COVID-19 AND TOBACCO: THE UNION BI-WEEKLY
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INTRODUCTION

This second brief synthesises the most recent studies, analysing important research published between the first Union brief (18 May) and 1 June. In total, the team reviewed five studies on smoking and COVID-19 infection as well as nine biochemical studies focused primarily on the relationship between smoking and SARS-Cov-2, the virus that causes COVID-19.

The studies are consistent with what was documented in the 18 May brief, and The Union maintains its previous positions with regard to smoking and COVID-19:

- **Findings:** It is important to be mindful of studies finding lower smoking rates observed in COVID-19 patients, but the evidence remains inconclusive. Premature conclusions should not be drawn.
- **Study Flaws:** Studies suggesting a protective relationship between nicotine or other tobacco smoke constituents and SARS-Cov-2 infection have significant limitations—in design, in sample size, or by virtue of the fact that they are pending peer review.
- **Logic Must Prevail:** While a precise link between smoking and COVID-19 infection remains to be established, we must rely on what is well-known: 1) that smoking is one of the leading causes of NCDs and 2) according to the WHO, people with cardiovascular disease, chronic respiratory diseases and cancer, among other NCDs, are more likely to experience serious illness or death from COVID-19.
- **Biochemistry:** The relationship between the receptor ACE2 and SARS-CoV-2 has yet to be fully understood. It is premature to draw conclusions about the interplay between smoking, ACE2 and coronavirus infection and disease progression.

Smoking and COVID-19 infection

Of the five new studies on COVID-19 and infection, we eliminated one set in Italy (Rossato et al)[i] because it provided very limited details on study design. Two studies from the US and the UK—Rentsch et al[ii] and de Lusignan et al[iii], respectively—found that smokers were less likely to test positive for COVID-19. Jin et al[iv] used medical records to review 651 confirmed COVID-19 cases in China's Zhejiang province. The authors found a surprisingly low smoking rate (~6percent) among confirmed cases, as compared to the general population.

In the largest study to date (not peer reviewed), Hopkinson et al.[v] used a population-level "symptom app" and asked 2.4 million UK participants to log daily symptoms. Those that reported not feeling "physically normal" were then prompted to respond to an additional 14 questions about COVID-19 symptoms and hospital attendance. Smokers were more likely to develop symptoms suggesting and indicative of a COVID-19 diagnosis, as well as a higher symptom burden. Interestingly, though, smokers were under-represented among a subset who actually *tested* positive for the virus, thereby contradicting the entire sample's findings.

All four studies suffer design limitations; most notable is the potential misclassification of smokers as non-smokers and the high percentage of healthcare workers among the studied patients.

Smoking, COVID-19 and Biochemisty

In an attempt to explain lower smoking rates among COVID-19 patients, several recently published studies have tried to elucidate the smoking and SARS-Cov-2 interaction. Of central interest is ACE2,

a receptor and entry port that allows SARS-Cov-2 to invade human cells. Important clinical data[vi] shows smokers with increased expression of ACE2 in airway and lung tissues. But another study[vii] shows that smokers' ACE2 receptors were suppressed in adipose (fat) tissues.

There is general consensus that increased ACE2 expression leads to higher risk of SARS-Cov-2 infection. At the same time, some speculate that smokers' elevated ACE2 levels may reduce lung injury morbidities from COVID-19[viii] (Lippi et al). This would mean that while smokers are more likely to become infected with the coronavirus, they are less likely to experience adverse disease outcomes.

At the present time, we cannot draw a conclusion on the net impact of smoking on ACE2 and SARS-Cov-2 infection. It is likely that multiple mechanisms, with counteracting effects, are involved in the interaction between smoking and ACE2.

Additional research is needed to clarify the relationship.

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[i] Rossato M, Russo L, Mazzocut S, Di Vincenzo A, Fioretto P, Vettor R. Current Smoking is Not Associated with COVID-19 [published online ahead of print, 2020 Apr 29]. *Eur Respir J.* 2020;2001290. doi:10.1183/13993003.01290-2020 https://erj.ersjournals.com/content/early/2020/04/27/13993003.01290-2020.full

[ii] Rentsch et al: Covid-19 Testing, Hospital Admission, and Intensive Care Among 2,026,227 United States Veterans Aged 54-75 Years https://www.medrxiv.org/content/10.1101/2020.04.09.20059964v1

[iii] de Lusignan S, Dorward J, Correa A, et al. Risk factors for SARS-CoV-2 among patients in the Oxford Royal College of General Practitioners Research and Surveillance Centre primary care network: a cross-sectional study [published online ahead of print, 2020 May 15]. *Lancet Infect Dis*. 2020;S1473-3099(20)30371-6. doi:10.1016/S1473-3099(20)30371-6

[iv] Jin X, Lian J, Hu J, et al. "Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infect disease 2019 (COVID-19) with gastrointestinal symptoms." *Gut, BMJ*. 2020; 69:1002-1009. doi: http://dx.doi.org/10.1136/gutjnl-2020-321195

[v] Hopkinson et al Current tobacco smoking and risk from COVID-19: results from a population symptom app in over 2.4 million people. https://www.medrxiv.org/content/10.1101/2020.05.18.20105288v1.full.pdf

[vi] Li G, He X, Zhang L, et al. Assessing ACE2 expression patterns in lung tissues in the pathogenesis of COVID-19 [published online ahead of print, 2020 Apr 13]. *J Autoimmun*. 2020;102463. doi:10.1016/j.jaut.2020.102463)

[vii] Buil, A., et al. Gene-gene and gene-environment interactions detected by transcriptome sequence analysis in twins. Nature genetics 47, 88-91 (2015).

[viii] Lippi G, Sanchis-Gomar F, Henry B. "Active Smoking and COVID-19: A Double-Edged Sword." *European Journal of Internal Medicine*. 2020. doi: https://doi.org/10.1016/j.ejim.2020.04.060