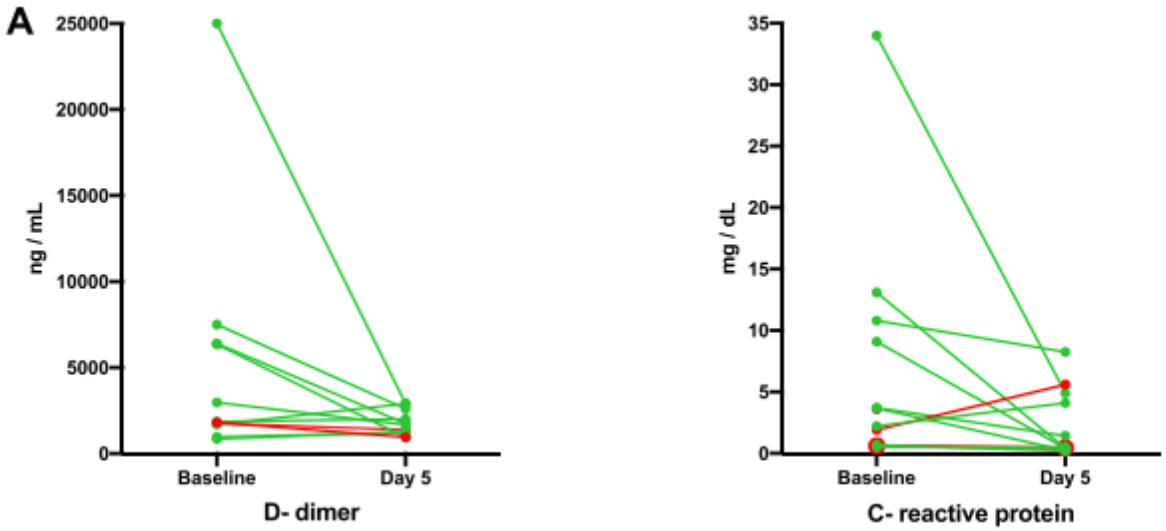
I hope everyone had a cool and safe weekend.

Lots to share today. First a proof of concept publication on the use of Adipose-derived mesenchymal stromal cells for the treatment of patients with severe SARS-CoV-2 pneumonia. The next two articles are on use of convalescent plasma. Both articles conclude that giving plasma < 3days of diagnosis and use of high-tittered AB plasma improved outcomes. The next two articles demonstrate the power of using data sets to analyze important aspects of this pandemic. The first paper reviews the experience of a large healthcare system in the Houston metropolitan area. The second is from NHS on the associations of type 1 and type 2 diabetes with COVID-19- related mortality. Imagine if multiple healthcare systems were to data share? This information would be invaluable to optimize and analyze current and future treatments. This pooling of data would provide faster results of clinical trials and provide a platform to better inform the collective response to current and future health crises. The last article suggested by John Butler is the overnight camp experience in Georgia and the high rates of SARS-CoV-2 transmission when you do not open safely!

Have a great week

Ed

Adipose-Derived Mesenchymal Stromal Cells for the Treatment of Patients with Severe SARS-Cov-2 Pneumonia Requiring Mechanical Ventilation. A Proof of Concept Study
EClinMed published online August 11, 2020
Among the potential therapeutic options to reduce this clinical and biological picture of massive inflammation the use of mesenchymal stromal cells (MSCs) is generating increasing interest. MSC have been approved for the treatment of Crohn's disease or graft-versus-host disease after hematopoietic transplantation [Cell Stem Cell 2018;22:824–33.] based in their anti-inflammatory and immunomodulatory effects thus suggesting that adipose tissue derived MSCs (AT-MSCs) could be an attractive therapeutic option for the treatment of severe SARS-CoV-2 pneumonia. In this proof of concept trial, thirteen COVID-19 adult patients under invasive mechanical ventilation who had received previous antiviral and/or anti-inflammatory treatments (including steroids, lopinavir/ritonavir, hydroxychloroquine and/or tocilizumab, among others) were treated with allogeneic AT-MSC. After a median follow-up of 16 days (IQR 9 days) after the first dose of AT-MSCs, 9 patients (70%) had improved clinically and 7 (53%) were extubated. Two patients died, one from massive gastrointestinal bleeding and another one from secondary fungal pneumonia by Saccharomyces spp. One patient developed a concurrent respiratory pneumonia due to MRSA and one patient developed a fungal infection due to a Candida spp. When they analyzed the nine patients that improved clinically, a decrease in inflammatory parameters associated with AT-MSC therapy was observed at day 5 after infusion with a decrease in CRP in 8 patients (88%), LDH in 9 (100%), and D-dimer and ferritin in 5 of 8 evaluable patients (63%). In six patients in which lymphocyte counts were measured by flow cytometry, an increase in the levels of total lymphocytes was observed in five of them (86%), as well as an increase in B- (67%) and CD4+ and CD8+ (100%) T lymphocytes. Lymphocyte subset analysis was available in six patients that improved after MSC therapy.



