COVID-19 and TOBACCO: THE UNION MONTHLY BRIEF
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INTRODUCTION

This seventh brief synthesizes the most relevant recent studies, analysing important research published between the last Union brief (1 September) and today. The team reviewed nearly 80 studies and felt it important to highlight three epidemiological studies—two are marked yellow to indicate they are not peer-reviewed—on smoking and COVID-19. One study further strengthens previous findings on the adverse relationship between smoking and COVID-19 disease progression; the second suggests that smoking is significantly associated with poorer COVID-19 recovery; and a third—"a living rapid evidence review"— is a meta-analysis of 233 published or pre-print studies.

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.

Smoking and COVID-19 Progression, Severity, and Recovery

In "Smoking and COVID-19: Adding Fuel to the Fire," Kashyap et al [1] review 181 studies and provide an overview on what is presently understood about smoking's effect on COVID-19 clinical manifestations, disease progression, inflammatory responses, immunopathogenesis, racial ethnic disparities, and disease incidence. Though not a systematic analysis, the authors' review of the epidemiological literature leads them to conclude that smoking is associated with increased COVID-19 disease severity and death in hospitalized patients. In reviewing the biochemical literature, they find that as it upregulates ACE-2 receptors, smoking creates a cytokine storm, which can exacerbate COVID-19 outcomes. In addition, despite limited literature on the relationship between smoking cessation and COVID-19's three disease stages, the authors note that it "is expected to reduce the risk of COVID-19 emerging and severe COVID-19 complications." The paper makes an urgent appeal for research on the relationship between novel products and COVID-19 virulence and tobacco's role in exacerbating COVID-19, with the authors calling for well-designed, population-based studies that control for age and relevant risk factors.

Hussein et al. [2] administered an online questionnaire to 444 recovered COVID-19 patients to determine the effect of age, gender and comorbidities—including smoking—on "post-COVID-19 functional status." (PCFS). Thirteen percent of the sample was current smokers. Eighty percent of cases had functional restrictions—these are categorized as "negligible" (63%); slight (14%); moderate (2%) or severe (0.5%). Though the authors found substantial variance between PCFS score and smoking status (P < 0.001), it is important to note that the scale is both new and not peer reviewed. Smoking's impact on PCFS is an important emerging topic and will be closely monitored in future Union briefs.

In another study on Qeios, Simons et al. [3] used random-effects, hierarchical Bayesian meta-analyses on 233 published or pre-print studies to directly examine the association between smoking status and COVID-19 infection, hospitalization, disease severity and mortality. Of the 233 studies, only 32 were considered "good/fair" quality and included in this updated meta-analysis. (Seventeen of the 32 have not been evaluated in Union briefs.)

The authors find the curious result that current smokers (vs. never smokers) are at reduced risk of infection (RR=0.74, 0.58-0.93). They also find that former smokers were at increased risk of hospitalisation, greater disease severity, and mortality.

The authors identify 11 main study limitations. While the team has enumerated these in previous briefs, their severity—and frequency— warrants additional mention here:

1) There is potential for bias because different subgroups are at increased risk of exposure (e.g. health care workers or family members of positive patients)

2) Prevalence of COVID-19 like symptoms (e.g. cough) may cause smokers to seek testing, thereby increasing the sample size denominator.

3) Acute infection testing requires mucosal epithelium swabbing; these may be disrupted in current smokers, potentially altering assay sensitivity;

4) COVID-19 RT-PCR diagnostic tests may use different platforms with varying sensitivity and specificity to detect infection;

5) Electronic health records often fail to capture smoking status yet remain the most widely used data collection method;

6) Patients with severe COVID-19 symptoms may have stopped smoking just immediately before hospital admission, causing them to be erroneously recorded as non-smokers;

7) Limited access to healthcare may make smokers with COVID-19 less likely to receive a SARS-CoV-2 test and less likely to seek hospitalization but more likely to die at home from sudden complications that are not recorded;

8) If nicotine has a protective effect on COVID-19 disease outcomes, abrupt nicotine withdrawal upon hospitalization may lead to extreme outcomes;

9) When healthcare resources are constrained, current and former smokers with extensive comorbidities may have reduced priority for intensive care admission; this could facilitate higher in-hospital mortality;

10) Studies may not be monitoring patients for the duration sufficient to report complete survival outcomes; and

11) Hospitalizations—and rationale for seeking admission—vary by country and pandemic stage, which might have skewed early data towards less severe cases.

References:

1. Kashyap, V.K., et al., *Smoking and COVID-19: Adding Fuel to the Flame.* International Journal of Molecular Sciences, 2020. **21**(18): p. 6581.
2. Mohamed-Hussein, A.G., Islam; et al., *Post-COVID-19 Functional Status: Relation to age, smoking, hospitalization and comorbidities.* MedRxiv, 2020.
3. Simons, D., et al., *The association of smoking status with SARS-CoV-2 infection, hospitalisation and mortality from COVID-19: A living rapid evidence review with Bayesian meta-analyses (version 7).* Qeios, 2020.