

# Obesity and COVID-19 Pandemics: Epidemiology, Mechanisms, and Management

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**Abstract:** Obesity is a principle causative factor of various metabolic dysfunctions, chronic inflammation, and multi-organ impairment. The global epidemic of obesity has constituted the greatest threat to global health. Emerging evidence has associated obesity with an increased risk of severe infection and poor outcomes from coronavirus disease 2019 (COVID-19). During current COVID-19 pandemic, the interaction between COVID-19 and obesity has exaggerated the disease burden of obesity more than ever before. Thus, there is an urgent need for consideration of universal measures to reduce the risk of complications and severe illness from severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in obesity population. In this review, we first summarized the clinical evidence on the effect of obesity on susceptibility, severity, and prognosis of COVID-19. Then we discussed the underlying mechanisms, including respiratory pathophysiology of obesity, dysregulated inflammation, upregulated angiotensin-converting enzyme 2 (ACE2) expression, hyperglycemia, and adipokines. Finally, we proposed recommendations on how to reduce the spread and pandemic of SARS-CoV-2 infection by prevention and treatment of obesity.

**Keywords:** obesity, COVID-19, metabolic syndrome, severe acute respiratory syndrome coronavirus 2, angiotensin-converting enzyme 2, inflammation

## Background

Since the emergence of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in December 2019, it has caused a global health crisis and affected more than 200 countries. Approximately 772 million cases of coronavirus disease- 2019 (COVID-19) and six million deaths have been reported globally as of November 2023.<sup>1</sup> Acute SARS-CoV-2 infection can range from asymptomatic to fatal disease, and the symptoms vary (fever, myalgia, headache, respiratory symptoms, loss of taste and smell, cardiovascular complications and gastrointestinal symptoms) and may persist for more than 4 weeks after initial diagnosis.<sup>2</sup>

Overwhelming studies have investigated the risk factors of for severe outcomes after SARS-CoV-2 infection, and obesity has been found as one of the most common underlying medical conditions associated with disease severity and mortality after adjusting for age and other potential confounders.<sup>3-5</sup> In addition to the direct risk, obesity causes metabolic syndrome and increases the risk of developing diabetes, hypertension, and cardiovascular disease. These underlying diseases are also related to an increased risk of severe COVID-19.<sup>6-8</sup> Furthermore, higher susceptibility to SARS-CoV-2 infection and serious long-term consequences, increased complications, and possible reduction in vaccine efficacy adds to the risk of acquiring SARS-CoV-2 infection in individuals with obesity.

Most of the existing studies discuss the impact of obesity on COVID-19 from a single perspective. The exact mechanism between obesity and the risk of COVID-19 infection is still unclear. Further studies are needed to understand the relationship and develop and customize intervention and prevention strategies suitable for person with obesity. In this review, we aim to summarize the evidence implicating the higher risk of severity COVID-19 in person with obesity, and discuss the mechanisms of how obesity might predispose patients to develop severe COVID-19. Additionally, we provided practical measures for governments, health care systems, and the public to reduce the transmission and

pandemic of SARS-CoV-2 infection by prevention and treatment of obesity. This is important for understanding the etiology of the COVID-19 pandemic, developing intervention strategies, and raising public awareness and health management. To some extent, it can protect the health of patients and reduce the risk of the spread of the epidemic and the deterioration of the disease.

## Epidemiology

Although vaccines against SARS-CoV-2 have proved highly effective at preventing COVID-19-associated hospitalization and death, some vaccinated individuals still develop severe outcomes. The rate of severe outcome including acute respiratory failure need hospitalization, need for noninvasive ventilation (NIV) or invasive ventilation, admission to ICU, or death were 18.0 per 10,000 in persons who completed primary vaccination.<sup>3</sup> With the rise of new variants of SARS-CoV-2 like Omicron,<sup>9</sup> the COVID-19 pandemic continues to threaten public health and the stability of medical systems worldwide. Identifying at risk population and understanding the underlying mechanisms will be important to reduce poor outcomes related to COVID-19. In addition to older age, risk factors for severe COVID-19 outcomes were male agender and underlying conditions such as obesity, diabetes, immunosuppression, chronic renal disease, organ transplantation.<sup>3,4</sup> Notably, up to 50% of death related to COVID-19 were found in people who had metabolic and vascular disorders.<sup>5</sup> There has been overwhelming evidence suggested obesity is associates with increased incidence, complications, severity and mortality of COVID-19.<sup>10</sup>