Comment: I must admit, I knew extraordinarily little regarding MSC therapy. MSC apparently detects an infection or an injury to those vessels/membranes, which in turn transforms and recruits and pump out immune-modulating and vessel-repair agents. These cells ameliorate crippling and deadly conditions when traditional chemical or biochemical drugs fail. The preliminary results indicate that MSC derived from adipose tissue can be safely administered in critically ill patients with COVID-19 pneumonia and that administration of AT-MSC was followed by clinical improvement and changes in inflammatory and immune populations, which suggest a potential biological effect of the cells. Mount Sinai in NY won FDA approval and NIH funding to conduct an RCT.

Effect of Convalescent Plasma on Mortality among Hospitalized Patients with COVID-19: Initial Three- Month Experience

MedRxiv published online August 12, 2020

This is a multicenter, observational trial including 2,807 acute care facilities in the US and territories. The antibody levels in the units collected were unknown at the time of transfusion. This cohort (35,000 patients) included a high proportion of critically ill patients, with 52.3% in the intensive care unit (ICU) and 27.5% receiving mechanical ventilation at the time of plasma transfusion. The seven-day mortality rate was 8.7% [95% CI 8.3%-9.2%] in patients transfused within 3 days of COVID-19 diagnosis but 11.9% [11.4%-12.2%] in patients transfused 4 or more days after diagnosis ($p<0.001$). Similar findings were observed in 30-day mortality (21.6% vs. 26.7%, $p<0.0001$). Importantly, a gradient of mortality was seen in relation to IgG antibody levels in the transfused plasma. For patients who received high IgG plasma (SARS-CoV-2 spike subunit 1 protein based on the sample signal-to-cut-off (S/Co) ratio (>18.45 S/Co), seven-day mortality was 8.9% (6.8%, 11.7%); for recipients of medium IgG plasma (4.62 to 18.45 S/Co) mortality was 11.6% (10.3%, 13.1%); and for recipients of low IgG plasma (<4.62 S/Co) mortality was 13.7% (11.1%, 16.8%) ($p=0.048$).

