Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

New insights into the association between body-mass index and severe COVID-19


Shutterstock

Published Online
April 28, 2021
https://doi.org/10.1016/S2213-8587(21)00109-1

See Articles page 350

The emerging SARS-CoV-2 pandemic captured worldwide attention in the first months of 2020.[1] Most people who become infected have mild disease or are asymptomatic, but many have severe and often fatal disease. Older age quickly emerged as the most important risk factor for poor outcomes, but obesity was one of a number of other factors rapidly identified as being associated with COVID-19-associated mortality.[2]

In *The Lancet Diabetes & Endocrinology*, Min Gao, Carmen Piernas, and colleagues[3] present detailed research on the risk of severe COVID-19 outcomes in people with high BMI. This comprehensive study builds on earlier evidence by examining a range of outcomes across the full spectrum of BMI. Using the QResearch database of electronic primary care records in England, UK, linked to SARS-CoV-2 testing results, hospital admissions, and death registration data, Gao and colleagues identified over 6·9 million individuals with at least one BMI record aged 20 years and older who had available data on the QResearch system between Jan 24 and April 30, 2020, among whom 13 503 hospital admissions, 1601 intensive care unit (ICU) admissions, and 5479 deaths due to COVID-19 occurred within the study period (data cutoff April 30, 2020). J-shaped associations were observed between BMI and COVID-19 hospital admissions and deaths; for hospital admissions, risk began to increase linearly above a BMI of 23 kg/m², whereas the increase in risk of death began to increase linearly at a slightly higher BMI of 28 kg/m², in keeping with the association between BMI and a wide range of cause-specific mortality outcomes.[4] A strong age interaction was observed, with unit increase in BMI being associated with large increases in risk for the youngest age group (20–39 years), and no association in the oldest age group (≥80 years).

The authors also identified an increased risk of admission to hospital and death due to COVID-19 at the lowest BMI levels, which is a new insight not addressed by early COVID-19 research that focussed on obesity. A limitation of the analysis presented by Gao and colleagues is that interactions were only assessed in those with a BMI of 23 kg/m² or higher, so that the association between underweight and risk in older age groups (in whom low BMI is common) could not be discerned. Interestingly, by contrast with other outcomes, BMI was approximately linearly associated with ICU admission throughout the BMI range, with no increase in risk at low BMIs. This observation is not straightforward to interpret. An ICU admission reflects not only severe disease, but also the complex clinical decision making process around whether a patient is likely to tolerate and benefit from intensive treatment.[5] The reduced risk of ICU admission in underweight individuals is likely to reflect the most at-risk underweight patients being deemed unsuitable for intensive care.

Another important limitation of the study is that over one million individuals had no BMI record available, and were excluded from the main analyses. The availability of many millions of routinely collected BMI records is a strength of UK primary care data sources, but missing data are a common problem, especially because BMI might be more likely to be recorded if outside the healthy weight range, violating the so-called missing at random assumption needed for popular multiple imputation approaches.[6] Gao and colleagues should be commended for providing descriptive data on these individuals, among whom a higher proportion were young (aged 20–39 years) and male than in the population with BMI measurements. Restriction of analyses to those with complete data can be a reasonable approach even if they are not fully representative of the broader patient population, provided the association between BMI and outcomes is correctly represented by those included.[7] A further important limitation is that investigating severe COVID-19 outcomes in a general population-based cohort does not allow one to disentangle whether BMI is associated with risk of infection, progression to severe disease once infected, or both. Mechanistic hypotheses to date have suggested that an imbalance in pro-inflammatory and anti-inflammatory cytokines at higher BMI might promote more severe COVID-19 disease than in those with a lower BMI.[8] However, any epidemiological study using available large-scale data is unlikely to be able to reliably isolate the association

between BMI and outcomes in infected individuals because this would require large-scale representative testing data to identify both asymptomatic and symptomatic infection. In reality, COVID-19 testing in the UK and most other settings has been systematically targeted towards those with symptoms, making a positive test an insensitive and selective marker of infection, and those testing positive a biased sample in which to examine severe disease outcomes. For similar reasons, Gao and colleagues rightly avoided a focus on outcomes among patients already in hospital.[9]

People with a BMI of more than 40 kg/m² were recognised early on in public health guidance as being at increased risk of severe COVID-19 outcomes, and BMI is now being used in risk prediction tools that are informing vaccine prioritisation,[10] highlighting the importance of obtaining a detailed understanding of the association between BMI and COVID-19 outcomes to inform policy. Key future research priorities will be to establish whether BMI affects vaccine efficacy, and to understand whether people outside the BMI range considered to be healthy (18·5–24·9 kg/m²) are at increased risk of post-COVID-19 sequelae. Further careful epidemiological study of these and other emerging questions will inform the ongoing public health response to this new disease that is likely here to stay.

