% (1.30)	52.30% (1.27)	−4.43%	0.09
Resistance exercise (%)	31.81% (1.17)	32.37% (1.31)	−0.57%	0.72
Total energy intake (kcal)	2,264.93 kcal (29.30)	2,335.72 kcal (27.3)	−70.79 kcal	0.09
Saturated fat intake (g)	19.19 g (0.47)	19.30 g (0.42)	−0.10g	0.98
Obesity (BMI ≥ 25) (%)	51.18% (1.64)	44.94% (1.75)	+6.25%	0.005*
BMI (kg/m^2)	25.18 kg/m^2 (0.10)	24.53 kg/m^2 (0.09)	+0.65 kg/m^2	<0.001*
Women				
Sedentary time (h)	8.64 h (0.09)	8.51 h (0.09)	+0.14 h	0.79
Walking (%)	38.67% (1.46)	41.94% (1.20)	−3.27%	0.19
Aerobic physical activity (%)	42.76% (1.20)	42.32% (1.25)	+0.44%	0.77
Resistance exercise (%)	17.34% (0.86)	14.59% (0.85)	+2.75%	0.03*
Total energy intake (kcal)	1,609.64 kcal (19.56)	1,630.36 kcal (18.55)	−20.72 kcal	0.62
Saturated fat intake (g)	14.41g (0.30)	13.89 g (0.27)	+0.52 g	0.09
Obesity (BMI ≥ 25) (%)	25.61% (1.11)	23.36% (1.00)	+2.25%	0.24
BMI (kg/m^2)	23.08 kg/m^2 (0.11)	22.91 kg/m^2 (0.10)	+0.17 kg/m^2	0.30

Walking rate was defined as the proportion of doing walk more than 30 min for more than 5 days per week. Aerobic physical activity was defined as doing moderate-intensity aerobic physical activity for 150 min or more per week or doing vigorous-intensity aerobic physical activity for 75 min or more per week. Resistance exercise rate was defined as the proportion of doing resistance training such as push-ups, sit-ups, and dumbbells, more than 2 days per week.
*The differences in variables between 2019 and 2020 were tested by using linear regression for continuous variables and logistic regression analysis for categorical variables adjusted by age.

countries demonstrated that the body weight and BMI of adolescents and children increased during the lockdowns due to COVID-19 (26). Considering our findings and those of previous studies, increases in weight and BMI during the COVID-19 pandemic seem to be another global obesity pandemic (27).

However, previous studies did not provide any clues as to whether a change in nutrient intake caused the rise in obesity or whether a decrease in physical activity was mainly responsible for the obesity pandemic. Interestingly, our study findings showed that physical activity, especially aerobic physical activity and walking, decreased, whereas nutrient intake did not show significant changes considering the trend before the COVID-19 pandemic. However, it is difficult to generalize these results to other countries. While most other countries implemented strong lockdown policies during the early COVID-19 pandemic, South Korea did not enforce lockdowns throughout the entire period of the COVID-19 pandemic (13, 28). Unlike other countries, South Korea did not implement a strong containment policy, including movement restrictions, and social distancing strategies for COVID-19 were based on the voluntary participation of individuals. South Korea has a very advanced food delivery system and access to grocery stores was not restricted. Therefore, accessibility to food in South Korea was not as difficult as it was in other countries during the COVID-19 pandemic. In fact, a nationwide cross-sectional study of Korean adolescents in 2020 reported that the consumption of fast food and carbonated drinks decreased during the pandemic (29). In addition, the proportion of individuals eating breakfast and home-cooked food increased, thus improving unhealthy dietary habits. These results support our finding that saturated fat intake decreased (29). Furthermore, in a cross-sectional study conducted in Italy, a large proportion of participants made efforts to follow dietary recommendations and improve their dietary habits during the

TABLE 3 Multiple logistic regression model for obesity and aerobic physical activity in 2020 compared to 2019.

	Unadjusted model	Age-adjusted model	Age- and SES-adjusted model
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Men			
Obesity			
2019	1.00 (reference)	1.00 (reference)	1.00 (reference)
2020	1.27 (1.07–1.50)	1.28 (1.08–1.52)	1.29 (1.08–1.55)
Aerobic physical activity			
2019	1.00 (reference)	1.00 (reference)	1.00 (reference)
2020	0.88 (0.75–1.03)	0.87 (0.74–1.02)	0.86 (0.74–1.01)
Walking			
2019	1.00 (reference)	1.00 (reference)	1.00 (reference)
2020	0.84 (0.73–0.98)	0.84 (0.72–0.97)	0.84 (0.73–0.97)
Women			
Obesity			
2019	1.00 (reference)	1.00 (reference)	1.00 (reference)
2020	1.10 (0.94–1.29)	1.10 (0.94–1.28)	1.08 (0.92–1.26)
Aerobic physical activity			
2019	1.00 (reference)	1.00 (reference)	1.00 (reference)
2020	0.99 (0.86–1.14)	0.98 (0.85–1.13)	0.98 (0.86–1.13)
Walking			
2019	1.00 (reference)	1.00 (reference)	1.00 (reference)
2020	0.91 (0.79–1.06)	0.91 (0.78–1.05)	0.90 (0.78–1.04)

Socioeconomic status (SES) was defined as quartile income level and education level. Income level was calculated as the individual income quartile and education level was classified as elementary school education, middle school education, high school education, and university education, or higher education. Multiple logistic regression models for obesity, aerobic physical activity, and walking in 2020 were compared with obesity, aerobic physical activity, and walking in 2019, after adjusting for age or age, income level, and education level.

lockdown period (10). In contrast, an international online survey reported that the dietary patterns of people became more unhealthy during the lockdown period compared to those before the COVID-19 pandemic (30). These differences in dietary patterns between countries may be partially attributed to differences in dietary habits and culture, the prevalence of COVID-19, degree of lockdown, and accessibility to food by country.