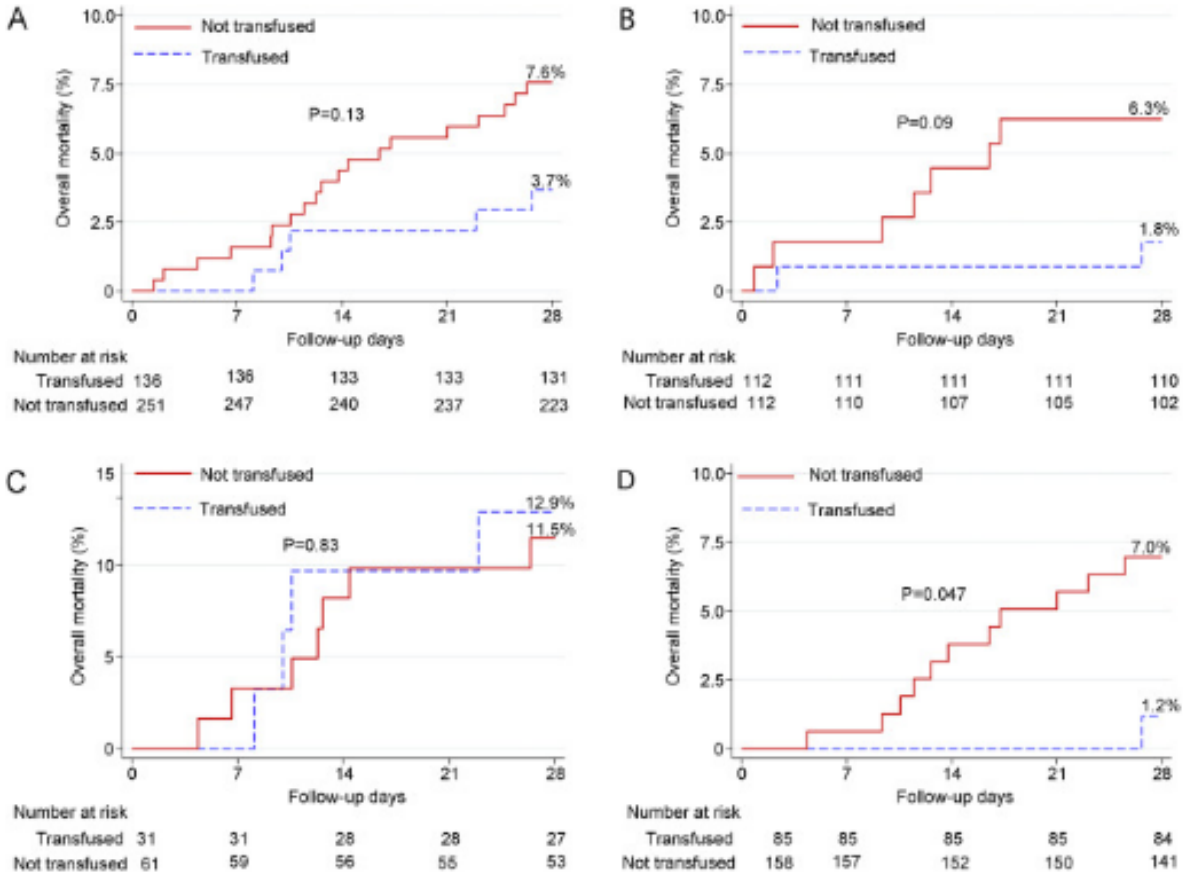
Comment: This was not an RCT. It was designed to provide access to CP largely at hospitals and acute care facilities that were not already part of an RCT or did not have the infrastructure to support complex RCTs. It was a pragmatic study design, organized to allow routine clinical care to dictate the timing and administration of plasma in a real-world setting. Last week I reviewed an article that demonstrated that by day 10 patients already had high-tittered COVID-19 AB-Their data safety monitoring board ending up stopping the study based on the antibody results and that results to date did not show benefit. I also

reviewed the Mayo Clinic testimony in front of the FDA which showed CP should be given <3 days of diagnosis to show benefit. We now have the posted manuscript which adds the impact pf high IgG antibodies and outcomes. This article has not undergone peer review, but this article along with article below continues to add to our knowledge of the most effective use of CP.

Treatment of COVID-19 Patients with Convalescent Plasma Reveals a Signal of Significantly Decreased Mortality

Am J Path published online August 10, 2020

The investigators conducted a prospective, propensity score-matched study assessing the efficacy of COVID-19 convalescent plasma (CP) versus standard of care as treatment for severe and/or critical COVID-19.This article shared the results of an interim analysis of 316 patients (n=316) enrolled from March 28 to July 6, 2020 at Houston Methodist. Of the 316 transfused patients, 136 met a 28-day outcome and were matched to 251 non-transfused control COVID-19 patients. Matching criteria included age, sex, BMI, comorbidities, and baseline ventilation requirement 48 h from admission, and in a second matching analysis, ventilation status at Day 0. Variability in the timing of transfusion relative to admission and titer of antibodies of plasma transfused allowed for analysis in specific matched cohorts. The analysis showed a significant reduction (*P* = 0.047) in mortality within 28 days, specifically in patients transfused within 72 h of admission with plasma with an anti-spike protein receptor binding domain titer of ≥1:1350.



