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BRIEF19

A daily review of covid-19 research and policy

RESEARCH BRIEFING

Smoking found to increase covid-19 risk.

Biological plausibility is a fancy way for scientists to say that something "makes sense." But in the real world of research, biological plausibility is not enough. You need data to back up an idea. For example, most people assumed that asthma might be a risk factor for covid-19. It just "seems logical." But so far, the data have not found this to be the case. So while there is compelling biological plausibility that smokers might be at increased risk of severe disease from covid-19 than non-smokers, real data has been lacking. Previously, there has been some evidence that smoking was associated with worse covid-19 outcomes in people with lung cancer. But until today, data assessing any association between smoking and the severity of covid-19 symptoms had not been published.

Enter the Cleveland Clinic, which maintains a covid-19 registry that tracks patients who test positive for SARS-CoV-2 allowing researchers to examine different characteristics and outcomes in all included patients. Smoking is one of those characteristics. Using electronic medical records a team of investigators measured whether cumulative years of smoking meant worse covid-19 outcomes. The findings were published today in *JAMA Internal Medicine.*

Heavy smoking was associated with a 2.25 greater rate of hospitalizations among covid-19 patients. These same heavy smokers were 1.89 times more likely to die from covid-19. These findings elevate the idea that smoking could be a risk factor for worse covid-19 outcomes from "biologically plausible" to supported by actual data.

That said, relying on data extracted from electronic medical records is not the most accurate method for determining how much a person *actually* smokes. People know smoking is not great for their health, so they often underestimate how much they smoke when asked about it by their doctors. Also, for that information to even be in a medical chart (let alone up-to-date), a patient would have to be going to the doctor and getting check-ups on a fairly regular basis. Not everyone gets a yearly physical in the United States. So while the researchers looked at 7,102 patient records, we can't say whether these patients are representative of the whole population of the United States, nor even whether the datasets are accurate. That said, it's likely that the categorizations used (i.e. never smoked versus long-term tobacco exposure) might be reasonably accurate approximations of peoples' overall behaviors and exposures. .

While data showing a correlation between smoking and worse covid-19 outcomes might seem like a no-brainer, these data are crucial for two reasons. First, as mentioned, plausibility is not enough. Data matters. (Few would have guessed that asthma would *not* correlate to worse outcomes). Second, knowing these findings might help policymakers reconsider who should be prioritized to receive the covid-19 vaccine. Non-smokers may find this frustrating. But remember, we treat people without judgment for their behaviors. Smokers aren't lighting up to make you angry. Many wish they could quit but they are addicted to nicotine. Targeted marketing and the brain stimulating effects of nicotine makes quitting (especially without help) extremely challenging for most, especially true in times of stress—a global pandemic, for example. Deciding whose lives are most at risk has nothing to do with any kind of morality. It's about following the data and responding accordingly. We want everyone to get the vaccine in a timely fashion. And while some people might not think it's fair, there's a good argument to be made that smokers should be at least some priority over people who have been able to make healthier choices.

—Joanna Parga-Belinkie, MD

Does colchicine save lives or reduce hospitalizations in covid-19? (And yes, we purposely buried the lede on this one).

Among the list of medications that researchers have tried to repurpose in an effort to treat covid-19, almost all have failed spectacularly. Colchicine—a drug with anti-inflammatory properties that has long been used for conditions ranging from gout to inflammation of the tissues surrounding the heart—has been proposed as a possibility.

A small study, GRECCO-19, covered in *Brief19* back in June, found that patients who received colchicine were less likely to experience "clinical deterioration" within 3 weeks. The COLCORONA study is a much larger endeavor. That study aimed to randomize 4,488 patients (GRECCO-19 included just 105 patients). Unfortunately, the results are only available via press release, without raw numbers or confidence intervals (i.e. the range of statistically likely outcomes). Therefore, we must be cautious with the figures and interpretations provided by the researchers. That caution is especially warranted given that the language used in the press release was *highly suspect* and even alarming to many researchers. The released statement announced that the primary outcome of the study "approached statistical significance." This language implies with near certainty that this trial will actually be interpreted by experts as having uncovered *no* significant difference at all.

Details about the study design have been published online elsewhere. From that, we know that the study included patients ages 40 and over with at least 1 "high risk criteria. These criteria were: ≥70 years old, obesity, diabetes, lung disease, heart failure, known coronary artery disease, and difficulty breathing. The trial excluded patients who were already sick enough to be hospitalized or under consideration for hospitalization, advanced kidney disease, liver disease, and pregnant patients (colchicine is a drug that must be avoided during pregnancy).

Test subjects were randomized to receive either 0.5mg of colchicine twice per day for three days and then once daily for 27 days or a placebo pill on the same schedule. The primary outcome of interest was a combination of death *or* hospitalization rates due to covid-19 within 30 days. The press release claims that a 21 percent reduction in deaths or hospitalizations was seen among patients who were randomized to receive colchicine. That said, of the 4,488 patients included, 92.7 percent (4,159 patients) actually had test-confirmed diagnoses of SARS-Cov-2. When only that group was analyzed, those who received colchicine the rate hospitalizations was 25 percent lower and the rate of mechanical ventilation was 50 percent lower. In addition, 44 percent fewer deaths were observed among those who received colchicine.

Such results could be seen as "game changing," and indeed the press release sells these results as such. That's why the *actual data* are so desperately needed now, especially given the million-dollar caveat that the findings "approached statistical significance." While the barrier between what scientists consider to be significant and non-significant is somewhat arbitrary, given the impressive size of this study, any clinical benefit may be questionable. That's especially true given that any potential test subjects who were sick enough to even be *considered* for hospitalization at the time they entered the study implies that very few of them progressed towards more severe illness. So while the reported reduction in mechanical ventilation and deaths appears staggering, the absolute number of patients with these outcomes is likely to be quite small. Without the raw numbers or comparative proportions, it's inappropriate to make sweeping conclusions. It could be that hundreds of patients would need to be treated for one hospitalization to be averted. We simply do not know. While we eagerly await a positive breakthrough for outpatient management of covid-19 that is capable of preventing disease progressions, based on the preliminary results of this study as reported so far, we remain

skeptical that colchicine is a miracle drug. But the full data, once released, could reveal a different story. If that turns out to be the case, we will gladly report on those findings when they become available.

—Lauren Westafer, DO MPH

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