I hope your week is going well.

Today under COVID-19 News the first is the FDA EUA for the Pfizer vaccine for children ages 12-15. The second item is the WHO adding the B.1.617 as a variant of concern.

Under Journal Review, I begin with an interesting article on obesity and adverse outcomes after infection with SARS-CoV-2. This highlights the robust data capability in the UK. The next article is the peer review publication from the RECOVERY Trial on tocilizumab in Lancet. As you will see the results are similar to the medRxiv online version reviewed a few months back in the Daily Briefing. The last article is a very nice review on the Danish and Norwegian experience with the AstraZeneca vaccine. As with the J&J vaccine they conclude the possibility of hemostatic events associated with the vaccine.

Have a wonderful day

Ed

COVID-19 News

FDA Expands Pfizer-BioNTech COVID-19 Vaccine for Adolescents 12-15 Years Old
May 10, 2021
The US Food and Drug Administration (FDA) has expanded the Emergency Use Authorization (EUA) granted to Pfizer-BioNTech, allowing the companies' COVID-19 vaccine for administration in persons age 12-15 years old. Effectiveness data in patients aged 12-15 years old showed the vaccine provided a noninferior immune response among 190 participants of the age group, when compared to 170 participants aged 16-25 years old, 7 days following the second mRNA dose. In fact, the vaccinated 12-15 years old had higher geometric mean titer of SARS-CoV-2 neutralizing antibodies (1239.5 vs 705.1) compared to persons 16-25 years old. An analysis of cases among COVID-19-naïve, vaccinated participants aged 12-15 years old showed no cases of COVID-19 occurred among 1005 recipients, versus 16 cases among 978 placebo recipients. Available safety data supporting the new EUA showed the most reported adverse events among 1131 vaccinated adolescents included injection site pain, tiredness, headache, chills, muscle pain, fever, and joint pain, 1-3 days following administration. The CDC's ACIP will meet later today.

WHO Declares B.1.617 a "Variant of Concern"
On Monday, the WHO classified the variant first identified in India known as B.1.617 as a "variant of concern". On Tuesday, India reported almost 4000 more deaths in the last 24 hours, bringing the death toll to almost 250,000 with over 300,000 new cases daily. The variant appears to be more transmissible.

The B.1.617 variant was first detected in western India in October 2020. The B.1.617 variant has now been identified in more than 30 countries including the US. B.1.617 is the fourth strain to be classified as a variant of concern by the WHO.

The definition of a variant of concern is it must demonstrate through scientific research to be more contagious or to cause more severe disease. It may also reduce the effectiveness of therapeutics and vaccines. People who have previously had COVID-19 may become reinfected by the new strain. The CDC is tracking five variants of concern.