Regarding physical activities, our findings showed that the walking rate significantly decreased, while that of people performing resistance exercise increased. We inferred that the frequency and duration of movement may have decreased due to fear of COVID-19 or policies such as social distancing, while the frequency of performing resistance exercises increased to compensate for the lack of daily activities. Although there is no clear evidence to support this inference, it was reported that motivation or perceived effort decreased compared to those before the lockdown, but most people maintained the practice of performing resistance training in the multinational survey (11). In addition, the Korea Youth Risk Behavior Web-based Survey (KYRBWS) study also reported that although vigorous physical activity decreased in 2020 compared to 2019 in Korean adolescents, the frequency of strength exercise increased in 2020 (29). Another international online survey study also reported substantial decreases in physical activity, including walking, moderate-intensity physical activity, and vigorous-intensity physical activity (30).

In our study, walking and aerobic physical activity rates decreased, but resistance exercise rates increased slightly. Unlike physical activity, sedentary behavior did not show a significant change during 2020 compared to the pre-pandemic period. This was contrary to the results of a previous study that reported an increase in sedentary time compared to the pre-pandemic period across all age groups, although the study examined relatively small samples (n = 1,035) (30). In addition, a systematic review of 26 studies on physical activity also reported that sedentary behaviors increased during the pandemic lockdown period compared with those before the lockdown (2). Further research is needed to determine the cause of the differences between South Korea and other countries.

Although this study used the KNHANES database, which was representative of the South Korean population, it may include regions and periods that were not actually affected by the COVID-19 epidemic. In addition, our study may be statistically unstable because we only evaluated the impact of COVID-19 for the year 2020. Future studies are necessary to evaluate the long-term impact of COVID-19 on obesity, physical activity, and nutrient intake, including the year 2021. Regarding nutrient intake, only the total energy intake and saturated fat intake were evaluated in our study, and it is necessary to evaluate whether there were changes in dietary patterns and the intake of other nutrients. Additionally, South Korea had a unique

response to the COVID-19 pandemic. Unlike other countries, South Korea did not implement a lockdown but strengthened social distancing measures step-by-step, relying on individual voluntary participation. Therefore, our findings cannot easily be extrapolated to other countries. Nevertheless, this study has a great advantage because it examined not only the changes in obesity rates but also the changes in physical activity and nutrient intake that can affect obesity rates using the reliable and large-volume KNHANES database at the national level.

In conclusion, the obesity rate significantly increased in 2020 when the COVID-19 pandemic began in South Korea, compared to that before the COVID-19 pandemic. This increase in the obesity rate in 2020 was accompanied by a decrease in physical activity, especially aerobic physical activity and walking rates, rather than a change in nutrient intake, especially in men. However, further research is necessary to determine whether this phenomenon is limited to South Korea or whether other countries show similar patterns because South Korea did not implement a containment policy such as a nationwide lockdown.

Data availability statement

We used the Korean National Health and Nutrition Examination Survey data from 2014 year to 2020 year, which is freely open to researchers at the Korea Centers for Disease Control and Prevention. Any researcher can obtain data from the following site. (Available from: https://knhanes.kdca.go.kr/knhanes/main.do).

Ethics statement

The studies involving human participants were reviewed and approved by Kyung Hee University (KHSIRB-22-114(RA)). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

C-MO designed the research. HJY conducted the research. HJY and C-MO analyzed the data. HJY and SRP wrote the paper. T-YY, SKP, JYJ, J-HL, and J-HR interpreted the study findings and critically revised the study protocol and manuscript. C-MO was primarily responsible for the final content. All authors have read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Self-managed weight loss by smart body fat scales ameliorates obesity-related body composition during the COVID-19 pandemic: A follow-up study in Chinese population

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Background: Since 2020, longer stay-at-home time in response to the coronavirus disease 2019 (COVID-19) pandemic has changed the weight-related behaviors of Chinese population.

Objectives: To explore the demographic and basic characteristics of body fat scale users and to investigate the changes in obesity-related body composition of overweight and obese users during COVID-19. Further, we analyzed the factors associated with successful weight loss and improved body composition changes in overweight and obese people.

Methods: The study included 107,419 Chinese adults registered in the smart app connecting to the body fat scale in 2020 to describe the demographic characteristics of body fat scale users by Unpaired Student's t-test and Chi-Square test. Subsequently, overweight and obese participants with body mass index (BMI) of more than 24 kg/m^2 were screened to investigate the independent factors associated with effective weight loss and improved body composition changes by multivariable logistic regression analyses.

Results: During the pandemic, the number of body fat scale users increased markedly compared with pre-pandemic. Over half of the participants were women and with normal baseline BMI. Based on BMI classification, multivariable logistic regressions showed that age, gender, measurement frequency classification, baseline BMI, visceral adipose index and skeletal muscle rate were associated with weight loss and fat loss in the overweight and obese population, with the high-frequency measurement being the most important factor for effective weight and fat loss. In the population with normal BMI obesity, younger age was the most significant factor for effective fat loss.