Kaplan-Meier curves for mortality within 28 days post-Day 0 for secondary matched cohorts. A. All secondary matched patients. B. Secondary matched patients transfused within 72 h of admission. C. Secondary matched patients transfused >72 h after admission. D. Secondary matched patients transfused within 72 h of admission with plasma with anti-RBD IgG titer ≥ 1:1350.

Comment: These data suggest that treatment of COVID-19 with high anti-receptor binding domain (RBD) IgG titer convalescent plasma appears efficacious in early-disease patients (< 3 days). This is not an RCT and the numbers in this trial are much smaller compared to the Mayo Clinic article. This article, however, along with article above have a common theme: earlier is better with high titers plasma.

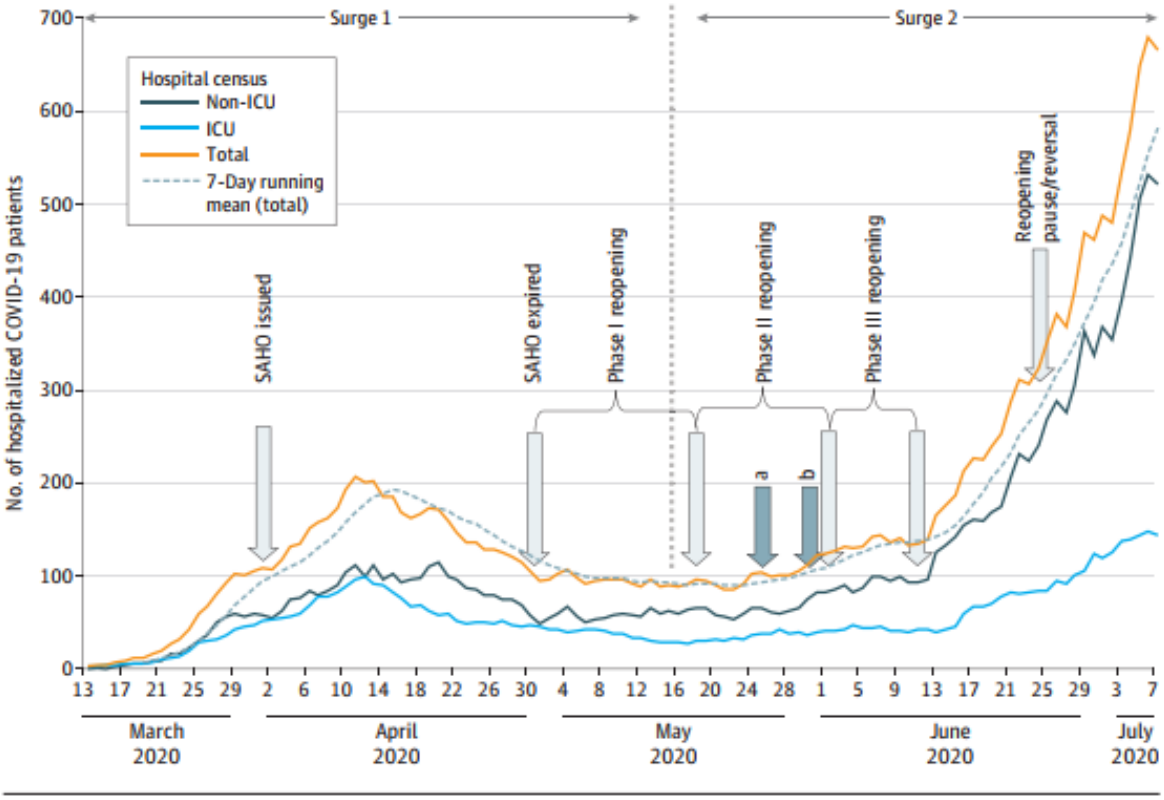
Characteristics and Outcomes of COVID-19 Patients During Initial Peak and Resurgence in the Houston Metropolitan Area