Before the pandemic of SARS-CoV-2, the prevalence of obesity increased dramatically. Obesity is defined as a BMI  $\geq 30$  kg/m<sup>2</sup>, and overweight as a BMI  $\geq 25$  kg/m<sup>2</sup> for adults.<sup>11</sup> The incidence of obesity has been nearly tripled worldwide since 1975.<sup>11</sup> According to WHO, more than 650 million adults were person with obesity, making up of 13% of the whole population aged 18 years and older, along with 1.9 billion adults over-weight in 2016. Obesity may exert physical, metabolic and molecular effects on multiple organ systems, and is a major risk factor for multiple comorbidities in critically ill patients.<sup>12</sup>

## Susceptibility

Epidemiological studies have found that people with obesity are more susceptible to SARS-CoV-2 infection. In a cross-sectional study, BMI was associated with a positive test of SARS-CoV-2 independent of ethnicity, deprivation, population density, and smoking.<sup>13</sup> A meta-analysis of 20 studies showed the risk of testing positive for COVID-19 in individuals with obesity were 46% higher than non-obese individuals (OR: 1.46; 95% CI: 1.30–1.65).<sup>14</sup> The increase in odds of SARS-CoV-2 positivity related to person with obesity reported in two other meta-analyses was even higher, up to 78%.<sup>15</sup> Even in persons have been fully vaccinated, higher rate of breakthrough infection were also found in person with obesity.<sup>16</sup>

## Severity

For persons infected with SARS-CoV-2, obesity is also one of the most important risk factors predicting severe COVID-19. A large nationwide study from England, the OpenSAFELY study, included more than 17 million adults had COVID-19 showed obesity and diabetes mellitus were independently associated with increased COVID-19 related mortality.<sup>17</sup> A body mass index (BMI) of over 40 kg/m<sup>2</sup> was associated with nearly twice as much mortality related to COVID-19 when compared with those without obesity. In Qresearch database from England, BMI  $\geq 23$ kg/m<sup>2</sup> was related to a linear increase in the risk of hospitalization and death from COVID-19.<sup>10</sup> Moreover, there have been several meta-analyses reported the association between obesity and adverse outcomes of COVID-19. With various outcomes and prevalence of obesity in these studies, the results constantly supported BMI as a risk factor for poor outcomes in COVID-19. Higher BMI was associated with 2–4 times higher risk for hospitalization, 21–88% higher risk for ICU admission or 66–113% higher risk for invasive mechanical ventilation support.<sup>18–23</sup> The risk related to obesity differs in old and young population. The higher risk due to obesity was particularly notable in younger adults.<sup>10</sup> In consistent, a nationwide study in two representative British birth cohorts found that an earlier age of first obesity was associated with 2–3 times higher risk of long COVID-19 and also hospitalization.<sup>24</sup>

In addition, certain socioeconomic variables may increase the risk of obesity, thereby increasing the severity and transmission risk of COVID-19. Studies had found that people living in areas with low socioeconomic indices had high rates of overweight or obesity, and that existing negative sociodemographic factors (unemployment, income insecurity, and education) seemed to have a cumulative effect.<sup>25</sup> They may face more economic pressures and restrictions and

choose cheap and unhealthy foods,<sup>26,27</sup> leading to unhealthy dietary choices and lifestyles. The impact was particularly severe for both disproportionately affecting marginalized/disadvantaged populations. Faced with greater barriers to health care services and relatively insufficient medical resources, problems such as obesity cannot be diagnosed and treated in time, which may increase the risk of COVID-19 and poor prognosis.<sup>28</sup>