Conclusion: During the COVID-19 pandemic, participation in self-monitored weight loss increased markedly compared with pre-pandemic, and women accounted for the majority. We found that many overweight and obese participants achieved weight loss goals by smart body fat scales, and the effectiveness of weight and fat loss was greater in obese participants than in overweight participants, both based on BMI and PBF classification. In addition, promoting the usage of smart body fat scales could contribute to more effective weight and fat loss in the overweight and obese population based on BMI classification. However, in the population with normal BMI obesity, young subjects might be easier to successfully lose fat compared with the elder. Digital self-management by smart body fat scales could become a promising approach for the obese population with high BMI to lose weight and keep healthy.

KEYWORDS

COVID-19, weight loss, obesity, smart body fat scales, normal weight obesity

Introduction

Due to the rapid improvement of economic level and the westernization of dietary habits in China, the proportion of overweight and obese patients in the adult population climbed from 18.9% and 2.9% in 2002 to 34.3% and 16.4% in 2020, respectively (1). According to previous studies, obesity and metabolic syndrome were closely related to the occurrence and development of diabetes (2), hyperlipidemia, cardiovascular disease (3), cerebrovascular disease (4), and cancers (5). Obesity has become a critical metabolic disease threatening people's health and is the most common comorbidity reported among patients with severe coronavirus disease 2019 (COVID-19) (6), thus the prevention and treatment of obesity care are crucial to avoid complications and a high rate of hospitalization. Several studies confirmed the potential efficacy of lifestyle interventions in reducing obesity in Caucasians (7, 8). These studies found that interventions, such as establishing appropriate weight loss goals, self-monitoring, and adjusting dietary intake and physical activity, could achieve the purpose of weight loss (9). Because of stay-at-home for more time than before, Chinese people have changed their daily behaviors including dietary intake and physical activity during the COVID-19 pandemic (10).

On account of the progression of the Internet and smartphones, various types of online health management software have appeared. Wang Y analyzed 17 reviews and found that health self-management depending on mobile apps was beneficial to the treatment of diabetes and obesity (11). In the meta-analysis by Flores M et al., patients using online methods had significantly greater reductions in body weight and body mass index (BMI) compared with patients using other traditional methods such as diary records (12). Notably, the frequency of self-weighing was higher in the group that uploaded weight data *via* Bluetooth compared with the group that entered weight data manually, and the percentage of participants who achieved weight-loss goals was also noticeably higher (13).

BMI is the most commonly used indicator for diagnosing obesity. At present, 24 kg/m^2 and 28 kg/m^2 of BMI values are used as the boundary values for being overweight and obese in China (14). However, it fails to determine whether the changes in BMI caused by fat mass (FM) or non-fat mass (FFM) (15). The concept of percentage of body fat (PBF) refers to the proportion of body fat mass in total body weight. Normal BMI obesity refers to people with normal BMI and high PBF. Previous studies found this specific population was susceptible to metabolic disorders and PBF could be used to help assess the metabolic risk (16–18). Thus, it is more reliable to establish PBF as an index to assess the improvement effect of body composition in this specific population. Nevertheless, most previous studies on the effect of weight loss were carried out in European Caucasians. Few studies focused on the effectiveness of self-managed weight loss *via* body fat scales in Chinese population, especially during the COVID-19 pandemic.

According to the aforementioned studies (11–13), online software-based self-management helped weight loss and alleviated diabetes and obesity. However, the effects of self-management based on online software and its independent factors during the COVID-19 pandemic are unclear, which are our current study concerns. Here, we conducted a cohort study based on the data of obesity-related anthropometric indices from

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the Qingniu Health app connecting to the body fat scale in overweight and obese people for at least one year self-monitoring, to test our hypotheses that online software might help self-management during the COVID-19 pandemic and measurement frequency would be an important factor.

Materials and methods

Subjects

The inclusion of participants were adult users aged 18 to 79 years in China, who signed up to use the Qingniu Health app connecting to the body fat scale in 2020 during the COVID-19 pandemic. Participants with extremely abnormal initial weight (below 30kg), BMI (below 14 kg/m^2 and above 60 kg/m^2) and PBF (below 10%) were excluded. Furthermore, participants whose annual measurement frequency was less than 2 times were also excluded. 107,419 subjects were included to describe the basic and demographic characteristics of body fat scale users registered in 2020. Then, 31,227 overweight participants with BMI of 24-27.9 kg/m^2 and 15,509 obese participants with BMI ≥28 kg/m^2 were followed up to investigate the improvement of obesity-related body composition indices for at least one year, which meant the time span from the first measurement to the last measurement was more than 1 year. Moreover, 13,724 participants with normal BMI but excessive PBF were also followed up (Figure 1). Electronic consent for the inclusion of participants was obtained. The study was approved by Xinhua Hospitals' Ethics Committee.

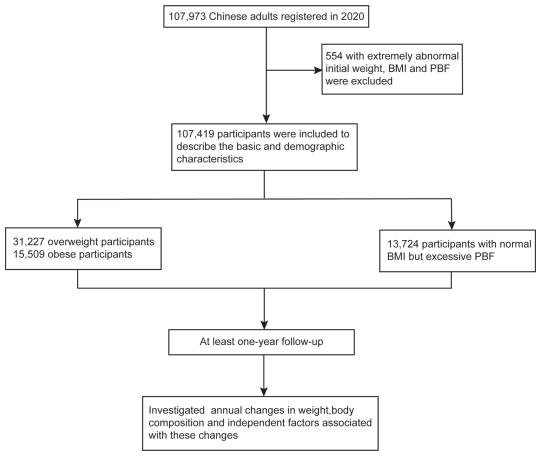

FIGURE 1
Flowchart of participant inclusion. BMI, Body Mass Index; PBF, Percentage of Body Fat.