Journal Review

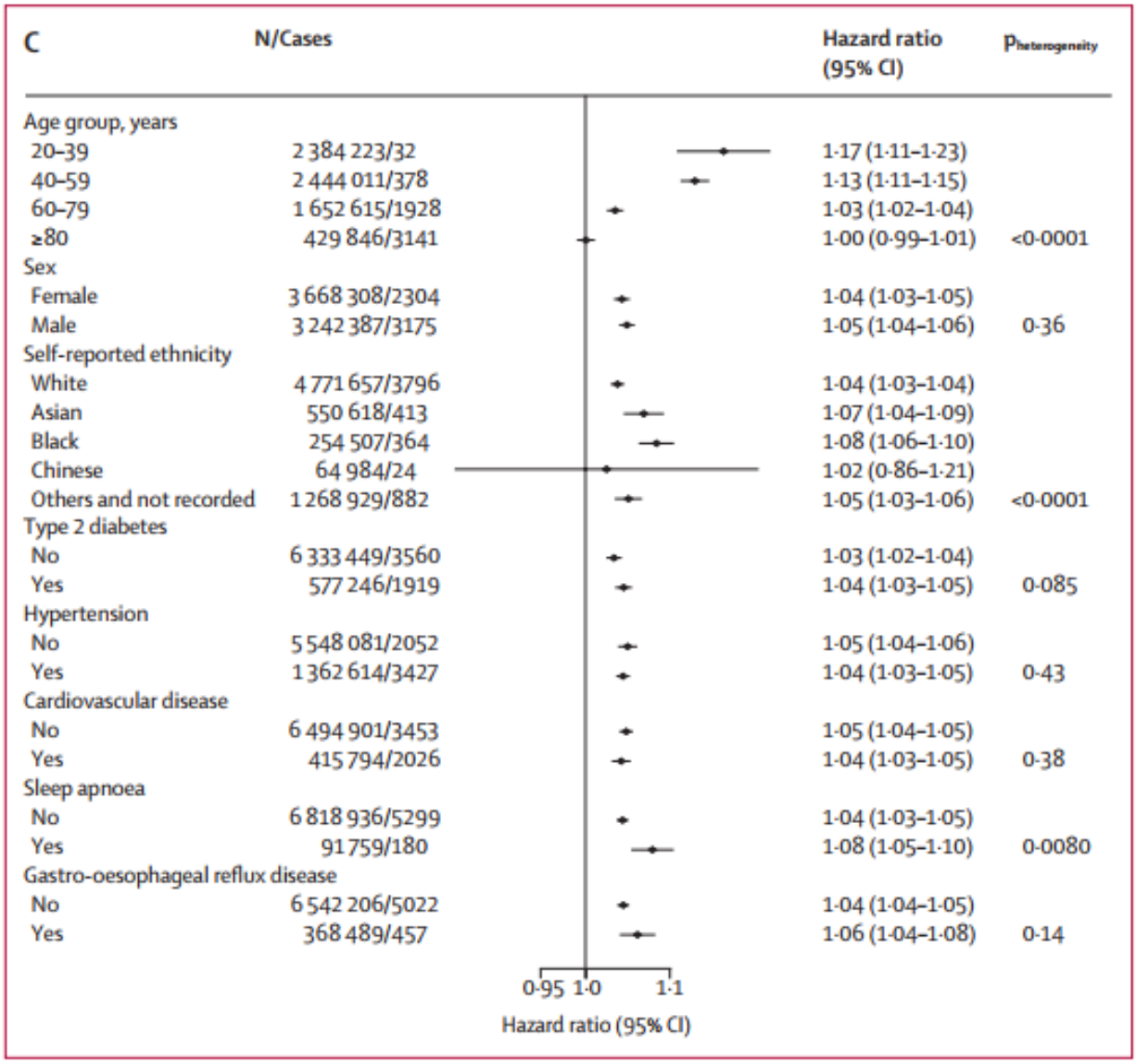
Associations Between Body-Mass Index and COVID-19 Severity in 6·9 Million People in England: A Prospective, Community-Based, Cohort Study

Lancet Diabetes Endocrinol published online April 28, 2021
doi.org/10.1016/ S2213-8587(21)00089-9

Obesity has been identified as a major risk factor for adverse outcomes after infection with SARS-CoV-2. This is a prospective, community-based, cohort study. The investigators used de-identified patient-level data from the QResearch database of general practices in the UK. They extracted data for patients aged 20 years and older who were registered at a practice eligible for inclusion in the QResearch database between Jan 24, 2020 (date of the first recorded infection in the UK) and April 30, 2020, and with available data on BMI. Data extracted included demographic, clinical, clinical values linked with Public Health England's database of positive SARS-CoV-2 test results, and death certificates from the Office of National Statistics. Outcomes, as a proxy measure of severe COVID-19, were admission to hospital, admission to an intensive care unit (ICU), and death due to COVID-19. They used Cox proportional hazard models to estimate the risk of severe COVID-19, sequentially adjusting for demographic characteristics, behavioral factors, and comorbidities.

Among 6,910,695 eligible individuals (mean BMI 26·78 kg/m² [SD 5·59]), 13,503 (0·20%) were admitted to the hospital, 1601 (0·02%) to an ICU, and 5479 (0·08%) died after a positive test for SARS-CoV-2. They found a significant interaction between BMI and age and ethnicity, with higher HR per kg/m² above BMI 23 kg/m² for younger people (adjusted HR per kg/m² above BMI 23 kg/m² for hospital admission 1·09 [95% CI 1·08–1·10] in 20–39 years age group *vs* 80–100 years group 1·01 [1·00–1·02]) and Black people than White people (1·07 [1·06–1·08] *vs* 1·04 [1·04–1·05]). The risk of admission to hospital and ICU due to COVID-19 associated with unit increase in BMI was slightly lower in people with type 2 diabetes, hypertension, and cardiovascular disease than in those without these morbidities.

