

Unraveling the Connection Between Obesity and Outcomes in COVID-19

David Atkins 

The pace of scientific discovery in the coronavirus disease 2019 (COVID-19) pandemic has been astounding. Along with the unprecedented pace of vaccine development, the spread of electronic health records has enabled researchers to document the natural history of COVID-19 infection, elucidate risks factors for severe outcomes, and document effects of changing management of COVID-19 in near real time. The path from data to insight, however, has not always been straightforward. It is often difficult to distinguish the pathway through which individual factors are associated with poor outcomes in COVID-19. Do they affect the risk of becoming infected by the virus or risk of ending up in the hospital? Are they causally related to the progression to severe disease or simply associated with other causal factors (i.e., confounders)? The role of race and ethnicity is a good example. The disproportionate toll of COVID-19 among Black and Hispanic populations during the March 2020 surge in the New York metropolitan area initially appeared to signal a possible underlying genetic component of risk or the effects of greater comorbidity. Later studies have suggested that the biggest drivers of disparate COVID-19 mortality rates were the social determinants such as housing conditions and inability to work from home that placed minority populations at higher risk of acquiring COVID-19 (1).

What patient factors raise the risk of severe outcomes from COVID-19 infection? Age is far and away the strongest risk factor for COVID-19-related mortality. The risk of death triples with each decade above age 30; compared with those 18 to 29 years old, the mortality risk is 87 times higher for someone 65 to 74 years old and 187 times higher for someone 75 to 84 years old (2). Other risk factors for COVID-19 mortality are much weaker, and these include chronic obstructive pulmonary disease, vascular disease, and chronic kidney disease.

The role of obesity in COVID-19 has been more complicated. Although most studies have indicated that risk of severe COVID-19 rises with increasing BMI, studies differ on the shape of the association and the effect of age. Two studies from the US Department of Veterans Affairs (VA) bring things into clearer focus thanks to the size of their samples and their focus on the interaction of obesity and age. The VA population is an especially useful one for examining the role of comorbidity in COVID-19. A longitudinal electronic health record allows VA researchers to construct a much more complete picture of comorbidity than hospital-based studies, VA has patients in all states and territories, and its population has a high prevalence of obesity and other comorbid chronic diseases. Finally, outcomes in different groups are not confounded by unequal access to health care.

In the study by Breland et al. of more than 9,000 patients diagnosed through May 2020, investigators found a J-shaped relationship

between BMI and severe COVID-19; BMI above 30 kg/m² was positively associated with increased risk of hospitalization or death, but the association was negative in the overweight range of BMI 23 to 30 (i.e., risk decreased as BMI increased from 23 to 30). Both effects were strongest for those under age 60 but they held up to age 75 (3). McKenna et al. expanded the analysis to examine more than 270,000 patients tested for COVID-19 in the VA through June 2021 (4). Patients with BMI of 35 or greater had a 30% higher likelihood of testing positive. Among the nearly 26,000 veterans with a positive result, having BMI greater than 35 was associated with a 77% higher risk of mechanical ventilation and a 42% increased risk of death relative to those of normal weight. The effects were strongest in those under age 65 and smaller or nonexistent in older veterans. Being underweight (BMI < 18.5) was also a risk factor for hospitalization and death.

Taken together, these findings support several conclusions. It is possible that obesity could increase the risk of acquiring COVID-19 since obesity may impair immune function; an increased risk of influenza has been documented in patients with obesity despite vaccination (5). But it is a modest risk factor at best (prevalence of positive tests was 11% for those with BMI 35 and above vs. 8% in those of normal weight) and it could just be an artifact of differences in test-seeking behavior.

For infected patients, age dominates all other risk factors for severe outcomes. This may partly explain why the risk of obesity is evident only in patients below age 65. Similarly, the J-shaped relationship observed between weight and COVID-19 mortality has been observed for all-cause mortality across numerous studies (6), reflecting the prevalence of smoking and underlying illnesses in patients at the lower end of the BMI scale. While these studies support the Centers for Disease Control and Prevention conclusions that obesity and severe obesity increase risk of severe outcomes in COVID-19, clinicians should remember that risk is a function of multiple factors and not a single risk factor. Another VA study found that scores on the Charlson Comorbidity Index, which reflects both number and severity of comorbidities, were much better at discriminating those at highest risk for COVID-19 mortality (7).

What are the lessons for researchers trying to understand risk in a fast-changing pandemic? First, researchers should continually test their early findings as new data accumulate. Mortality analyses early in the pandemic were clouded by high mortality rates due to overwhelmed hospitals and inexperienced staff. Researchers would be advised to exclude the first several months of the pandemic in examining risk factors and predictive models. Second, the dominant

| Department of Veterans Affairs, Office of Research and Development, Washington, DC, USA. Correspondence: David Atkins (david.atkins@va.gov)
See accompanying articles, pg. 828 and pg. 906.

Published 2021. This article is a U.S. Government work and is in the public domain in the USA.

Received: 8 February 2021; Accepted: 9 February 2021; Published online 1 April 2021. doi:10.1002/oby.23153

effect of age may obscure the role of other risk factors. Age should be included as a continuous variable, and interactions between age and other risk factors should be tested. Most importantly, analyses should consider how risk information will be used. Knowing that obesity increases risk may help get patients to take preventive measures against COVID-19 more seriously. But in considering who to vaccinate, a 40-year-old with BMI of 40 is still at much lower risk than a healthy 65-year-old. Finally, vaccination should also consider those social determinants that raise the risk of infection for patients and communities, even if those are not major independent risk factors for severe disease. **O**

Acknowledgments

The views expressed here represent those of the author alone and do not reflect official policy of the Department of Veterans Affairs or any other Federal agency.

Disclosure: DA declared no conflict of interest.

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