Data collection

Data were collected in the Qingniu Health app, which contained the baseline information of participants at the time of initial registration, including gender, age, height, and residential city, as well as the measurements including weight, PBF, visceral adipose index (VAI), skeletal muscle rate (SMR) and fat-to-muscle ratio (FMR) by using the same brand, the same type of body fat scales (CS10C; Yolanda Technology Co., Ltd., Shenzhen, China). The measurement principle of the body fat scales is the multi-frequency bioelectrical impedance analysis (BIA), as same as the previous study (19). The participant's body fat scales measurement data were synchronized to the Qingniu Health app platform *via* Bluetooth.

In the following analyses, participants were grouped by gender, age, BMI, PBF, measurement frequency, and the residential city level, respectively. Participants aged <40, 40 - 59, and ≥60 years were defined as the adults, middle-aged and elderly group. Participants of BMI <18.5 kg/m^2, 18.5 - 23.9 kg/m^2, 24 - 27.9 kg/m^2, and ≥28 kg/m^2 were considered as underweight, normal, overweight and obesity respectively. Male with PBF ≥25.0% and female with PBF ≥30.0% were regarded as obese (20, 21), and the others were regarded as non-obese subjects. Normal BMI obesity refers to people with normal BMI and high PBF. Participants were categorized into tertiles of measurement frequency as low, middle, and high-frequency groups. As the usage of body fat scales was irregular during the follow-up period, we adopted the last measurement indices at least more than 1 year from baseline as the end-point results. The annual changes in weight, PBF and SMR were calculated as follows: (last measurement value – initial measurement value)/time (month) * 12. A study showed weight loss by 5% of initial weight reduced the risk of obesity-related comorbidities (22). Therefore, we defined participants with a decrease of more than 5% of initial body weight as effective weight loss. Likewise, a decrease of more than 5% of initial PBF was considered effective fat loss (23). The annual growth rate of SMR increased by more than 5%, which was also considered beneficial muscle gain.

Statistical analyses

Continuous variables were described as mean and standard deviation (SD), measurement frequency was described as median and interquartile range (IQR), and categorical variables were described as count and percentage. Unpaired Student's t-test or one-way ANOVA was used to analyze differences among groups, and differences in constituent ratios were analyzed by Chi-Square test. Univariable and multivariable logistic regression analyses were used to assess the independent influencing factors of the annual change rates of body weight, PBF, and SMR, respectively. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS v.26.0, SPSS Inc.). Statistically significance was set at p value <0.05.

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Results

General baseline characteristics of body fat scale users during the COVID-19 pandemic

The annual number of users registered in 2020 during the pandemic (N=107,419) was significantly higher than that in 2019 before the pandemic (N=73,307). During the pandemic, over half of the participants were women (84.7%) and with normal BMI. On average, participants were 32.87 ± 8.51 years and consisted of underweight (4.1%), normal (52.4%), overweight (29.1%), and obesity (14.4%) (Table 1). Participants in economically developed cities such as first-tier, new first-tier, and second-tier cities accounted for 86.5%. According to the users' annual measurement frequency, participants were divided into three groups: low, middle, and high-frequency groups (13.33 IQR: 10.53; 42.03 IQR: 21.58; and 129.73 IQR: 101.61 times per year). At baseline, the average age of female users was younger than that of males (P <0.0001); the average weight of men was 79.13 ± 13.97 kg, and that of women was 61.62 ± 11.12 kg (P <0.0001); the average BMI of men was significantly higher than that of women (26.26 ± 4.20 vs 23.59 ± 4.00 kg/m^2, P <0.0001), the proportion of overweight and obese users was also higher in men than in women (69.4% vs 38.9%, P <0.0001). Interestingly, the largest proportion of female users was in the normal BMI group (56.4%), and the average annual measurement frequency of female users was much higher than that of male users (44.44 IQR: 79.62 vs 30.89 IQR: 52.45 times per year, P <0.0001).

TABLE 1 Baseline characteristics of the participants grouped by gender during the COVID-19 pandemic.