## Complications

The effect of obesity on the outcome of COVID-19 may be partially attributed to increased complications. Adipose tissue led to increased baseline pleural pressure from the abdominal and chest wall, susceptibility to atelectasis, and collapse of the upper airway, as seen in obstructive sleep apnea. Severe obesity also increases the work load of breathing and hypoventilation may cause hypercapnia.<sup>12</sup> Acute respiratory distress syndrome (ARDS), a significant cause of death from COVID-19, develops as a result of excess inflammation after SARS-CoV-2 infection, while inflammatory process has been recognized as a common characteristic of obesity.<sup>29,30</sup> Person with obesity with COVID-19 also have predisposition to cardiovascular complications such as hypertension, cardiomyopathy, dysrhythmias, and stroke, due to an increase in total blood volume and cardiac output,<sup>31</sup> hypoxia and inflammatory stress,<sup>32</sup> and hypercoagulability.<sup>33</sup> A study by Onder et al indicated that obesity was associated with the increased probability of acute renal failure in COVID-19 patients,<sup>34</sup> while the later contributed significantly to the higher mortality.<sup>35</sup> It is also reported that short-term risk of post-COVID-19 venous thromboembolism in person with obesity was about twice of the risk in the counterpart.<sup>36</sup>

## Vaccine Efficacy

As a major risk for poor outcomes in COVID-19, the efficacy of vaccines against SARS-CoV-2 in person with obesity has been of concern. By now, solid evidence suggesting the effect of obesity on SARS-CoV-2 breakthrough the infection or waning of immune memory from vaccines is lacking. A preliminary retrospective study of subject with obesity found that grade III obesity was more common in patients with COVID-19 vaccine breakthrough than those without.<sup>37</sup> These findings were in line with the study by Juthani et al which showed the overweight was one of the pre-existing comorbidities in patients with severe break-through infection.<sup>16</sup> A cohort study showed that higher waist circumference but not BMI was associated with lower SARS-CoV-2 antibody titers after two COVID-19 mRNA vaccine (Pfizer/BioNTech),<sup>38</sup> while another study found higher anti-Spike protein IgG concentrations in obesity people.<sup>39</sup> However, the RCT studies which evaluated efficacy of Pfizer-BioNTech and Moderna COVID-19 vaccines showed comparable efficacy between obese and non-obese subgroup within 2 months after vaccination.<sup>40,41</sup> Additional studies evaluating long-term maintenance of vaccine induced immunity in person with obesity are warranted.

## Viral Load

Studies have shown that COVID-19 patients with obesity also had higher SARS-CoV-2 viral loads in the upper respiratory tract (log10 1.89 genome equivalents for the N1 gene and log10 2.62 for the N2 gene),<sup>39,42</sup> implying uncontrolled virus replication in the upper respiratory tract and/or an inefficient immune response in person with obesity. Notably, patients with high viral load tended to have a higher risk of death and incubation.<sup>42</sup>

## Genetic

Albeit overwhelming epidemiological evidence on associations between obesity and susceptibility, there is confounding that additional evidence of causal effect of BMI on susceptibility or severe outcome of COVID-19 is still limited. Freuer et al conducted a multivariable two-sample Mendelian randomization (MR) study which used summary statistics of genome-wide association studies to analyze the causal impact of overall obesity on the susceptibility and severity of COVID-19 disease. The result showed BMI was strongly associated susceptibility after adjustment for genetically predicted visceral obesity traits.<sup>43</sup>

