Circulation

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# Obesity Is a Risk Factor for Severe COVID-19 Infection

## Multiple Potential Mechanisms

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The coronavirus disease 2019 (COVID-19) pandemic has led to worldwide research efforts to identify people at greatest risk of developing critical illness and dying. Initial data pointed toward older individuals being particularly vulnerable, as well as those with diabetes mellitus or cardiovascular (including hypertension), respiratory, or kidney disease. These problems are often concentrated in certain racial groups (eg, African Americans and Asians), which also appear to be more prone to worse COVID-19 outcomes.[1] Increasing numbers of reports have linked obesity to more severe COVID-19 illness and death.[1–3] In a French study, the risk for invasive mechanical ventilation in patients with COVID-19 infection admitted to the intensive treatment unit was more than 7-fold higher for those with body mass index (BMI) >35 compared with BMI <25 kg/m$^2$.[2] Among individuals with COVID-19 who were <60 years of age in New York City, those with a BMI between 30 to 34 kg/m$^2$ and >35 kg/m$^2$ were 1.8 times and 3.6 times more likely to be admitted to critical care, respectively, than individuals with a BMI <30 kg/m$^2$.[3]

We suggest obesity or excess ectopic fat deposition may be a unifying risk factor for severe COVID-19 infection, reducing protective cardiorespiratory reserve as well as potentiating the immune dysregulation that appears, at least in part, to mediate the progression to critical illness and organ failure in a proportion of patients with COVID-19 (Figure). Whether obesity is an independent risk factor for susceptibility to infection requires further research.

From a cardiovascular perspective, trial and genetic evidence conclusively show that obesity (and excess fat mass) are causally related to hypertension, diabetes mellitus, coronary heart disease, stroke, atrial fibrillation, renal disease, and heart failure. Obesity potentiates multiple cardiovascular risk factors, the premature development of cardiovascular disease, and adverse cardiorenal outcomes. There is also a metabolic concern. In individuals with diabetes mellitus, or at high risk of diabetes mellitus, obesity and excess ectopic fat lead to impairment of insulin resistance and reduced β-cell function. Both the latter limit ability to evoke an appropriate metabolic response on immunologic challenge, leading some patients with diabetes mellitus to require substantial amounts of insulin during severe infections. Overall, the integrated regulation of metabolism required for the complex cellular interactions, and for effective host defense, is lost, leading to functional immunologic deficit. COVID-19 may also directly disrupt pancreatic β-cell function through an interaction with angiotensin-converting enzyme 2. Furthermore, obesity enhances thrombosis, which is relevant given the association between severe COVID-19 and prothrombotic disseminated intravascular coagulation and high rates of venous thromboembolism.

Beyond cardiometabolic and thrombotic consequences, obesity has detrimental effects on lung function, diminishing forced expiratory volume and forced vital capacity (Figure). Higher relative fat mass is also linked to such adverse changes, perhaps relevant to emerging reports of greater critical illness from COVID-19 in



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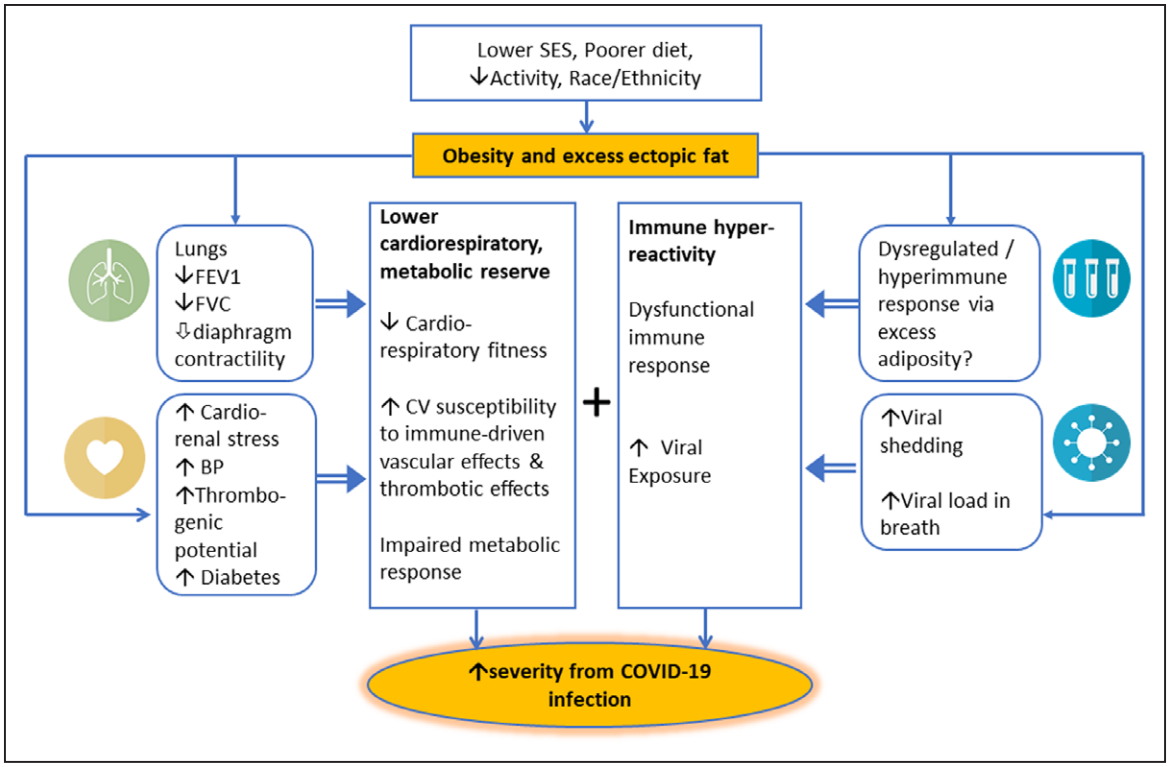