	Total	Man	Woman	p-Value*
N (%)	107419 (100)	16447 (15.3)	90972 (84.7)	/
Age (years)	32.87 (8.51)	33.25 (9.95)	32.80 (8.22)	<0.0001
Classification (Age, years)			N (% of N_{column})	
[18, 40)	87197 (81.2)	12731 (77.4)	74466 (81.9)	<0.0001
[40, 60)	19375 (18.0)	3414 (20.8)	15961 (17.5)	
[60, 80)	847 (0.8)	302 (1.8)	545 (0.6)	
Baseline weight (kg)	64.30 (13.20)	79.13 (13.97)	61.62 (11.12)	<0.0001
Baseline BMI (kg/m^2)	24.00 (4.14)	26.26 (4.20)	23.59 (4.00)	<0.0001
Classification (BMI, kg/m^2)			N (% of N_{column})	
Underweight (<18.5)	4392 (4.1)	94 (0.6)	4298 (4.7)	<0.0001
Normal [18.5~24)	56291 (52.4)	4940 (30.0)	51351 (56.4)	
Overweight [24~28)	31227 (29.1)	6781 (41.2)	24446 (26.9)	
Obesity [>28)	15509 (14.4)	4632 (28.2)	10877 (12.0)	
Baseline PBF (%)	29.50 (5.50)	25.08 (5.75)	30.30 (5.06)	<0.0001
Classification (PBF, %)			N (% of N_{column})	
Normal (<25/30)	50022 (46.6)	7806 (47.5)	42216 (46.4)	0.012
Obesity [>25/30)	57397 (53.4)	8641 (52.5)	48756 (53.6)	
Baseline SMR (%)	41.72 (4.00)	47.79 (3.57)	40.62 (2.95)	<0.0001
Baseline FMR	0.72 (0.20)	0.54 (0.17)	0.76 (0.18)	<0.0001
Baseline VAI	6.58 (3.76)	8.73 (3.86)	6.19 (3.61)	<0.0001
Measurement frequency (times/year)	42.03 (75.47)	30.89 (52.45)	44.44 (79.62)	<0.0001
Classification (Frequency)			N (% of N_{column})	
Low	35812 (33.3)	7022 (42.7)	28790 (31.6)	<0.0001
Middle	35795 (33.3)	5563 (33.8)	30232 (33.2)	
High	35812 (33.3)	3862 (23.5)	31950 (35.1)	
Classification (City)			N (% of N_{column})	
First-tier	24482 (33.4)	4138 (36.6)	20344 (32.8)	<0.0001
New first-tier	24420 (33.3)	3759 (33.2)	20661 (33.3)	
Second-tier	14541 (19.8)	2148 (19.0)	12393 (20.0)	
Third-tier	5884 (8.0)	761 (6.7)	5123 (8.3)	
Fourth-tier	3066 (4.2)	383 (3.4)	2683 (4.3)	
Fifth-tier	987 (1.3)	122 (1.1)	865 (1.4)	

Continuous variables were described as mean (SD), "Measurement frequency" was described as median (IQR), and categorical variables were described as count (percentage). *All p values were compared between different gender. BMI, Body Mass Index; PBF, Percentage of Body Fat; SMR, Skeletal Muscle Rate; FMR, Fat-to-Muscle Ratio; VAI, Visceral Adipose Index.

Annual changes in weight and body composition for overweight and obese participants based on BMI classification

A total of 46,736 overweight and obese participants (N=31,227, 15,509 respectively) at baseline who had healthy needs of weight loss were followed up for longer than one year. There was no statistical difference in the annual weight loss of participants among different age groups. Nevertheless, the group aged 18-40 years experienced a greater decrease in PBF and a greater increase in SMR compared with the group aged 40-60 years. According to BMI classification, obese participants showed greater changes in all indices, including weight, BMI and PBF compared with overweight participants (P <0.0001). In obese men, on average, the annual body weight decreased by 3.90 ± 7.77 kg (Figure 2A), and the BMI decreased by 1.42 ± 2.59 kg/m^2. In obese women, the annual weight loss was 4.74 ± 8.78 kg, and the BMI decreased by 1.80 ± 3.36 kg/m^2. Grouped by PBF, obese participants showed greater changes in all indices than normal individuals as well (P <0.0001). Among different measurement frequency groups, the changes of all obesity-related indices in the high-frequency group were significantly greater than those of the low and middle-frequency groups (P <0.0001) (Figure 2B; Table 2).

Independent factors associated with weight loss, fat loss, and muscle gain

Based on the above findings, we further performed univariable and multivariable logistic regression analyses to find the independent factors associated with successful weight, fat loss and muscle gain. Univariable logistic analysis showed that age, gender, measurement frequency classification, baseline weight, BMI, PBF, VAI and SMR were associated with weight loss (Table S1). Multivariable logistic regression models revealed that participants of the female sex, with lower age, lower VAI, higher baseline BMI, PBF, SMR and measurement frequency were more likely to succeed in losing weight (Table 3). As described in Bajaj NS' study (24), the importance of each factor in the logistic regression model was measured as the partial chi-square statistic minus the predictor degrees of freedom (χ^2 - df). High measurement frequency was the largest predictor for effective weight loss (OR = 2.101, 95% CI 1.997-2.211, χ^2 - df = 818.81, P <0.0001) when other associated factors were corrected, including age, gender, baseline BMI, PBF, VAI and SMR (Figure 3A).

Multivariable logistic regression analysis showed that lower age, male sex, lower baseline VAI, SMR, higher baseline BMI and measurement frequency were independent factors for effective fat loss (Table 3). Especially, high measurement frequency was a most contributing factor for success of fat loss (OR = 1.999, 95% CI 1.895-2.108, χ^2 - df = 645.50, P <0.0001).

Table S1 showed age, gender, measurement frequency classification, baseline weight, BMI, PBF, VAI and SMR were associated with muscle gain. Multivariable logistic regression models showed age was a most significant factor for muscle gain (OR = 0.958, 95% CI 0.954-0.962, χ^2 - df = 384.43, P <0.0001) when other factors were corrected. Other than lower age, significant factors associated with successful muscle gain were male sex, higher measurement frequency, higher baseline BMI, lower baseline VAI and SMR (Table 3).