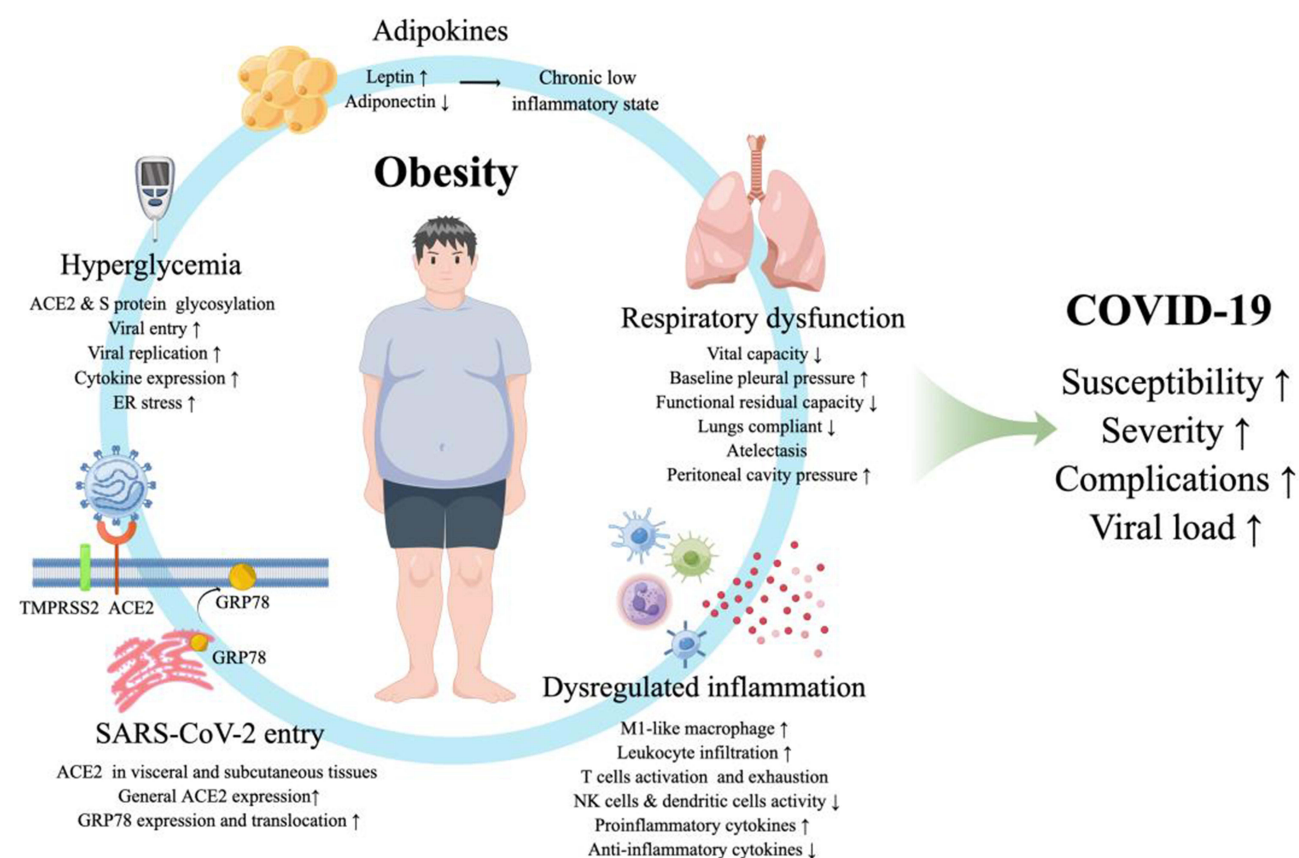
## Mechanisms Linking Obesity to COVID-19

Obesity is a heterogeneous disease, and the effect of obesity on patients with COVID-19 may vary substantially (Figure 1). Some of the physical, metabolic, and molecular effects may only occur in patients with severe obesity (BMI  $\geq 40$ –50 kg/m<sup>2</sup>), others may depend on the adipose distribution or lean muscle mass to BMI.<sup>12</sup>

### Respiratory Pathophysiology of Obesity

Excessive subcutaneous adipose tissue around the chest and abdomen restricts lung expansion and result in decreased vital capacity. Shallow breathing in obesity facilitates respiratory tract infections. In addition, increased baseline pleural pressure leads to reduced expiratory reserve volume and functional residual capacity, which increases the risk of collapse of peripheral dependent airways and atelectasis. In this condition, tidal breathing initiates from low end-expiratory, where the lung are less compliant.<sup>44</sup> Basilar atelectasis may cause ventilation/perfusion mismatch and resultant hypoxemia. In addition to subcutaneous adipose, visceral fat depots cause high peritoneal cavity pressure and restrict diaphragm movement and limit lung activity. Visceral fat depots have been reported as the risk factor for severe COVID-19 and a predictor for ICU admission.<sup>45,46</sup>

