

## COVID-19 and TOBACCO: THE UNION BI-WEEKLY BRIEF Issue #5 (5 August 2020)

### INTRODUCTION

This fifth brief synthesizes the most relevant recent studies, analysing important research published between the last Union brief (17 July) and today. The team reviewed nearly 40 studies and felt it important to highlight four epidemiological studies and three biochemical studies on smoking and COVID-19. Studies that are yet to be peer-reviewed are highlighted to differentiate them from those that have been peer-reviewed.

The four epi studies included in this brief all examine COVID-19 patients in hospital settings, providing additional data on the relationship between smoking and disease progression in stages 1 and 3 (Please refer to our [main brief](#) for comprehensive definitions of the three disease stages). The two most recent biochemical studies are far from conclusive but raise important questions about smokers' ACE2 expression—and how nicotine and smoking may impact SARS-cov-2 infection (disease stage 1).

### Smoking and COVID-19 progression

In a retrospective study from Kuwait, Almazeedi et al. [4] used electronic medical records to analyse the clinical characteristics of 1,096 COVID-19 patients from a large hospital. The smoking rate in the sample was 4%, much lower than the general population. Because patients were part of a government-led mass screening effort, the study captured both symptomatic and asymptomatic cases; its ability to include cases from the general population makes it more representative than many studies drawing from a single source. It also found that smoking was significantly associated with an increased risk of ICU admission, as well as an increased risk of death. Because tobacco use was not the primary focus of the analysis, smoking was not clearly defined; it is unclear if former smokers were classified as non-smokers and if water pipe, cigarette, and bidi users were defined as smokers.

Of the four new studies, there are two from the United Kingdom [1, 2] with vastly different sample sizes. [Thompson et al \[1\]](#) conducted a retrospective analysis of 470 adult patients admitted to the UK's Royal Oldham Hospital with COVID-19. Electronic medical records were used to conduct retrospective data analysis to determine mortality characteristics and predictors of the 169 patients (36%) who died. Of the total sample, 14% were current smokers and 27% were former smokers. There were more current and former smokers among the survivor group, but the researchers did not run a statistical analysis. Docherty et al [2] conducted a prospective observational cohort study of 20,133 COVID-19 inpatients across 208 acute care hospitals in England, Wales, and Scotland to determine both clinical characteristics of admitted patients and mortality risk factors. Their study found a lower current smoking rate—6% of patients were current smokers and 31% were former.

In a research letter to *JAMA*, Bilaloglu et al [3] described a New York City study of 3,334 COVID-19 hospitalized patients in a large urban hospital system. The study had a specific focus on the incidence of and risk factors for venous and arterial thrombotic events. Current smoking status was collected for chart reviews and included as a covariate. The results found that 24% of the sample were current smokers, and current smoking was associated with thrombosis at a statistically significant level. Hospital records are not a reliable source of data on smoking history, especially during pandemic time. As discussed in previous briefs, self-reporting and reliance on hospital medical records comprise serious study limitations.

And, in a retrospective study from Kuwait, Almazeedi et al. [4] used electronic medical records to analyse the clinical characteristics of 1,096 COVID-19 patients from a large hospital. The median age for the sample was 41—lower than from two other retrospective studies out of New York City and China. Because patients were part of a government-led mass screening effort, the study captured both symptomatic and asymptomatic cases; its ability to include cases from the general population makes it more representative than many studies drawing from a single source. It found that while 96% of the sample were non-smokers, smoking was significantly associated with an increased risk of ICU admission as well as an increased risk of death. An important limitation is the limited number of smokers as demonstrated in the multivariable analyses confidence intervals.

### **Smoking, COVID-19, and Biochemistry**

Three new biochemical studies provide more preliminary evidence on the complicated interplay between nicotine, smoking, and SARS-cov-2 infection. In examining ACE2 expression among current smokers and current e-cigarette users, Lee et al. [5] found that while ACE2 expression was upregulated among the former, this was not the case with the latter. This finding warrants further research as the authors contest that tobacco constituents besides nicotine might be responsible for ACE2 upregulation among smokers.

Researchers are also divided on whether SARS-cov-2 infection begins in the respiratory system. Hikmet et al [6] mapped ACE2 levels in various body tissues and observed zero or minimal levels in the respiratory system but much higher levels in other tissues—intestine, colon, and kidney. The researchers maintain that SARS-cov-2 infection may occur through alternate receptors or even non-receptor dependent mechanisms. In their study, Ziegler et al [7] suggest that the initial host immune response to SARS-CoV-2 may trigger an interferon-driven upregulation of ACE2, which would increase the number of cells in respiratory epithelia susceptible to SARS-CoV-2 infection. This might offer a mechanism for SARS-CoV-2 to enter via ACE2 respiratory tract receptors, despite low ACE2 expression under normal conditions.

### **References:**

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2. Docherty, A. B., et al. *Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study.* *BMJ*: m1985, 2020.
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4. Almazeedi, S., et al. *Characteristics, risk factors and outcomes among the first consecutive 1096 patients diagnosed with COVID-19 in Kuwait.* *EClinicalMedicine*: 100448, 2020.
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7. Ziegler, C. G. K., et al. *SARS-CoV-2 Receptor ACE2 Is an Interferon-Stimulated Gene in Human Airway Epithelial Cells and Is Detected in Specific Cell Subsets across Tissues.* *Cell* **181**(5): 1016-1035.e1019, 2020.