Independent factors associated with fat loss in the population with normal BMI but excessive PBF

13,724 participants with normal BMI but excessive PBF were observed, and women accounted for 99.5% of this specific obese population. In the group with normal BMI, the measurement

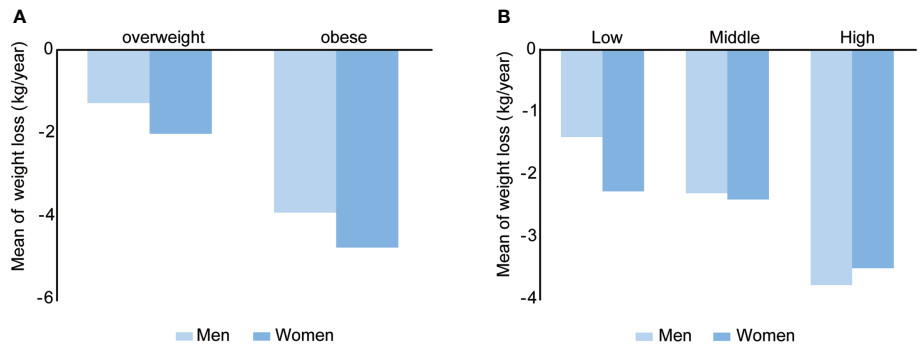

FIGURE 2
Mean of weight loss during the COVID-19 period in different BMI **(A)** and measurement frequency **(B)** groups. Overweight, men: n=6781, women: n=24446; obese, men: n=4632, women: n=10877. Low frequency, men: n=4475, women: n=8602; middle frequency, men: n=3900, women: n=11117; High frequency, men: n=3038, women: n=15604.

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TABLE 2 Changes of obesity-associated body composition associated with baseline characteristics.

	Weight (kg)	BMI (kg/m^2)	PBF (%)	SMR (%)
Age (years)				
Man				
18-40	-2.34 (6.36)	-0.86 (2.13)	-0.99 (2.78)*	0.64 (1.83)*
40-60	-2.25 (4.64)	-0.80 (1.57)	-0.82 (2.11)*	0.54 (1.43)*
60-80	-2.55 (4.26)	-0.90 (1.38)	-0.99 (1.99)	0.67 (1.36)
p-Value	0.566	0.226	0.007	0.017
Woman				
18-40	-2.88 (6.26)*	-1.08 (2.40)	-1.03 (2.30)*	0.60 (1.35)*
40-60	-2.68 (4.98)*	-1.02 (1.95)	-0.82 (1.79)*	0.48 (1.06)*
60-80	-2.87 (5.42)	-1.11 (2.12)	-0.84 (1.79)	0.50 (1.05)
p-Value	0.016	0.102	<0.0001	<0.0001
BMI (kg/m^2)				
Man				
24-28	-1.26 (4.08)	-0.46 (1.36)	-0.59 (2.21)	0.39 (1.49)
≥28	-3.90 (7.77)	-1.42 (2.59)	-1.48 (3.09)	0.96 (2.02)
p-Value	<0.0001	<0.0001	<0.0001	<0.0001
Woman				
24-28	-2.00 (3.97)	-0.75 (1.55)	-0.78 (1.89)	0.46 (1.11)
≥28	-4.74 (8.78)	-1.80 (3.36)	-1.45 (2.73)	0.85 (1.60)
p-Value	<0.0001	<0.0001	<0.0001	<0.0001
PBF (%)				
Man				
<25	-0.80 (3.88)	-0.31 (1.26)	-0.22 (2.23)	0.18 (1.48)
≥25	-2.83 (6.48)	-1.02 (2.18)	-1.19 (2.72)	0.77 (1.81)
p-Value	<0.0001	<0.0001	<0.0001	<0.0001
Woman				
<30	-1.46 (3.88)	-0.47 (1.37)	0.59 (2.89)	-0.40 (1.77)
≥30	-2.85 (6.03)	-1.07 (2.32)	-1.00 (2.20)	0.58 (1.29)
p-Value	<0.0001	<0.0001	<0.0001	<0.0001
Measurement frequency classification				
Man				
Low	-1.39 (6.29)	-0.52 (2.07)	-0.60 (2.80)	0.39 (1.87)
Middle	-2.29 (5.63)	-0.85 (1.91)	-0.95 (2.55)	0.63 (1.65)
High	-3.76 (5.76)	-1.32 (1.97)	-1.48 (2.42)	0.94 (1.63)
p-Value	<0.0001	<0.0001	<0.0001	<0.0001
Woman				
Low	-2.26 (6.98)	-0.84 (2.67)	-0.77 (2.47)	0.45 (1.46)
Middle	-2.39 (5.94)	-0.90 (2.28)	-0.83 (2.17)	0.48 (1.27)
High	-3.49 (5.42)*	-1.32 (2.10)*	-1.22 (2.04)*	0.71 (1.19)*
p-Value	<0.0001	<0.0001	<0.0001	<0.0001

All data were annual changing amplitude of obesity-associated body indices and expressed as mean (SD). * indicated that there were statistical differences among different groups.

frequency was higher in people with excessive PBF than in people with normal PBF (51.51 IQR: 87.12 vs 33.87 IQR: 57.79, P <0.0001), which indicated that participants were not only concerned about changes in weight and BMI, but PBF management was also an important part of health monitoring (Table S2). Multivariable logistic regression analysis displayed male sex, lower age and BMI, higher baseline weight, PBF and measurement frequency were promoting factors for effective fat loss and muscle gain, among which, lower age was the most important contributing factor (Table 4; Figure 3B).

Discussion

Obesity, closely related to chronic metabolic diseases such as hypertension and diabetes, endangers the health of Chinese (25,

TABLE 3 Factors associated with the effective change of weight and obesity-associated body composition.