In addition, excess parapharyngeal adipose is associated with higher airway resistance and causes the upper airway obstruction or collapse, as reported in obstructive sleep apnea.<sup>47</sup> Severe obesity increases respiratory load, resulting in higher oxygen consumption dedicated to respiratory work at baseline,<sup>48</sup> and also substantially increases neural respiratory drive to 2–3 times that of non-obese subjects, especially at spine position.<sup>49</sup> In patients with Obesity hypoventilation syndrome, when the increased neural drive cannot be maintained, hypercapnia occurs due to hypoventilation. These patients prone to have acute- on -chronic respiratory failure and require non-invasive ventilation in COVID-19.<sup>50</sup>



**Figure 1** Mechanisms linking obesity to COVID-19. The mechanisms linking obesity to COVID-19 is elaborated from several aspects such as respiratory dysfunction, dysregulated inflammation, SARS-CoV-2 entry, hyperglycemia and adipokines, which may lead to increased viral load, increased susceptibility, increased complications, and deterioration of disease severity.

## Dysregulated Inflammation

There has been substantial evidence suggesting a low grade chronic inflammatory state in obesity. It is characterized by the higher concentration of pro-inflammatory cytokines such as TNF- $\alpha$ , IL-1 $\beta$ , MCP-1 and IL-6, and reduced anti-inflammatory cytokines, such as IL-10, IL-4 and IL-13.<sup>51</sup> Previous studies have attributed obesity-related inflammation to activated macrophages in adipose tissue.<sup>52</sup> The number of macrophages in adipose tissue in obesity people is increased. Meanwhile, macrophages in adipose tissue are activated and polarized into M1-like macrophages, which secrete proinflammatory cytokines, rather than M2-like macrophages producing anti-inflammatory cytokines. In addition, the inflammation in the adipose tissue induces adipocyte apoptosis and the production of chemotactic mediators, which promote leukocyte infiltration and subsequent accumulation of CD8+ T cells and CD4+ Th1 cells. The leukocytes and T cells, in turn, induce M1 and adipocytes to produce pro-inflammatory, which causing a vicious cycle of inflammation.<sup>53</sup> Similar to obesity, SARS-CoV-2 infection also induces an excess production of pro-inflammatory cytokines, which is a quick and robust immune response that is closely associated with severe infection and leads to multiorgan failure.<sup>54</sup> Obesity-related chronic low-grade inflammation potentiates dysregulated cytokine response in SARS-CoV-2 infection, and contributes to more severe COVID-19 and mortality.

Obesity has been also associated with increased number but reduced activity in NK cells,<sup>55</sup> dendritic cells,<sup>56</sup> increased T cell exhaustion and reduced T cell proliferation,<sup>57</sup> and defects in antibody production and class-switch recombination in B cells.<sup>58</sup> Overall, chronic inflammation and impaired innate and adaptive immunity in obesity increases the risk of severe COVID-19.

## SARS-CoV-2 Entry

SARS-CoV-2 uses the ACE2 receptor to enter the host cells and transmembrane protease serine 2 (TMPRSS2) for cleaving the spike protein of the virus to facilitate the fusion of virus and host cell membranes. Spike (S) protein priming. Mice with diet-induced obesity showed increased expression of the ACE2 gene in the lungs.<sup>59</sup> In addition, ACE2 expressed in adipose tissue can also serve as a target of SARS-CoV-2 virus, and gene expression profile have shown that ACE gene expression is higher in the visceral and subcutaneous tissues than lung tissue,<sup>60</sup> suggesting excess adipose tissue in obesity subjects may serve as a reservoir for the virus. Consistently, in COVID-19 patients, high serum ACE2 level was associated with obesity.<sup>61</sup> Studies have found that ACE2 expression can be upregulated by a wide range of pro-inflammatory cytokines,<sup>62,63</sup> which is increased in individuals with obesity as previously mentioned. Overall, these findings imply the elevated expression of ACE2 in person with obesity may play a role in facilitating SARS-CoV-2 entry, and thus result in severe COVID-19. In addition to ACE2, another receptor that provides viral entry for SARS-CoV-2 is glucose-regulated protein 78 (GRP78). GRP78 is overexpressed and translocated to the cell membrane or cell surface, when ER stress is induced in obesity and related insulin resistance, nutritional imbalance and excessive fat storage.<sup>64,65</sup> Thus increased cell surface GRP78 in patients with obesity may facilitate entry of SARS-CoV-2 into host cells.<sup>66</sup>

