COVID-19 and TOBACCO: THE UNION'S SCIENTIFIC BRIEF Issue #4 (17 July 2020)

INTRODUCTION

This fourth brief synthesises the most relevant recent studies, analysing important research published between the last Union brief (29 June) and today. The team reviewed over 50 studies and felt it important to highlight four epidemiological studies and two 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 epi studies in this brief provide evidence that smokers are more likely to become infected with SARS-CoV-2 (stage 1 disease) and more likely to develop COVID-19 symptoms, possibly requiring hospitalization (stage 2 disease) (Please refer to our main brief for definitions of the three disease stages). These studies suffer several limitations; most notably, their reliance on hospital records to determine smoking status is highly problematic as tobacco use is often underreported in this context. In addition, because the studies are limited in number, further evidence is required before definitive conclusions can be drawn.

The latest biochemical studies on nicotine and SARS-Cov-2 are as weak and inconsistent as those preceding them.

Smoking and COVID-19 progression

Of the four new studies, there are two from the United States [1, 2]; both have relatively small sample sizes, and both further illuminate the challenges in relying on hospital records for smoking status determination. Killerby et al [1] analysed 531electronic medical records, including 220 hospitalized and 311 non-hospitalized COVID-19 patients in a large metropolitan area. Smoking was associated with hospitalization, and smoking prevalence (current or past) was much higher among hospitalized patients compared to non-hospitalized patients (25% vs.12%). Missing data on smoking status—it was not recorded for 17% of non-hospitalized patients and was also absent for 4% of hospitalized patient—is a major study limitation, as is potential for a number of confounding characteristics among the sample population. Mendy et al [2] also used electronic medical records for their data source, analysing information on 689 COVID-19 patients to determine factors associated with hospitalization and severe disease progression. The authors found that current/former smokers comprised 25% of the sample and that there were significantly higher rates of smoking (40%) among hospitalized patients and those with severe disease progression (41%). As with the Killerby study, reliance on hospital records resulted in missing data—smoking status was not available for nearly 23% of patients.

In Mexico City, Bello-Chavolla et al. [3] analysed convenience samples from over 60,000 COVID-19 patients, classifying individuals in three groups—those with respiratory symptoms; those with non-respiratory symptoms; and those who were pre or asymptomatic. The higher smoking rate (11%) among the 54,139 symptomatic patients (compared to 7% among the 3,530 asymptomatic patients) provides some early evidence that smokers may be at increased risk of developing symptoms, but reliance on convenience samples may render the data not representative of the general population.

And, in the UK, Tattan-Birch et al. [4] examined the relationship between COVID-19 and smoking, vaping, NRT usage, and quit attempts among a representative population sample of 3,179 patients. Participants were asked if they had—or think they had—COVID-19 infection; current smokers and

long-term formers smokers were significantly more likely to think they had been infected compared to never smokers. The study is seriously limited by the self-assessment criteria.

Smoking, COVID-19, and Biochemistry

In a published letter to the editor—"COVID-19 and Smoking: Is Nicotine the Hidden Link?"—Russo et al. [5] wrote that they had used in vitro experiments to generate further evidence that nicotine upregulates ACE2 expression through an nAchR mechanism, as previously hypothesized by Olds et al. [6]

In late June, Hedenstierna et al [7] proposed that intermittent high doses of Nitric Oxide emitted from mainstream smoke may inhibit early stage SARS-Cov-2 replication. The authors cited evidence from the 2003 SARS epidemic, noting that Nitric Oxide improved arterial oxygenation in a small sample in China. This theory has not been tested among COVID-19 patients. In addition, one of the co-authors' affiliation with a Nitric Oxide inhaler machine manufacturer raises potential conflict of interest concerns.

The current biochemical evidence on nicotine and SARS-Cov-2 infection is both weak and inconsistent. The impact of smoking and nicotine on COVID-19 progression must be further and more properly addressed in biochemical research.

References:

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2. Mendy, A.A., Senu; et al. , *Factors Associated with Hospitalization and Disease Severity in a Racially and Ethnically Diverse Population of COVID-19 Patients.* MedRxiv, 2020.
3. Bello-Chavolla, O.Y.A.-V., Neftali E.; et al., *Profiling pre-symptomatic and asymptomatic cases with confirmed SARS-CoV-2 infection in Mexico City.* MedRxiv, 2020.
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6. Olds, J.L. and N. Kabbani, *Is nicotine exposure linked to cardiopulmonary vulnerability to COVID-19 in the general population?* Febs j, 2020.
7. Hedenstierna, G., et al., *Nitric oxide dosed in short bursts at high concentrations may protect against Covid 19.* Nitric Oxide, 2020. **103**: p. 1-3.