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.

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Obesity could shift severe COVID-19 disease to younger ages

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 was first reported in China in late December, 2019, and has since evolved into a global pandemic. As of April 29, 2020, COVID-19 has been confirmed in more than 3 million individuals in 185 countries and regions, with an overall mortality rate of more than 6%.[1] Severe disease involves bilateral interstitial pneumonia requiring intensive care unit (ICU) ventilatory support and can evolve into adult respiratory distress syndrome with high mortality. The largest study of 1591 ICU patients from Italy reported a median age of 63 years, with only 203 patients (13%) younger than 51 years.[2] Common comorbidities are hypertension, cardiovascular disease, type 2 diabetes, and, more rarely (42 [4%] of 1043), obstructive pulmonary disease. Similar data have been reported from China.[3]

When the COVID-19 epidemic began in the USA, we anticipated a similar ICU population. News reports and communications from the US Federal Government had emphasised that COVID-19 was a particular problem for older people, and a resistance to social distancing and sheltering in place by younger people might have been informed by this idea. However, as the pandemic hit the Johns Hopkins Hospital in late March, 2020, younger patients began to be admitted to our ICU, many of whom were also obese. An informal survey of colleagues directing ICUs at other hospitals around the country yielded similar findings. At this time, news editorials were noting obesity as an underappreciated risk factor for COVID-19.[4] This risk is particularly relevant in the USA because the prevalence of obesity is around 40%, versus a prevalence of 6·2% in China, 20% in Italy, and 24% in Spain.[5]

With use of least squares univariate and multivariate linear regression, we examined the correlation between body-mass index (BMI) and age in patients with COVID-19 admitted to ICU at university hospitals at Johns Hopkins, University of Cincinnati, New York University, University of Washington, Florida Health, and University of Pennsylvania (appendix). Acquisition of the de-identified data for this analysis was approved by the Johns Hopkins University Institutional Review Board.

In our dataset of 265 patients (58% male patients), we found a significant inverse correlation between age and BMI, in which younger individuals admitted to hospital were more likely to be obese (figure). There was no difference by sex (p=0·9). The median BMI was 29·3 kg/m², with only 25% of individuals having a BMI of less than 26 kg/m², and 25% exceeding a BMI of 34·7 kg/m².

Obesity can restrict ventilation by impeding diaphragm excursion, impairs immune responses to viral infection,[6] is pro-inflammatory, and induces diabetes and oxidant stress to adversely affect cardiovascular function.[7] We conclude that in populations with a high prevalence of obesity, COVID-19 will affect younger populations more than previously reported. Public messaging to younger adults, reducing the threshold for virus testing in obese individuals, and maintaining greater vigilance for this at-risk population should reduce the prevalence of severe COVID-19 disease.

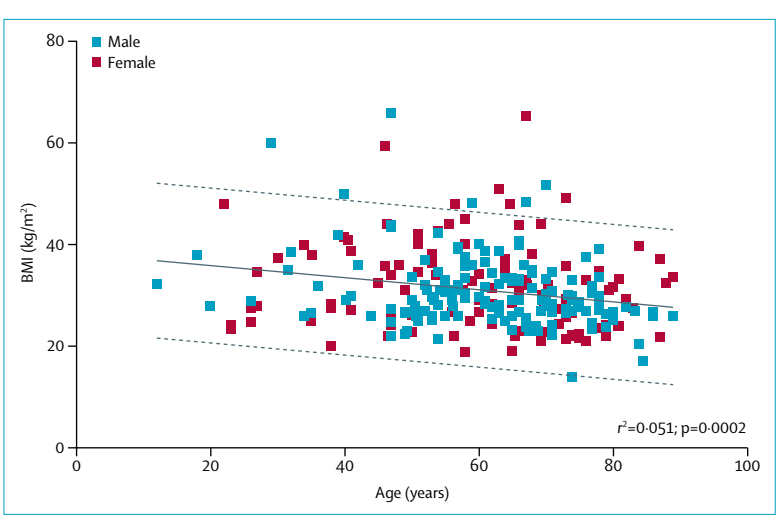

Figure: **Negative correlation between BMI and age in 265 patients with coronavirus disease 2019 in intensive care units in the USA**
BMI=body-mass index. The solid line is the least squares linear regression model fit. Dashed lines are 95% prediction bands.

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Considering BCG vaccination to reduce the impact of COVID-19

In addition to its specific effect against tuberculosis, the BCG vaccine has beneficial non-specific (off-target) effects on the immune system that protect against a wide range of other infections and are used routinely to treat bladder cancer.[1,2] This has led to the suggestion that vaccination with BCG might have a role in protecting health-care workers and other vulnerable individuals against severe coronavirus disease 2019 (COVID-19).

Randomised controlled trials have provided evidence that the BCG vaccine's immunomodulatory properties can protect against respiratory infections. In Guinea-Bissau, a high-mortality setting, BCG-Danish reduced all-cause neonatal mortality by 38% (95% CI 17–54), mainly because there were fewer deaths from pneumonia and sepsis.[3] In South Africa, BCG-Danish reduced respiratory tract infections by 73% (95% CI 39–88) in adolescents.[4]

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a single-stranded positive-sense RNA virus, and the BCG vaccine has been shown to reduce the severity of infections by other viruses with that structure in controlled trials. For example, the BCG vaccine reduced yellow fever vaccine viraemia by 71% (95% CI 6–91) in volunteers in the Netherlands,[5] and it markedly reduced the severity of mengovirus (encephalomyocarditis virus) infection in two studies in mice.[6,7]

Many of the mechanisms underlying the beneficial off-target effects of the BCG vaccine are now understood. The BCG vaccine and some other live vaccines induce metabolic and epigenetic changes that enhance the innate immune response to subsequent infections, a process termed trained immunity.[8] The BCG vaccine might therefore reduce viraemia after SARS-COV-2 exposure, with consequent less severe COVID-19 and more rapid recovery.

Randomised controlled trials are underway in the Netherlands and Australia to assess whether BCG-Danish reduces the incidence and severity of COVID-19 in health-care workers, and the effect this has on time away from work (NCT04327206, NCT04328441). It is possible that BCG-Tokyo would be preferable to BCG-Danish.[9]

Until these trials are complete, there are four main reasons why it is very important to adhere to WHO's recommendation that the BCG vaccine is used for COVID-19 only in randomised controlled trials.[10] First, the BCG vaccine is already in short supply, and indiscriminate use could jeopardise the supply needed to protect children against tuberculosis in high-risk areas. Second, whether BCG will be effective remains unknown: findings from the ecological studies suggesting less COVID-19 in countries with routine BCG immunisation are weak evidence because they are based on population rather than individual data and are prone to confounding.[11] Also, it is unlikely that a BCG vaccine given decades ago in childhood will ameliorate COVID-19 now. One reason for this is that the beneficial off-target effects of the BCG vaccine might be altered by subsequent administration of a different vaccine.[1] Third, if the BCG vaccine is not effective against COVID-19, BCG vaccination could engender a false sense of security. Fourth, careful safety monitoring in randomised trials is needed to guard against the remote possibility that up-regulation of immunity by BCG will exacerbate COVID-19 in a minority of patients with severe disease.

If the BCG vaccine or another inducer of trained immunity provides non-specific protection to bridge the gap before a disease-specific vaccine is developed, this would be an important tool in the response to COVID-19 and future pandemics.

NC is the lead investigator of the BRACE trial (NCT04327206), and MGN is one of the lead investigators of the BCG-CORONA trial (NCT04328441). TAG is Director-General of WHO. AS declares no competing interests.

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