JAMA published online August 13, 2020

From electronic health records, the authors identified patients with positive PCR nasopharyngeal swab test results for severe acute respiratory syndrome due to SARS-CoV-2. They extracted age, sex, race/ethnicity, comorbidity, medication, ICU admission, and mortality information. The assessment of race/ethnicity was driven by prior analyses of our data that demonstrated higher SARS-CoV-2 infection rates among racial and ethnic minorities. They tracked daily total, ICU, and non-ICU (medical/surgical units) hospital census across the reporting period. They divided patients into wave 1 for admissions between March 13 and May 15, 2020, and wave 2 between May 16 and July 7,2020. Spike 2 started 2 weeks after a phased statewide reopening. They provided summary statistics as means or medians and proportions for various sociodemographic, clinical, and outcome characteristics of hospitalized COVID-19 patients. Proportional differences with 95% CIs are provided for bivariable comparisons across waves 1 and 2.

As of July 7, 2020, 2904 unique COVID-19 patients had been hospitalized, representing 774 and 2130 patients during wave 1 and 2, respectively. Patients in wave2 (vs wave 1) were younger (mean age, 57.3 vs 59.9 years), the proportion identifying as Hispanic was higher, and the median zip code–based income was lower ($60 765 vs $65 805; difference, -$5040; 95% CI, -$7641 to -$2439). Wave 2 patients had a significantly lower burden of overall and specific comorbidities such as diabetes, hypertension, and obesity. A greater proportion of wave 2 patients received remdesivir and enoxaparin. A smaller proportion of wave 2 patients were admitted to the ICU (20.1% vs 38.1%). Length of hospital stay was less (4.8 vs 7.1 days). In-hospital mortality was significantly lower compared with that for wave 1 (5.1% vs 12.1%). However, in-hospital mortality among discharged and deceased ICU-treated patients during wave 2 was not significantly lower than that during wave 1 (49/214 [22.9%] vs 81/295 [27.5%). During wave 2, the absolute number of PCR tests performed increased, as did the proportion of positive results. Therefore, higher hospital census likely reflects higher rates of community COVID-19 prevalence. Wave 2 data indicated a demographic shift of the pandemic toward a younger, predominantly Hispanic, and lower socioeconomic patient population with an overall lower comorbidity burden, ICU admission rate, and in-hospital mortality.

Figure. Daily Hospital Census of Total, Intensive Care Unit, and Non–Intensive Care Unit COVID-19 Patients Across Houston Methodist



Comments: Although this was from only 1 healthcare system in Houston, similar patterns were observed throughout the greater Houston area. The increased use of remdesivir and enoxaparin during wave 2 reflects better treatments/prevention based on evolving knowledge. Dexamethasone and other steroids were becoming standard based on the RECOVERY Trial. The use of CP was also more widespread. Kudos to Houston Methodist for the two studies reviewed in today's Briefing. It demonstrates the power of using data sets to analyze important aspects of this pandemic. However, single healthcare systems may not have a large enough data set to answer critical questions quickly. Imagine of all the organizations in Houston worked together? Instead of ~2500 patients we could analyze ~30,000 patients? This collaborative effort could provide timely data to better respond to current clinical and public health challenges. The goal of a "research community" could be to come up with answers in weeks or months rather than years. What if we had real-time pooling of clinical data by identifying minimal data sets representing information needed for both clinical trials and interventions. Use AI to better understand the dynamics of inflammatory and clinical parameters to predict which patients are at greater risk for progression or which interventions and when are more likely to improve outcomes? This information would be invaluable to optimize and analyze current and future treatments. This pooling of data would provide faster results of clinical trials and provide a platform to better inform the collective response to current and future health crises.

Associations of Type 1 and Type 2 Diabetes with COVID-19-Related Mortality in England: A Whole-Population Study

Lancet Diabetes Endocrinol published online August 13, 2020

The investigators performed a nation-wide study assessing risks of in-hospital death with COVID-19 between March 1 and May 11, 2020. They included all individuals registered with a general practice in England who were alive on Feb 16, 2020. They used multivariable logistic regression to examine the effect of diabetes status, by type, on in-hospital death with COVID-19, adjusting for demographic factors and cardiovascular comorbidities.