## Hyperglycemia

Hyperglycemia and type 2 diabetes are common metabolic dysregulation in obesity. Studies have shown that despite strict glycemic control, diabetic patients have a higher risk of developing ICU-acquired blood stream infection than non-diabetic patients.<sup>67</sup> Similarly, diabetes is independently associated with a higher risk of mild and moderate patients developing to severe type of COVID-19 and death.<sup>68,69</sup> Another study found that uncontrolled hyperglycemia had a particularly high mortality compared to diabetic patients, underscoring the importance of in-hospital glycemic management.<sup>70</sup> Possible molecular mechanisms of correlation between hyperglycemia and SARS-CoV-2 have been proposed. Given both the ACE2 receptor and the spike protein are heavily glycosylated, hyperglycemia might contribute to glycosylation of ACE2 and the viral spike protein, which increase the binding activity of ACE2 and SARS-CoV-2 in obesity and facilitate viral entry. The glycosylation of human ACE2 at the N322 site interacts with the receptor binding domain of the virus spike protein and strengthens the complex, while glycosylation at the N90 site have opposite effects.<sup>71</sup> The factors that determine the glycosylation site remain unclear. After viral entry into human cells, excess glucose may promote fast viral replication from the hexosamine biosynthetic pathway (HBP) hijacking substrates from the metabolic environment, which induces overexpression of interferon 5, leading to cytokine overexpression and endoplasmic reticulum (ER) stress.<sup>72</sup>



## Hypertriglyceridemia

Person with obesity tend to have high blood lipid content, especially triglyceride, which is one of the common biochemical indexes of these people. Most person with obesity have triglyceride levels well above normal values.<sup>73</sup> Obesity and hypertriglyceridemia are important risk factors for severe COVID-19 and mortality, which are negatively correlated with the prognosis.<sup>74,75</sup> Caricchio et al<sup>76</sup> found that triglycerides could well explain the relationship between obesity and the severity of COVID-19. Cytokine storm was the main cause of poor prognosis of person with obesity and the triglyceride contents were found to be twice as high in patients who experienced cytokine storms as in those who did not. There is a hypothesis that explains this phenomenon from the perspective of ACE2 and fat metabolism. After COVID-19, the virus enters and infects adipocytes by binding to the ACE2 of adipocytes through surface spike proteins. Adipocytes with high triglyceride levels rapidly promote virus reproduction and release, which further aggravates infections.<sup>77–79</sup> In addition, adipocytes can produce angiotensinogen, which promotes adipocytes to convert excess glucose into triglycerides. Then ACE2 converts angiotensin I / II into angiotensin 1–7, which reduces the production of triglycerides and inhibits the inflammatory response of macrophages.<sup>80–82</sup> After COVID-19, massive virus replication consumes ACE2, resulting in reduced inhibition of triglycerides and a large number of inflammatory reactions.

## Adipokines

Adipokines are cytokines produced by adipocytes to regulate and maintain energy metabolic homeostasis. Leptin and adiponectin are crucial adipokines reported to play a role in severe COVID-19.<sup>83,84</sup> Leptin is a pro-inflammatory adipokine highly produced in obesity, which contributes to obesity-related chronic low-grade inflammation.<sup>85</sup> Higher levels of serum leptin were associated with the risk for mechanical ventilation in COVID-19 patients.<sup>83</sup> In contrast, as an anti-inflammatory adipokine, adiponectin is decreased in obesity subjects.<sup>86</sup> Adiponectin reduces T cell response to pathogens, modulates macrophage phenotype to M2 type, and stimulates the production of anti-inflammatory IL-10 by macrophages.<sup>87</sup> Clinical study also found reduced antiprotection level in the circulation of COVID-19 patients.<sup>88</sup> Alterations in leptin and adiponectin levels in obesity may lead to a dysregulated immune response to SARS-CoV-2 infection.