**Figure. Pathways potentially linking obesity or excess ectopic fat to more severe coronavirus disease 2019 (COVID-19) illness.**
There are multiple pathways by which obesity (or excess ectopic fat) may increase the effect of COVID-19 infection. These include underlying impairments in cardiovascular, respiratory, metabolic, and thrombotic pathways in relation to obesity, all of which reduce reserve and ability to cope with COVID-19 infection and the secondary immune reaction to it. At the same time, there are several reasons why obese individuals may have amplified or dysregulated immune response, linked both to greater viral exposure, as well as the possibility that excess adipose tissue potentiates the immune response. BP indicates blood pressure; COVID-19, coronavirus disease 2019; CV, cardiovascular; FEV1, forced expiratory volume; FVC, forced vital capacity; and SES, socioeconomic status.

certain ethnicities, eg, Asians.[1] Asians often display lower cardiorespiratory fitness and carry proportionally more fat tissue at lower BMIs. With extreme obesity (eg, BMI >40 kg/m$^2$), care for individuals admitted to intensive therapy units is often impeded as these patients are more difficult to image, ventilate, nurse, and rehabilitate.

With respect to the immune response, there is a clear association between obesity and basal inflammatory status characterized by higher circulating interleukin 6 and C-reactive protein levels. Adipose tissue in obesity is "proinflammatory," with increased expression of cytokines and particularly adipokines. There is also dysregulated tissue leukocyte expression, and inflammatory macrophage (and innate lymphoid) subsets replace tissue regulatory (M2) phenotypic cells. Obesity per se is an independent and causal risk factor for the development of immune-mediated disease, eg, psoriasis,[4] suggesting that such adipose state may have systemic immune consequence on additional environmental provocation. In terms of host defense, obesity impairs adaptive immune responses to influenza virus[5] and conceivably could do so in COVID-19. Obese individuals may exhibit greater viral shedding, suggesting potential for great viral exposure, especially if several family members are overweight. This may be aggravated in overcrowded multigenerational households, which are more common in the socioeconomically deprived communities in which obesity is prevalent. All these observations point toward a potential for obesity to give rise to a more adverse virus versus host immune response relationship in COVID-19. Poorer nutritional status and hyperglycemia may further aggravate the situation in some obese individuals.

Much of the focus of COVID-19 has been on older people. However, it is important to remember that weight and muscle mass start to decline at advanced age but relative fat mass increases, particularly in those with comorbid diseases such as cardiovascular and respiratory conditions. Older age is also associated with more hypertension and diabetes mellitus because of stiffer vessels and impaired metabolic efficiency, respectively. People who are older (eg, >70 years of age), similar to younger obese individuals, have less cardiorespiratory reserve to cope with COVID-19 infection. Immune senescence is well recognized, as is the concept of *inflammaging*, and both may influence virus–host dynamics in the elderly and infection outcomes.

What are the implications of these emerging observations for future research and public health messaging? With respect to research, predictive instruments for those most at risk of severe outcomes should consider

BMI. Mechanistic understanding of the relationship between obesity and COVID-19 may suggest therapeutic interventions (eg, proven weight loss drugs, low-calorie diets) to potentially reduce the risk of developing severe COVID-19 illness. With respect to public health, it is important to communicate risks without causing anxiety. People worldwide should be encouraged to improve their lifestyle to lessen risk both in the current and subsequent waves of COVID-19. In addition to increasing activity levels, there should be improved messaging on better diet, focusing on simpler advice to help people adopt sustainable changes. This is particularly challenging with current stay-at-home rules limiting activity levels—the lockdown cost of weight gain. Even more worrying is that the resultant economic downturn may worsen obesity, especially in the most vulnerable individuals, a risk that governments need to address after the current pandemic. Indeed, this pandemic has highlighted that more—not less—must be done to tackle and prevent obesity in societies for the prevention of chronic disease and greater adverse reactions to viral pandemics.

## ARTICLE INFORMATION

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