Deaths

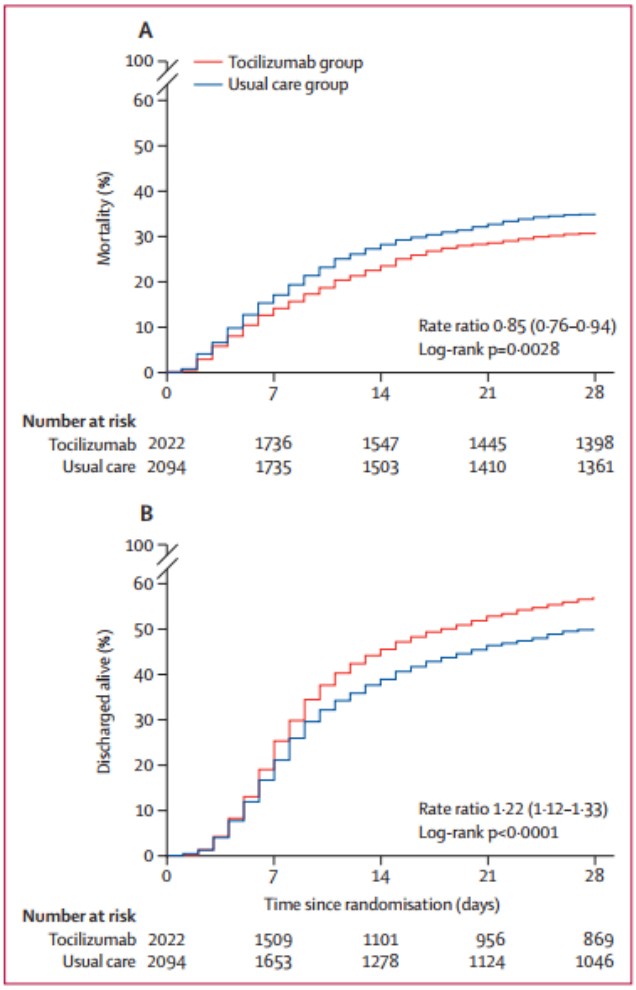


Comment: Even a small increase in BMI above 23 kg/m² is a risk factor for adverse outcomes after infection with SARS-CoV-2. At a BMI of more than 23 kg/m², they found a linear increase in risk of severe COVID-19 leading to admission to hospital and death, and a linear increase in admission to an ICU across the whole BMI range, which was not attributable to excess risks of other related diseases. The relative risk due to increasing BMI is particularly notable people younger than 40 years and of Black ethnicity. Finally, as with any observational analyses, residual confounding due to unmeasured covariates (e.g., population density and occupation) might have occurred.

Tocilizumab in Patients Admitted to Hospital with COVID-19 (RECOVERY): A Randomised, Controlled, Open-Label, Platform Trial
Lancet 2021; 397: 1637–45

This was a randomized, controlled, open-label, platform trial (Randomized Evaluation of COVID-19 Therapy [RECOVERY]), to assess several possible treatments in patients hospitalized with COVID-19 in the UK. Those trial participants with hypoxia (oxygen saturation <92% on air or requiring oxygen therapy) and evidence of systemic inflammation (C-reactive protein ≥75 mg/L) were eligible for random assignment in a 1:1 ratio to usual standard of care alone versus usual standard of care plus tocilizumab at a dose of 400 mg-800 mg (depending on weight) given intravenously. A second dose could be given 12-24 h later if the patient's condition had not improved. The median time from hospitalization to random assignment was 2 days.

Between April 23, 2020, and Jan 24, 2021, 4,116 adults of 21,550 patients enrolled into the RECOVERY trial were included in the assessment of tocilizumab, including 3,385 (82%) patients receiving systemic corticosteroids. Overall, 621 (31%) of the 2,022 patients allocated tocilizumab and 729 (35%) of the 2,094 patients allocated to usual care died within 28 days (rate ratio 0·85; 95% CI 0·76–0·94; p=0·0028). Consistent results were seen in all prespecified subgroups of patients, including those receiving systemic corticosteroids. Patients allocated to tocilizumab were more likely to be discharged from hospital within 28 days (57% *vs* 50%; rate ratio 1·22; 1·12–1·33; p<0·0001). Among those not receiving invasive mechanical ventilation at baseline, patients allocated tocilizumab were less likely to reach the composite endpoint of invasive mechanical ventilation or death (35% *vs* 42%; risk ratio 0·84; 95% CI 0·77–0·92; p<0·0001).