## Clinical Implications

Growing evidence has identified obesity or ectopic fat deposition as independent risk factor for COVID-19 severity and death as indicated. Overlapping with the COVID-19 pandemic, the global pandemic of obesity and its comorbidities are great challenges for preventing morbidity and mortality from COVID-19 and other future pandemic viral infections. Moreover, extended self-quarantine, widespread shutdown duration, and adverse psychological reactions result from measures for reducing transmission of SARS-CoV-2 have led to unintended consequence of weight gain,<sup>89</sup> which in turn could increase the risk for poor prognosis of COVID-19.

## Management

Obesity is one of the most common modifiable risk factors for COVID-19, more efforts in improvements in lifestyle as well as additional measure to control obesity may benefit in reducing transmission and pandemic of SARS-CoV-2 infection.<sup>90</sup> Weight loss is a fundamental way to reduce the negative effects of obesity. Physical exercise, dietary changes and both surgical and non-surgical weight loss strategies are suggested as measures to reverse obesity and treat its associated co-morbidities.<sup>53</sup> Appropriate physical activities can be added according to their own physical conditions, such as light aerobic exercise, family exercises or stretching exercises, to promote physical recovery and improve cardiopulmonary function.<sup>91</sup> Evidence has showed benefit of intermittent fasting regimens in improve glucose homeostasis and insulin sensitivity.<sup>92</sup> Future clinical studies testing the role of dietary strategies, including IF, in improving antiviral immunity and reducing the severity of COVID-19 is needed. Obesity is associated with an increased risk of chronic diseases such as diabetes and hypertension. Continuous monitoring of blood pressure, blood glucose and blood lipid levels is needed.<sup>93,94</sup> Meanwhile, more investment in health care systems to work with physicians, professional dietitians, and other healthcare professionals to provide timely mental health support and facilitate access to interventions to determine the best management strategy for the individual.<sup>95,96</sup> Currently, the efficacy of anti-inflammatory drugs (eg

Tocilizumab, non-steroidal anti-inflammatory drugs, etc.) or combination therapy of anti-viral with anti-inflammatories is yet to be evaluated in person with obesity. No strong evidence suggested reduced efficacy of vaccination against SARS-CoV-2, thus vaccination is still the best choice for prevention and control of COVID-19 for person with obesity.

## Conclusions

The overlapping two pandemics of SARS-CoV-2 and obesity have resulted in a major global health crisis. In this review, we summarized the clinical evidence for the impact of obesity on susceptibility, severity, and prognosis COVID-19, and discussed and the underlying mechanisms. Success in reducing the obesity-related disease burden of COVID-19 will require not only individual lifestyles changes but also coordinated efforts and investments from governments, health care systems, and the public in obesity prevention and treatments. Further research should focus on a deeper understanding of how obesity and obesity-related metabolic dysregulation modulate the specific inflammatory pathways involved in SARS-CoV-2 infection and new drug targets that preferentially suppress detrimental inflammatory responses in person with obesity.

## Abbreviations

COVID-19, Coronavirus disease 2019; SARS-CoV-2, Severe acute respiratory syndrome coronavirus-2; ACE2, Angiotensin-converting enzyme 2; NIV, Noninvasive ventilation; BMI: Body mass index; ARDS, Acute respiratory distress syndrome; TNF- $\alpha$ , Tumor necrosis factor  $\alpha$ ; IL, Interleukin; MCP-1, Monocyte chemoattractant protein-1; NK cell, natural killer cell; TMPRSS2, transmembrane protease serine 2; GRP78, Glucose-regulated protein 78; HBP, Hexosamine biosynthetic pathway.

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## Disclosure

The authors declare that they have no competing interests.

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