Of the 61414470 individuals who were alive and registered with a general practice on Feb 16, 2020, 263 830 (0·4%) had a recorded diagnosis of type 1 diabetes, 2 864 670 (4·7%) had a diagnosis of type 2 diabetes and 58 244220 (94·8%) had no diabetes. 23 698 in-hospital COVID-19- related deaths occurred during the study period. A third occurred in people with diabetes: 7434 (31·4%) in people with type 2 diabetes, 364 (1·5%) in those with type 1 diabetes. Adjusted for age, sex, deprivation, ethnicity, and geographical region, compared with people without diabetes, the odds ratios (ORs) for in-hospital COVID-19-related death were 3·51 (95% CI 3·16–3·90) in people with type 1 diabetes and 2·03 (1·97–2·09) in people with type 2 diabetes. These effects were attenuated to ORs of 2·86 (2·58–3·18) for type 1 diabetes and 1·80 (1·75–1·86) for type 2 diabetes when also adjusted for previous hospital admissions with coronary heart disease, cerebrovascular disease, or heart failure. However, the mortality was low for patients < 40 with diabetes.

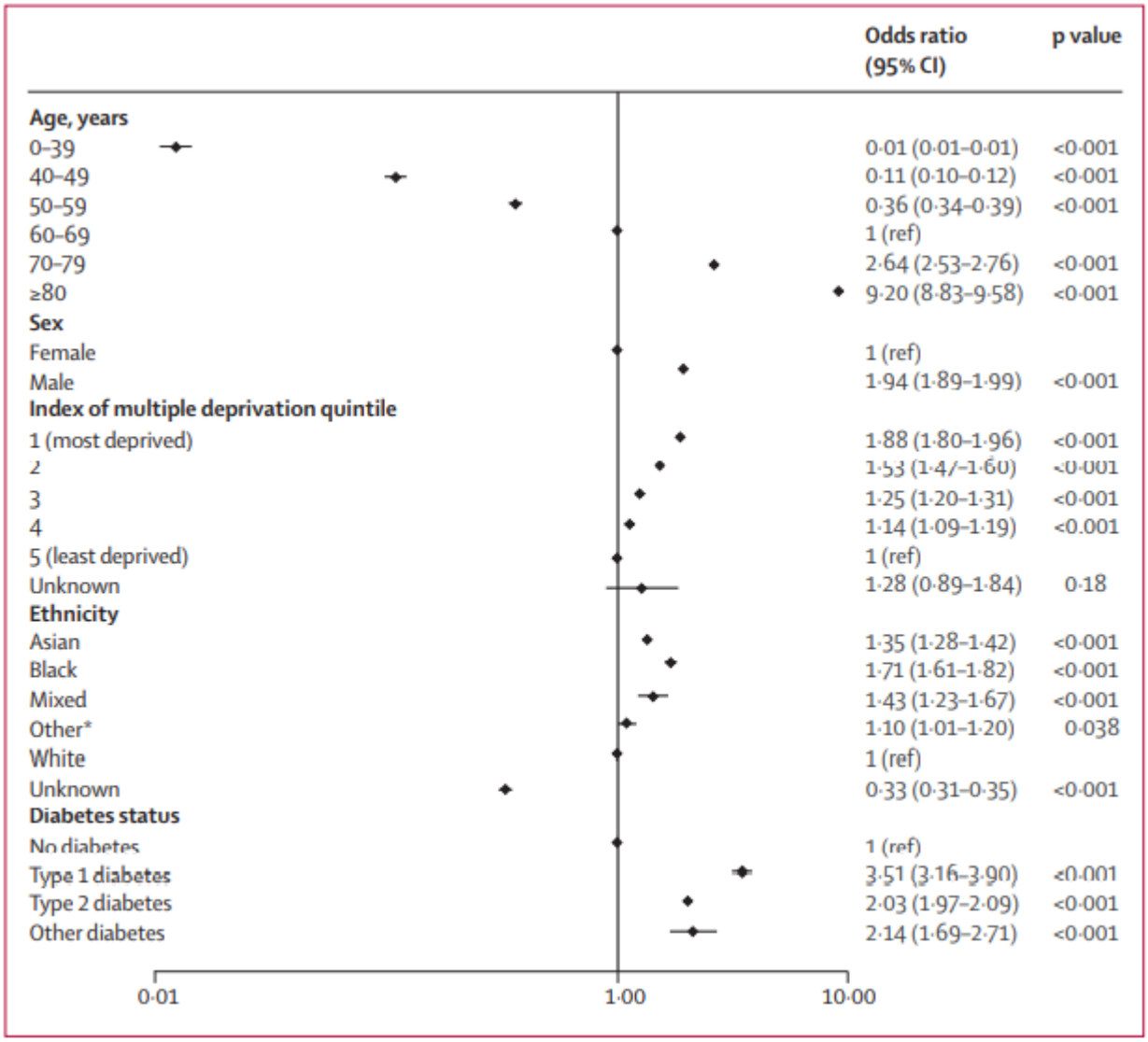


***Figure 2*: Adjusted odds ratios for in-hospital deaths for people with COVID-19 in England, March 1 to May 11, 2020, by demographic characteristics and diabetes status**

Comment: They were unable to adjust for BMI, hypertension, kidney disease, and tobacco smoking, as well as other potential confounders, is likely to have left large residual confounding in the associations described. [incomplete recording in the hospital-derived segmentation dataset.] Despite this weakness, this is the largest COVID-19-related whole-population study, covering almost the entire population of England, and is the first study to investigate the relative and absolute risk of death in hospital with COVID-19 by type of diabetes, adjusting for key (but not all) confounding factors. It again demonstrates using robust data sets what questions and answers can be answered quickly.

SARS-CoV-2 Transmission and Infection Among Attendees of an Overnight Camp — Georgia, June 2020

MMWR July 31, 2020 article suggested by John Butler

During June 17–20, an overnight camp in Georgia (camp A) held orientation for 138 trainees and 120 staff members; staff members remained for the first camp session, scheduled during June 21–27, and