Factors	Weight loss		Fat loss		Muscle gain	
	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Age	0.985 (0.983-0.988)	<0.0001	0.970 (0.967-0.973)	<0.0001	0.958 (0.954-0.962)	<0.0001
Gender	1.461 (1.178-1.811)	0.001	0.318 (0.261-0.389)	<0.0001	0.112 (0.086-0.145)	<0.0001
Baseline BMI	1.129 (1.087-1.172)	<0.0001	1.161 (1.118-1.206)	<0.0001	1.209 (1.149-1.273)	<0.0001
Baseline PBF	1.082 (1.061-1.103)	<0.0001	/	/	/	/
Baseline VAI	0.916 (0.876-0.957)	<0.0001	0.836 (0.799-0.875)	<0.0001	0.798 (0.750-0.849)	<0.0001
Baseline SMR	1.066 (1.032-1.100)	<0.0001	0.913 (0.893-0.934)	<0.0001	0.750 (0.727-0.774)	<0.0001
Measurement frequency classification						
Middle-low	1.237 (1.172-1.305)	<0.0001	1.256 (1.188-1.329)	<0.0001	1.081 (0.994-1.177)	0.070
High-low	2.101 (1.997-2.211)	<0.0001	1.999 (1.895-2.108)	<0.0001	1.599 (1.479-1.729)	<0.0001

All p values were results of multivariable logistic regression analysis in participants with BMI ≥ 24 kg/m^2.

26). Recently, the harm of obesity has become more visible, and people have paid more attention to weight management (27). More and more body fat scales accompanied with their supporting weight management apps have appeared, and have been popularized in Chinese population because of convenience and economy (28). However, the role of self-managed weight loss through the use of smart body fat scales in Chinese during the COVID-19 pandemic is to be assessed. Our present study is a follow-up study based on the data of a Chinese commercial online weight management app connecting a smart body fat scale. We found online software might help self-management during the COVID-19 pandemic and measurement frequency would be an important factor.

The COVID-19 pandemic has resulted in overall changes to weight-related behaviors, including dietary intake and physical activity (29). Based on the baseline characteristics of all included users, we found that the young and middle-aged women were the main population using body fat scales during the COVID-19 pandemic, which suggested that they were more concerned about weight, body composition, and their health conditions compared with other groups. Furthermore, female users with normal BMI were more than half, which suggested that women placed more emphasis on overweight and obesity prevention than men, consistent with other research findings (28). Overweight persons predominated in male participants, nevertheless, their annual average measurement frequency was

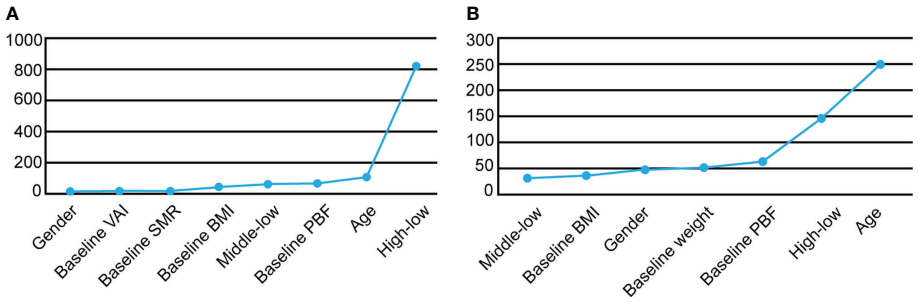

FIGURE 3
The importance of factors in logistic regression model which was measured as the partial chi-square statistic minus the predictor degrees of freedom (χ^2 - df) was shown. **(A)** χ^2 - df values for the prediction of weight loss success in the overweight and obese population with BMI ≥24. **(B)** χ^2 - df values for the prediction of effective fat loss in the obese population with normal BMI.

TABLE 4 Factors associated with the effective fat loss and muscle gain in participants with normal BMI but high PBF.

Factors	Fat loss		Muscle gain	
	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Age	0.926 (0.918-0.935)	<0.0001	0.893 (0.879-0.907)	<0.0001
Gender	0.059 (0.027-0.130)	<0.0001	0.004 (0.002-0.012)	<0.0001
Baseline weight	1.056 (1.040-1.072)	<0.0001	1.067 (1.038-1.097)	<0.0001
Baseline BMI	0.688 (0.610-0.776)	<0.0001	0.631 (0.518-0.768)	<0.0001
Baseline PBF	1.314 (1.229-1.404)	<0.0001	1.495 (1.368-1.635)	<0.0001
Measurement frequency classification				
Middle-low	1.441 (1.272-1.632)	<0.0001	1.084 (0.819-1.436)	0.572
High-low	2.071 (1.841-2.330)	<0.0001	1.804 (1.399-2.327)	<0.0001

lower than female users. Thus, it was necessary to increase men's awareness of preventing obesity in daily life through self-managed weight loss. In addition, participants in economically developed cities accounted for 86.5%, reflecting that the degree of urban development and economic level affected the usage of smart body fat scales.

Self-monitoring was the core of behavioral intervention for weight loss, including weight monitoring. Several studies found that self-monitoring was positively correlated with weight loss (30–33). However, the previous researches had some limitations, for example, the subjects of those study were a relative small sample size and confined to Caucasians. In the present study, we found the changes in weight, BMI and obesity-associated body composition were significantly different among different age, baseline BMI, PBF and measurement frequency groups in the overweight and obese participants. The changes in body composition were more obvious in the young, compared with the middle-aged person. The annual average weight loss of obese men was 3.90kg and that of obese women was 4.74kg, which implied that many overweight and obese participants based on BMI classification still achieved weight loss goals during the COVID-19 epidemic. According to PBF classification, the annual average weight loss of obese men was 2.83kg and that of obese women was 2.85kg, which showed a greater reduction than participants with normal PBF. At the same time, we found that the values of weight loss and fat loss were higher in obese participants than in overweight participants, both based on BMI and PBF classification, which indicated high PBF was also an important index, as in other studies (34). The current study provided evidence for the value of self-managed weight loss by using an online weight management app in the overweight and obese population.

