COVID-19 and TOBACCO: THE UNION MONTHLY BRIEF
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INTRODUCTION

This sixth brief synthesizes the most relevant recent studies, analysing important research published between the last Union brief (5 August) and today. The team reviewed 92 studies and felt it important to highlight seven epidemiological studies and four biochemical studies on smoking and COVID-19. Studies that are yet to be peer-reviewed are highlighted.

In the epi category, there are two new studies and five systematic reviews and meta-analyses providing data and hypotheses on the relationship between tobacco and e-cigarette use and COVID-19 disease progression in stages 1, 2 and 3 (Please refer to our main brief for comprehensive definitions of the three disease stages). The systematic reviews and meta-analyses strengthen previous findings that show an association between smoking and severe COVID-19 disease (stage 3).

Two biochemical studies continue to raise important questions about smokers' ACE2 expression—and how nicotine and smoking may impact SARS-cov-2 infection (disease stage 1); another biochemical study focuses on the relationship between smoking, interferon response and SARS-CoV-2 (disease stage 2); the fourth biochemical study proposes a new hypothesis to explain the low smoking rate among people infected with SARS-CoV-2 (disease stage 1).

Smoking and COVID-19: Infection and Disease Progression

Gaiha et al [1] received significant media attention for their study examining the relationship between use of e-cigarettes, cigarettes, and dual usage with COVID-19 symptoms, testing, and diagnosis among 4,351 young people aged 13-24. Using an online cross-sectional multivariate logistic regression, the researchers found that a COVID-19 diagnosis was nearly 7 times more likely among dual-users who had smoked cigarettes and vaped within the past 30 days. Testing was 9 times more likely among past 30-day dual users and 2.6 times more likely among past 30-day users of e-cigarettes. Symptoms were nearly 5 times more likely among past 30-day dual users. Because cigarette smoking by itself was not associated with the three outcomes and past 30-day use of e-cigarettes was not associated with COVID-19 diagnosis or symptoms, the authors concluded that dual use presents the greatest risk. Though the authors control for confounders such as BMI and SES, the study suffers several limitations, including self-reporting, wide confidence intervals, and some imprecise conclusions on the relationship between dual use and testing and diagnosis.

In their retrospective cohort study of 1,016 COVID-19 patients in Bangladesh, Islam et al [2] studied risk factors for morbidity and mortality outcomes on the 14th and 28th days from disease diagnosis. The authors found that smokeless tobacco use was significantly higher among patients who died at the 14-day mark and also significantly higher among patients who were not cured on day 28. The authors also conclude—without any substantiating data—that current smoking was not significantly associated with morbidity and mortality outcomes. This study has significant limitations: self-reporting, an inordinate amount of missing data, and a sample with more than 30% of participants from the service industry.

Five recently published systematic reviews and meta-analyses examine risk factors for severe COVID-19 disease progression. All five—the Del Sole study [3]; the Reddy et al study [4]; the Zhao et al study [5]; the Zheng et al. study [6] and the Alqahtani et al. study [7]—are aligned with previous findings on the association between smoking and severe COVID-19 disease progression. It is important to note that these five meta-analyses include 53 studies that have not been covered in

previously published meta-analyses, strengthening the conclusion that there is a positive relationship between smoking and COVID-19 disease progression.

Here is a summary of the main findings as well as limitations of the meta-analyses:

1. **Zhao et al** included 11 case series, with a total of 2,002 cases from December to March 2020. The pooled OR of smoking and the development of severe COVID-19 was 1.98 (fixed‐effects model; 95% CI: 1.29‐3.05). This finding, however, was heavily influenced by one study found during sensitivity analysis; after its removal, the association between active smoking and severe COVID-19 was found to be nonsignificant.
2. **Zheng et al** included 13 studies and a total of 3,027 patients from literature published between January and March 2020. Current smoking was found to be associated with severe disease progression [OR = 2.51, 95% CI (1.39, 3.32), P = 0.0006]. Limitations include that the majority of studies were from China and were cross-sectional.
3. **Alqahtani et al** included a total of 15 studies and 2,473 confirmed COVID-19 patients from literature published up to March 2020. The calculated RR showed that current smokers were 1.45 times more likely [95% CI: 1.03–2.04] to have severe complications compared to former and never smokers. Current smokers also had a higher mortality rate of 38.5%. Limitations include small sample sizes, misclassification of smoking status, and omission of confounders. In addition, most of the studies included were from China, and the studies were heterogeneous in terms of location, setting, and design.
4. **Del Sole et al** included 12 studies with 2,794 patients from literature published up to May 2020 and found that smoking was associated with severe disease (OR: 1.54, 95%CI 1.07-2.22).
5. **Reddy et al** looked at 47 eligible studies reporting on 32,849 hospitalized COVID-19 patients. Current smokers had a significantly increased risk of severe COVID-19 (RR: 1.80; CI:1.14‐2.85; P = .012) and severe or critical COVID-19 (RR: 1.98; CI: 1.16‐3.38; P =.012). Sensitive analysis revealed that when only good quality studies were included—just two met this criteria therefore precluding meaningful interpretation—these associations became non-significant. There were no significant effects of current smoking on disease progression, ICU admission, mechanical ventilation requirement, or mortality. Patients with a smoking history (overall prevalence 26.9%) had a significantly increased risk of presenting with severe or critical COVID-19 (RR: 1.35; CI: 1.19‐1.53; P < .0001), in‐hospital mortality (RR: 1.26; CI: 1.20‐1.32; P < .0001), disease progression (RR: 2.18; CI: 1.06‐4.49; P = .035), and need for mechanical ventilation (RR: 1.20; CI: 1.01‐1.42; P = .043). There was no statistically significant difference in ICU admission. These significant results remained during sensitive analysis when only high quality studies were included.

Smoking, COVID-19, and Biochemistry

A new biochemical study from Cai et al. [8] provides additional evidence on the complicated interplay between nicotine, smoking, and SARS-cov-2 infection. As documented in other published studies, the authors found that ever-smoking substantially increased pulmonary ACE2 expression—in this case by 25%. It remains unclear, however, which particular tobacco smoke constituents cause ACE2 upregulation; some researchers have suggested nicotine, but a study by Zhang et al [9] exposing non-smokers to e-cigarette vapor (with and without nicotine) showed no ACE2 expression change.

In an in vitro study, Purkayastha et al. [10] exposed mucus cultures from non-smoker airway cells to cigarette smoke and then infected them with SARS-CoV-2. The researchers found that exposure to cigarette smoke increased the number of infected airway cells. They also determined that when

airway epithelial cells are infected with SARS-COV-2, interferon response genes are induced but when cells are infected with the virus *and* exposed to cigarette smoke, the interferon response is reduced, producing more severe viral infection and cell death.

And, in an attempt to explain the confoundingly low smoking rates among people infected with SARS-CoV-2, De Bernardis and Busa [11] offer an additional hypothesis. Their premature theory is that tobacco mosaic virus—it is frequently found in both smokers' saliva and cigarettes—induces beneficial interferon and cytokine production, which may protect against coronavirus infection.

References:

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