Comment: I included this article since when I first reviewed this data it was on medRxiv and had not been peer reviewed. The results are the same: In hospitalized COVID-19 patients with hypoxia and systemic inflammation, tocilizumab improved survival and other clinical outcomes. These benefits were seen regardless of the amount of respiratory support and were additional to the benefits of systemic corticosteroids if given early. The results are similar to the REMAP CAP trial. In summary, the RECOVERY trial provides the most definitive evidence thus far to address the controversy over whether tocilizumab should be added to our therapeutics for treatments for severely ill patients with COVID-19. I believe the answer is yes when administered in the first 24-48 hours.

Arterial Events, Venous Thromboembolism, Thrombocytopenia, and Bleeding After Vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: Population-Based Cohort Study
BMJ published online May 5, 2021
BMJ 2021;373:n1114
The study set out to assess rates of cardiovascular and hemostatic events in the first 28 days after vaccination with the Oxford-AstraZeneca (AZ) vaccine in Denmark and Norway and to compare them with rates observed in the general populations. All people aged 18-65 years who received a first vaccination with AZ from 9 February 2021 to 11 March 2021 were included. Main outcomes were observed 28-day rates of hospital contacts for incident arterial events, venous thromboembolism, thrombocytopenia/coagulation disorders, and bleeding among vaccinated people compared with expected rates, based on national age and sex specific background rates from the general populations of the two countries.

Among 281,264 people who received AZ, the standardized morbidity ratio for arterial events was 0.97 (95% confidence interval 0.77 to 1.20). 59 venous thromboembolic events were observed in the vaccinated cohort compared with 30 expected based on the incidence rates in the general population, corresponding to a standardized morbidity ratio of 1.97 (1.50 to 2.54) and 11 (5.6 to 17.0) excess events per 100,000 vaccinations. A higher-than-expected rate of cerebral venous thrombosis was observed: standardized morbidity ratio 20.25 (8.14 to 41.73); an excess of 2.5 (0.9 to 5.2) events per 100,000 vaccinations. The standardized morbidity ratio for any thrombocytopenia/coagulation disorders was 1.52 (0.97 to 2.25) and for any bleeding was 1.23 (0.97 to 1.55). 15 deaths were observed in the vaccine cohort compared with 44 expected.

Comment: Vaccinated participants were mostly health and social care workers, but investigators used historical pre-pandemic population cohorts (from 2016 to 2019) to quantify baseline event rates—obtained after adjustment (standardization) to match the age and sex profile of the vaccinated population. Important differences exist between the vaccinated cohorts and the general population. For example, vaccinated cohorts are likely to be healthier. At the same time, awareness of thromboembolic events might have been heightened during the pandemic, possibly inflating reporting among the vaccinated cohorts relative to pre-pandemic controls. While the rate of venous thromboembolism in vaccinated cohorts was higher than the background rate, we know that all vaccines against Covid-19, including the AZ vaccine, reduce mortality from Covid-19 substantially. We do know from vaccine trials that mortality reduction far outweighs any risk of adverse events. This is the same of the AZ vaccine as well as the J&J vaccine. We also know that Covid-19 is itself associated with cerebral venous thrombosis — an estimated 4.3 events per 100 000 infections, which is higher than the 2.5 per 100,000 reported by this report.

The choice we all are facing: SARS-CoV-2 infection or vaccination. The AZ vaccine is clearly a good choice, despite the possible risks found in this publication. The use of the AZ vaccine was very impactful in controlling COVID-19 in the UK. The European Union has concluded the benefits of the vaccine far outweigh the risk. We are extremely fortunate that we have 2 mRNA vaccines and a viral vector vaccine (J&J) approved for EUA in the US. Our challenge now is to overcome vaccine hesitancy.