A clinical study published by Carter et al. found that the participant's compliance with weight monitoring by smartphone was significantly improved compared with paper diary and website monitoring (35). In Thomas's study, participants with a BMI of 27-40 kg/m^2 weighed using a commercial online smart scale and received active weight loss therapy simultaneously. This study showed that higher weight monitoring frequency was associated with better weight loss, which was consistent with numerous studies (13, 33). Bennett and colleagues found that the weight loss of participants with more frequent self-weighing was significantly higher than others in the 12-month digital obesity treatment (36). The sustainability of long-term self-monitoring was a strong predictor of weight loss success through lifestyle interventions (37), which was confirmed by our study that the high-frequency monitoring group had greater weight loss, fat loss, and muscle gain in the overweight and obese population classified by BMI. For successful weight loss and fat loss, high-frequency measurement was the most significant promoting factor in our study, while some other related factors were not included, like lifestyle changes. However, younger age was the most significant factor for effective muscle gain when other factors were corrected, it meant younger people gained muscle more easily than older people. Interestingly, we found that younger age was the most contributing factor for effective fat loss in the population with normal BMI obesity, and moderate self-management by using a smart body fat scale could contribute to successful fat loss and muscle gain in the young people, which might be related to higher metabolic rates in young people (38). This interesting finding from our study suggests that early weight-related intervention at a younger age may lead to more successful fat loss in normal BMI obese people.

Our study revealed the beneficial role of self-monitoring of weight and body composition by a smart body fat scale in self-managed weight loss and amelioration of body composition in Chinese overweight and obese people during the COVID-19

pandemic. Moreover, we indicated promoting the usage of smart body fat scales could contribute to weight and fat loss in the overweight and obese population with high BMI, thus promoting remote weight self-monitoring by smart body fat scales in clinical practice might help the progression of weight loss in obese patients. However, there were also some limitations in our study, one of which was that participants' conditions were not taken into account, such as diabetes and thyroid-related disease, which might affect body composition. Moreover, other contributing factors of weight loss, such as dietary intake or physical activity were not included during the follow-up periods, and some accidental conditions might affect the accuracy of body fat measurements by BIA in our real-world study, such as the hydration status. A large randomized intervention trial could be performed to reinforce the results of this study. Nevertheless, this study analyzed a sizable population from the majority of Chinese urban cities, which implied the potential advantages of health economics through self-monitored weight loss by smart body fat scales.

In conclusion, during the COVID-19 pandemic, participation in self-monitored weight loss increased markedly compared with pre-pandemic, and women accounted for the majority. We found that many overweight and obese participants achieved weight loss goals by smart body fat scales, and the effectiveness of weight and fat loss was greater in obese participants than in overweight participants, both based on BMI and PBF classification. In addition, promoting the usage of smart body fat scales could contribute to more effective weight and fat loss in the overweight and obese population by BMI classification. However, in the population with normal BMI obesity, young subjects might be easier to successfully lose fat compared with the elder. Digital self-management by smart body fat scales could become a promising approach for the obese population with high BMI to lose weight and keep healthy.

Data availability statement

The datasets presented in this article are not readily available because restrictions apply to the availability of these data. Data were obtained from the Qingniu Health app and are available from the authors with the permission of the Qingniu Health app. Requests to access the datasets should be directed to Weixia Jian, jianweixia@xinhuamed.com.cn.

Ethics statement

The studies involving human participants were reviewed and approved by Xinhua Hospitals' Ethics Committee. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

XH, ML, YS, HY, ZL, WK, BL, JS, WZ and WJ implemented the study. XH, ML, and WJ wrote the manuscript. YS, HY and ZL analyzed the data. All authors participated in the design of the studies, analysis of the data and review of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2022.996814/full#supplementary-material

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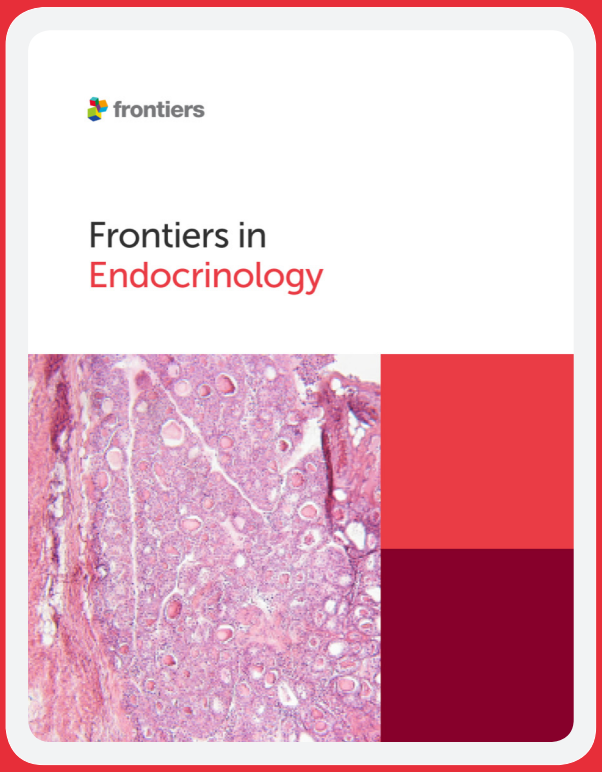

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