I declare no competing interests

Krishnan Bhaskaran
krishnan.bhaskaran@lshtm.ac.uk

Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, London WC1E 7HT, UK

1 WHO. WHO Director-General's opening remarks at the media briefing on COVID-19 — 11 March 2020. World Health Organization, March 11, 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020 (accessed April 2, 2021).
2 Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020; **584:** 430–36.
3 Gao M, Piernas C, Astbury N, et al. Associations between body-mass index and COVID-19 severity in 6·9 million people in England: a prospective, community-based cohort study. *Lancet Diabetes Endocrinol* 2021; published online April 28. https://doi.org/S2213-8587(21)00089-9.
4 Bhaskaran K, Dos-Santos-Silva I, Leon DA, Douglas IJ, Smeeth L. Association of BMI with overall and cause-specific mortality: a population-based cohort study of 3·6 million adults in the UK. *Lancet Diabetes Endocrinol* 2018; **6:** 944–53.
5 Griffiths F, Svantesson M, Bassford C, et al. Decision-making around admission to intensive care in the UK pre-COVID-19: a multicentre ethnographic study. *Anaesthesia* 2021; **76:** 489–99.
6 Bhaskaran K, Smeeth L. What is the difference between missing completely at random and missing at random? *Int J Epidemiol* 2014; **43:** 1336–39.
7 White IR, Carlin JB. Bias and efficiency of multiple imputation compared with complete-case analysis for missing covariate values. *Stat Med* 2010; **29:** 2920–31.
8 Post A, Bakker SJL, Dullaart RPF. Obesity, adipokines and COVID-19. *Eur J Clin Invest* 2020; **50:** e13313.
9 Griffith GJ, Morris TT, Tudball MJ, et al. Collider bias undermines our understanding of COVID-19 disease risk and severity. *Nat Commun* 2020; **11:** 5749.
10 Clift AK, Coupland CAC, Keogh RH, et al. Living risk prediction algorithm (QCOVID) for risk of hospital admission and mortality from coronavirus 19 in adults: national derivation and validation cohort study. *BMJ* 2020; **371:** m3731.

The knowns and unknowns of teprotumumab for thyroid eye disease

Published **Online** April 15, 2021 https://doi.org/10.1016/S2213-8587(21)00076-0

See **Articles** page 360

The clinical symptoms of thyroid eye disease (also termed Graves' orbitopathy) are the consequence of autoimmune-mediated inflammation in the eye muscles, periorbital connective tissue, and lacrimal gland. The treatment of moderate-to-severe thyroid eye disease remains a challenge and is focused mainly on: (1) achievement of stable euthyroidism and reducing other risk factors for progression (eg, smoking); (2) immunosuppression in the active phase; and (3) rehabilitative treatments (such as orbital decompression surgery, squint surgery, or eyelid surgery), which are mostly reserved for the inactive phase of the disease.[1] Immunosuppressive agents that have shown benefit in randomised trials of thyroid eye disease include high-dose intravenous glucocorticoid pulsed therapy, mycophenolate, tocilizumab, rituximab, and retrobulbar irradiation. Nearly three decades ago, it was recognised that orbital fibroblasts from patients with thyroid eye disease expressed receptors for insulin-like growth factor 1.[2] Progress in understanding the roles of thyroid-stimulating hormone receptors and insulin-like growth factor 1 receptors in the pathogenesis of thyroid eye disease has since led to a new targeted therapy, teprotumumab, which is an insulin-like growth factor 1 receptor-blocking human monoclonal antibody. On the basis of results from two placebo-controlled randomised trials,[3,4] teprotumumab became the first medical therapy approved by the US Food and Drug Administration (FDA) on Jan 1, 2020, for treating thyroid eye disease. However, thyroid eye disease is a heterogeneous condition that

For more on the **teprotumumab FDA approval** see https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-thyroid-eye-disease#:~:text=Today%2C%20the%20U.S.%20Food%20and,and%20bulge%20outwards%20(proptosis)