were joined by 363 campers and three senior staff members on June 21. Camp A adhered to the measures in Georgia's Executive Order that allowed overnight camps to operate beginning on May 31, including requiring all trainees, staff members, and campers to provide documentation of a negative viral SARS-CoV-2 test ≤12 days before arriving. Camp A adopted most components of CDC's Suggestions for Youth and Summer Camps to minimize the risk for SARS-CoV-2 introduction and transmission. Measures not implemented were cloth masks for campers and opening windows and doors for increased ventilation in buildings. Cloth masks were required for staff members. Camp attendees were cohorted by cabin and engaged in a variety of indoor and outdoor activities, including daily vigorous singing and cheering. On June 23, a teenage staff member left camp A after developing chills the previous evening. The staff member was tested and reported a positive test result for SARS-CoV-2 the following day (June 24). Camp A officials began sending campers home on June 24 and closed the camp on June 27.

Test results were available for 344 (58%) attendees; among these, 260 (76%) were positive. The overall attack rate was 44% (260 of 597), 51% among those aged 6–10 years, 44% among those aged 11–17 years, and 33% among those aged 18–21 years. Attack rates increased with increasing length of time spent at the camp, with staff members having the highest attack rate (56%).

Comment: Given the increasing incidence of COVID-19 in Georgia in June and July, some cases might have resulted from transmission occurring before or after camp attendance. Testing within 12 days of arriving at camp does not exclude early infection or infection that may have occurred after testing. Testing may have provided a false sense of security which is why CDC does not recommend routine screening for person to return to school. In addition, this report demonstrates that SARS-CoV-2 spread efficiently in a youth-centric overnight setting, resulting in high attack rates among persons in all age groups, despite efforts by camp officials to implement some, but not all of the recommended strategies to prevent transmission. It is likely campers did not maintain social distancing, did NOT wear masks, had poor ventilation, were singing etc. Asymptomatic infection was common and potentially contributed to undetected transmission, as has been previously reported. This investigation adds to the body of evidence demonstrating that children of all ages are susceptible to SARS-CoV-2 infection and under the right circumstances can play an important role in transmission. In addition, this is an example of the results of not opening safely! This is similar to the recent report of a GA HS which did not require students to wear masks and allowed them to congregate in hallways etc.