

Review of: "Low incidence of daily active tobacco smoking in patients with symptomatic COVID-19"

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This is a small study in a single hospital in Paris which examined smoking rates among patients with COVID-19. 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 not those most ill on intensive care), current smoking rates are low. Despite significant limitations in the study design which suggest it is likely to under-estimate levels of current smoking and, as it is based in a hospital where a significant proportion of cases were health care workers likely to acquire their infection in hospital, can say relatively little about the risk of acquiring infection in the community, it uses its tentative findings to claim that smoking protects against infection with SARS-CoV-2.

There are a number of concerns with this study which include the following:

1. Many of the cases are health-care workers (a fact only acknowledged in the discussion). Health-care workers are most likely to acquire the infection in hospital rather than in the community. The study can therefore say little about community acquisition of COVID-19.

Further, as health care workers have low rates of smoking and cannot smoke in the hospital, this study can say little about the very topic it purports to study – whether smoking influences the risk of COVID-19 within the population.

2. The study's estimates of current smoking among patients with COVID are likely to be an artefact of the study design:

- a. a lot of the cases were in health care staff who often have lower rates of smoking;
- b. the most severe cases (those admitted to ICU) were excluded, yet there is evidence that smoking is associated with severe disease.

- c. the study was in an area with below average smoking rates for France (see http://beh.santepubliquefrance.fr/beh/2018/14-15/2018_14-15_1.html)

- d. smoking status was based on self-reported survey questions, which tend to

underestimate smoking status due to social desirability bias (<https://academic.oup.com/ntr/article/11/1/12/1043552>). Furthermore, during a health crisis where hospital beds and access to ITU may be rationed based on potential for positive outcome there may be a particular incentive to report as an ex- rather than current-smoker.

3. While the proportion of current smokers (34/482, 7%)[¹] is lower than in the French population as a whole (32%, http://beh.santepubliquefrance.fr/beh/2019/15/2019_15_1.html), the study ignores the fact, that the proportion of ex-smokers (285/482, 59%) is much higher (31.4%). As such, the proportion of “ever smokers” (current and ex-smokers combined) in the study (66%) is broadly in line with the French population (63%). [2018 data for France - Figure 1 in http://beh.santepubliquefrance.fr/beh/2019/15/2019_15_1.html]. Yet:
 - a. The authors make no comment on this issue. While the underlying numbers are presented in the table, the authors do not calculate the prevalence of ex-, ever- or never smoking, nor compare these levels to the French population thus overlooking a significant weakness in the study.
 - b. Given both the incentives to self-report as an ex-smoker (see 2d), the unexpectedly low current smoking yet high ex-smoking rates, it seems inappropriate to compare just current smoking rates with the French population.

4. It is known that ex-smokers and particularly those who recently quit are likely to use nicotine (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4236146/>). Yet the study makes no attempt to determine whether the ex-smokers are using nicotine. Given the high proportion of ex-smokers in the study with COVID-19, it seems wholly inappropriate to suggest that nicotine, yet alone smoking, are protective without first obtaining this information. This is particularly the case when this hypothesis goes against more widely accepted hypotheses (for which there is arguably more evidence) that smoking (<https://www.mdpi.com/2077-0383/9/3/841>, both active and former smoking, <https://erj.ersjournals.com/content/early/2020/03/26/13993003.00688-2020>) and nicotine (<https://febs.onlinelibrary.wiley.com/doi/full/10.1111/febs.15303>) increase the expression of the ACE-2 receptors through which the virus enters cells (<https://blogs.bmj.com/bmj/2020/03/20/covid-19-the-role-of-smoking-cessation-during-respiratory-virus-epidemics/>). Indeed one study (<https://www.medrxiv.org/content/10.1101/2020.02.05.20020107v3>) finds that former smokers may be especially susceptible. It has also been hypothesised that nicotine might increase the risk (<https://www.medrxiv.org/content/10.1101/2020.02.05.20020107v3>) of

neuroinfection.

5. These very significant biases and weaknesses are under-explored and under-played in the paper which also fails to examine how the findings of this study differ to other studies and hypotheses on this topic. For example there is evidence that smoking (<https://www.mdpi.com/2077-0383/9/3/841>), former smoking (<https://erj.ersjournals.com/content/early/2020/03/26/13993003.00688-2020>), COPD (a smoking caused disease, <https://erj.ersjournals.com/content/early/2020/03/26/13993003.00688-2020>), and nicotine (<https://febs.onlinelibrary.wiley.com/doi/full/10.1111/febs.15303>) can all increase expression (<https://erj.ersjournals.com/content/early/2020/03/26/13993003.00688-2020>) of the ACE-2 receptors through which SARS-CoV2 infection occurs thus providing a hypothesis for why current and former smoking, as well as nicotine users, could in fact be at greater risk of infection. It has also been hypothesised that nicotine might increase the risk (<http://molpharm.aspetjournals.org/content/early/2020/04/01/molpharm.120.000014>) of neuroinfection. It would be normal practice for the authors to note this countervailing literature.

6. By failing to address these issues, the authors tend to overstate their findings (eg the abstract 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”). This has undoubtedly contributed to the way in which this study has been taken out of context by the press.

[i] This includes active (22) and occasional (12) smokers