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On April 21, two linked studies were published (<u>Miyara et al</u>. and <u>Changeux</u> <u>et al</u>.), neither of which has been formally peer-reviewed. Both are on the website <u>Qeios</u> which allows authors to upload studies without peer-review in order to expedite publication and access to findings. The <u>first study (Miyara et al.</u>) is a small study which examined smoking rates among patients with COVID-19 in a single hospital in Paris. It compared smoking rates in patients with smoking rates in the French population as a whole. The principal finding was that among patients with COVID-19 (including out-patients and in-patients, but excluding those most ill in intensive care), current smoking rates were low. <u>There are significant limitations in the study design</u> which suggest it is likely to under-estimate levels of current smoking. Further, as the study was based in a hospital where it appears that a significant proportion of the cases were health care workers, it can say little about the risk of acquiring infection in the community. Nevertheless, it used its tentative findings to make strong claims¹ that smoking protects against infection with SARS-CoV-2 and recommend that nicotine may therefore provide a route to protecting against disease.

These tentative findings are then expanded on in a <u>second study</u> (<u>Changeux et al.</u>) which proposes a new hypothesis of how the virus might enter the body and cause neurological disease, arguing that nicotine could reduce the risk and provide a new treatment option.

While the evidence base is changing rapidly, it is important to note that the findings of these studies are inconsistent with the broader emerging literature on the links between smoking and COVID-19 and more widely accepted <u>hypotheses on how infection occurs</u>.

Nevertheless, the press coverage of these studies has unfortunately failed to identify the study weaknesses and the existence of evidence to the contrary, leading to potentially dangerous misinformation that smoking may be protective and prompting people to <u>panic buy</u> nicotine.

Further, while no source of funding for his paper is detailed, we note that Changeux, the lead author of the second paper, has long-standing historical links with the tobacco industry: Between 1995 and 1998 he received grants amounting to a total of USD \$220,000 from the Council for Tobacco Research;² in the late 1990s he became a collaborator and advisor for Targacept, a pharmaceutical subsidiary of the tobacco company RJ Reynolds;³ and in 2006/2007 he supervised and published studies funded by Philip Morris International.⁴

¹ For example, the conclusions states that the study "strongly suggests that daily smokers have a very much lower probability of developing symptomatic or severe SARS-CoV-2 infection".

² The Council for Tobacco Research was formerly known as the Tobacco Industry Research Committee, which was established in 1953 by the major tobacco companies to help produce research that would help them obscure the links between smoking and serious illness. See <u>https://www.tobaccotactics.org/index.php/Tobacco_Industry_Research_Committee</u>

Changeux's involvement with the Council has been amply discussed in an investigation by Le Monde, available here: <u>https://www.lemonde.fr/sciences/article/2012/05/31/</u> guerre-du-tabac-la-bataille-de-la-nicotine_1710837_1650684.html

Changeux's letter in which he approaches the Council for funding is available here: https://www.industrydocuments.ucsf.edu/tobacco/docs/#id=xzkw0085 ³ For internal documents by Targacept identifying Changeux as a key advisor see https://www.industrydocuments.ucsf.edu/tobacco/docs/#id=mhkx0190 and https://www.industrydocuments.ucs

⁴ Changeux's ties with Philip Morris International have been discussed in Eker F, Béguinot E, Martinet Y, Ingérence de l'industrie du tabac dans les politiques de santé publiques. Comité National Contre Le Tabagisme, Paris, 2014, pp. 89, 280. Philip Morris-funded studies co-authored by Changeux include <u>https://www.pnas.org/content/103/45/16965</u>

Broader Context on Links Between Smoking and COVID-19

It is vital to put new studies in the broader context:

1. The best evidence to date on smoking and coronavirus suggests smokers are at greater risk of poor outcomes:

- Early in the pandemic, Chinese case series showed that current smoking is associated with more severe disease: For example, amongst <u>1,099 patients from 552 hospitals in China</u>, smokers were 2.4 times more likely to have adverse outcomes than non-smokers.¹
- One early <u>systematic review</u> of the evidence found that smoking is likely associated with negative progression and adverse outcomes, <u>another described "a trend towards higher risk but no significant</u> <u>association," and a third found that "smokers had 2.23 times the odds</u> <u>of severe COVID-19 outcomes than never smokers."</u>
- A more recent and <u>regularly updated "living" review</u>, currently including 28 studies, reaches similar conclusions—that the evidence suggests current and former smoking are associated with greater disease severity in hospitalized patients.

2. There is evidence to suggest that active and former smoking and possibly nicotine use can increase the risk of infection with SARS-CoV-2, including neuroinfection:

- It is known that SARS-CoV-2 enters the cells via the <u>ACE-2 receptor</u>. There is evidence that <u>smoking</u>, <u>former smoking</u>, <u>COPD</u> (a smoking-caused disease), and <u>nicotine</u> can <u>increase expression</u> of the ACE-2 receptors through which infection occurs thus providing a hypothesis for why current and former smoking, as well as nicotine users, could in fact be at greater risk.
- It has also been proposed that nicotine might <u>increase the risk</u> of neuroinfection.
- The WHO has also suggested that behavioural factors such as the hand-to-mouth action during smoking may also put smokers at greater risk of infection.
- Although some studies suggest smoking rates amongst those with coronavirus infection are lower than expected, continued careful analysis of these studies is required and their interpretation must take into account the broader evidence base as it develops.

3. More broadly, smoking is highly damaging to health and experts are urging smokers to quit:

• Smoking kills at least one in two, and likely <u>two in three</u>, long-term users. It damages the <u>immune system</u>, <u>increasing susceptibility</u> <u>to infections including</u> viral infection and pneumonia, and causes diseases such as lung and heart disease which are <u>linked to poor</u> <u>outcomes</u> from coronavirus. Smokers therefore have more reasons than ever to quit. ⁱ This is based on a relative risk of adverse outcomes in this study: Smokers had a relative risk of 2.4 (95% Confidence Interval: 1.43–4.04) compared to nonsmokers, this was not calculated in the original study but was derived by Vardavas et al in their systematic review using data provided in the tables of the article (https://www.ncbi.nlm.nih.gov/pmc/articles/ PMC7083240/)