

COVID-19 and TOBACCO: THE UNION MONTHLY BRIEF Issue #8 (21 December 2020)

INTRODUCTION

This eighth brief synthesizes the most relevant recent studies, analysing important new research published between the last Union brief (1 October) and today. The team reviewed nearly 90 studies and felt it important to highlight four epidemiological studies—one is marked yellow to indicate it was not peer-reviewed—including three on smoking and COVID-19 and one on vaping; the latter highlights similarities between COVID-19 and EVALI. One of the three smoking studies—by Tattan-Birch et al—discusses how collider bias skews data, making it appear that smoking protects against COVID-19 infection. In their study, Jackson et al. look at the association between smoking and COVID-19 outcome measures, including confirmed positive tests and stress levels. The latest study from Simons et al compared smoking prevalence among hospitalized COVID-19 patients and patients with other respiratory viruses a year before the pandemic, finding that the former had lower odds of being current smokers.

On the biochemical side, one study examines how cigarettes smoke exposure affects SARS-CoV-2 airway cell infection; another supports previous studies that show ACE2 as the entry point for SARS-CoV-2; and three studies, finding that cigarette smoke downregulates ACE2, add to the continuing debate about how tobacco smoke interacts with COVID-19.

Please refer to our [main brief](#) for comprehensive definitions of the three COVID-19 disease stages, as well as analysis on the critical questions regarding smoking, infection with SARS-CoV-2, hospital record limitations, biochemistry, and nicotine's alleged protective qualities.

Vaping and COVID-19

In “Vaping in today’s pandemic: E-cigarette, or vaping product-use associated with lung injury mimicking COVID-19 in teenagers representing with respiratory distress,” Darmawan et al [1] discuss three adolescents who presented at hospitals with respiratory distress during COVID-19. The trio presented at pediatric intensive care units with a range of symptoms—chest pain, cough, violent cough, laboured breathing, fever, nausea, sore throat, vomiting, and diarrhea. Two of the three tested negative for COVID-19, and all three were eventually diagnosed with EVALI. In addition to highlighting the common clinical symptoms of the two diseases, the authors urge clinicians to advise against the use of e-cigarettes and other vaping products—and encourage abstinence—as the best way to prevent lung injury. While distinct from the majority of smoking-related studies in The Union’s scientific briefs, this study provides an important reminder that adolescents who vape may be at dual risk for lung injuries—from COVID-19 and novel products.

Smoking and COVID-19

In their study, “Assessing and addressing collider bias in addiction research,” Tattan-Birch et al. [2] examine how collider bias—this occurs when researchers control for, stratify on, or select a sample based on a variable that is caused by both the exposure and outcome—impacts COVID-19 research. As discussed throughout The Union’s briefs, several studies have noted the paradoxical finding that smokers (both current and former) appear to be less at risk of testing positive for COVID-19. This finding, explain the authors, is likely due to the fact that smokers have a higher likelihood of having a cough (this is the collider), which is indicative of COVID-19 and often included among symptoms that warrant testing. If smokers—compared to non-smokers—are more likely to seek COVID-19 testing even when they do not have the disease, they will be over-represented in

the sample with the negative test results, thus making it appear that smokers are less likely to have COVID-19.

Using a cross-sectional online survey, Jackson et al. [3] examine COVID-19 and outcome measures—confirmed and suspected COVID-19; worry about catching or becoming seriously ill from COVID-19; and adherence to protective behaviours—in “COVID-19, smoking and inequalities: a study of 53200 adults in the UK.” The authors found that current smokers had higher prevalence (0.56%) of self-reported, confirmed COVID-19 compared to both non-smokers (0.26%) and former smokers (0.19%). Current smokers also had higher odds of a self-reported confirmed COVID-19 diagnosis. Stress about serious illness was also significant, with current and former smokers having higher odds of reporting it than never smokers. Despite this stress, however, current smokers were more prone to risks, reporting lower adherence to recommendations to prevent the spread of COVID-19 than never smokers.

And, in their latest, Simons and colleagues [4] conducted a case-control study to examine how smoking status affected COVID-19 hospitalization, as compared to respiratory viruses in the previous year. The study, which included 446 adult patients (cases) and 211 controls found that patients hospitalized with COVID-19 had lower odds of being current smokers than patients admitted with other respiratory viruses. They also found that smoking status was poorly recorded in electronic health records—a significant problem discussed in previous briefs—with this issue being more prominent in controls.

Smoking, Biochemistry and COVID-19

In an effort to understand how cigarette smoke exposure affects SARS-CoV-2 airway cell infection, Purkayastha et al. [5] conducted an experiment, directly exposing air-liquid interface cultures derived from primary human non-smoker airway basal stem cells (ABSCs) to short-term cigarette smoke. Next, they infected the cultures with SARS-CoV-2. The result was increased infected airway cells with a lack of ABSC proliferation. Single cell culture profiling showed that cigarette smoke exposure with infection reduced the normal interferon response.

While further supporting the theory that ACE2 is the main entry point for SARS-CoV-2, Zamorano et al.’s study [6] also recognizes the receptor is, at most, poorly expressed in cell respiratory epithelium. Co-receptors—NRP1, HS, or sialic acids—exposed at target cell surfaces may help explain a two-step attachment mechanism.

Finally, three new studies support previous findings that cigarette smoke downregulates ACE2. Wang et al found decreased levels of ACE2 among smokers [7]; Tomchaney et al [8] also reported decreased levels when exposing mice to cigarette smoke; and Caruso et al saw downregulation after exposing bronchial epithelial cells to cigarette smoke [9]. (The Caruso study, it must be noted, received funding from PMI’s Foundation for a Smoke-Free World.) While most research studies thus far find smoking to be associated with ACE2 upregulation, growing evidence showing otherwise—as indicated by the three studies in this review—shows there is far from consensus among researchers about the mechanism through which smoking affects COVID-19.

References:

1. Darmawan et al., *Vaping in today’s pandemic: E-cigarette, or vaping, product-use associated lung injury mimicking COVID-19 in teenagers representing with respiratory distress*. Sage Open Medical Case Reports, 2020. Volume 8.

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3. Jackson, S.E., et al., *COVID-19, smoking and inequalities: a study of 53 002 adults in the UK*. *Tobacco Control*, 2020: p. tobaccocontrol.
4. Simons, D., et al., *The association of smoking status with hospitalisation for COVID-19 compared with other respiratory viruses a year previous: A case-control study at a single UK National Health Service trust*. *MedRxiv*, 2020.
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6. Zamorano Cuervo, N. and N. Grandvaux, *ACE2: Evidence of role as entry receptor for SARS-CoV-2 and implications in comorbidities*. *eLife*, 2020. **9**.
7. Wang, G.-Z., et al., *Degradation of SARS-CoV-2 receptor ACE2 by tobacco carcinogen-induced Skp2 in lung epithelial cells*. *BioRxiv*, 2020.
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9. Caruso, M.D., Alfio; et al., *Role of Cigarette Smoke on ACE-2 Protein Membrane Expression in Bronchial Epithelial Cells Using an Air-Liquid Interface Model*. *PrePrints*, 2020.