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Commentary

Successful Cessation Programs that Reduce Comorbidity may Explain Surprisingly Low Smoking Rates among Hospitalized COVID-19 Patients

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Recent, non-peer-reviewed reports and meta-analyses suggest that smoking may reduce the risk of hospitalization with COVID-19, because the prevalence of smoking among hospitalized COVID-19 is less than that of the general population. However, there are two alternative classes of explanations for this phenomenon. Class (1) is the failure to report, or to accurately record, smoking history during emergency hospital admissions and other interviews. Face-to-face interviews can introduce bias into the responses to attitudinal and behavioral questions not present in the self-completion interviews typically used to measure smoking prevalence in the general population. Subjects in face-to-face interviews may be unwilling to admit socially undesirable behavior and attitudes under direct questioning. For example, urine testing of hospitalized patients for cotinine showed that smokers were under-counted by 37% because incoming patients failed to inform staff about their smoking behavior. Class (2), various types of "reverse" causation, including a pre-disposition to avoid smoking among COVID-19 patients with tobacco-related comorbidities, may also contribute to the difference between smoking prevalence in the COVID-19 and general population. Patient cohorts hospitalized with COVID-19 may be less prone to use tobacco than the general population. A potentially robust "reverse causation" hypothesis for reduced prevalence of smokers in the COVID-19 population is enrichment of patients in the population with serious comorbidities that have previously motivated them to quit smoking. We ask whether this "smoking cessation" mechanism accounts for a detectable fraction of the reduced prevalence of smokers in the COVID-19 population. Testing this hypothesis will require a focused research program.

There will never be a medical justification for smoking tobacco or using smoke-cured, tobacco products. Nevertheless, a recent non-peer-reviewed meta-analysis suggests that smoking may reduce the risk of hospitalization with COVID-19[1]. An early study of COVID-19 patients in Wuhan reported a value of 6% for the prevalence of smoking in 78 patients[2]. More recent (April, 2020), peer-reviewed studies report that Chinese and American patient populations hospitalized for COVID-19 present a prevalence for smoking that is markedly lower than (or insignificantly different from) that of the surrounding population[2][3][4]. A non-peer-reviewed paper makes similar claims about French COVID-19 patients[5]. In the meta-analysis cited above[1], values of smoking prevalence reported for Chinese COVID-19 patients range from 1.4% to 12.6%, with an overall prevalence of 6.5% in a population of 5960 patients (13 studies). In contrast, smoking prevalence for the Chinese population at large is estimated to be 26.65%. Thus, Chinese smokers appear to be less frequently counted among COVID-19 patients than among the population at large. Similar findings are reported for American and French COVID-19 patients.

Do these data mean that smoking protects smokers from being hospitalized with COVID-19? Frankly, it seems unlikely that smoking prevents viral exposure or viral entry into the respiratory system. However, it is conceivable that, once the virus enters the airways, a cellular / pharmacological mechanism allows nicotine or smoking to reduce the initial probability, or severity, of disease progression. Our research group has spent decades conducting research on the molecular actions of nicotine. It is of course possible, and perhaps eventually testable in animal models, that events downstream from interactions between nicotine and nicotinic acetylcholine receptors (nAChRs) (including α4β2, α3β4, and/or α7 nAChRs) exert protection against COVID-19. These mechanisms could include changes in angiotensin converting enzyme 2 (ACE2) levels[6][7] and/or suppression of inflammatory pathways[8][9]. Treatment with nicotine patches, nicotine gum, or even electronic nicotine delivery systems (ENDSs) could provide nicotine without the other harmful effects of smoking.

Yet, once COVID-19 patients are admitted to the hospital, any hypothesized protection apparently disappears. There is no evidence that smokers admitted to hospitals present less severe COVID-19 symptoms than non-smokers. Two meta-analyses show that smoking either increases, or does not affect, the odds ratio for finding smokers in the severely ill COVID-19 population. In fact, an extensive meta-analysis of the association between smoking and COVID-19 severity reports an overall two-fold increase in the odds ratio for finding smokers among the severe COVID-19 patients, and the increase is significant[2]. Inclusion in the severe COVID-19 patient group was based on the American Thoracic

Society guidelines for community-acquired pneumonia[4]. A less extensive meta-analysis reports no significant association between active smoking and COVID-19 severity[10]. Thus, smoking "protection"—if it exists--appears to apply only to non-hospitalized individuals. These surprising results call for confirmation and mechanistic explanations.

Other than the cellular / pharmacological "protection" mechanisms briefly described above, one can envision at least two straightforward, alternative explanations for the reduced prevalence of smokers in the COVID-19 patient population. The first explanation is systematic bias in identifying smokers in the hospital patient population, compared to the general population. The second is "reverse causation".

Hospital admissions staff could systematically underestimate the number of smokers among COVID-19 patient because (1) patients fail to inform hospital staff of their smoking history or (2) obtaining accurate medical histories under emergency conditions is problematic. For example, urine testing of hospitalized patients in Australia for the nicotine metabolite cotinine revealed that the admissions staff under-counted active or previous smokers by 37% because patients failed to accurately inform staff about their smoking behavior[11]. Previous studies by survey methodologists show that face-to-face interviews can introduce biases in certain types of attitudinal and behavioral questions not present in self-completion interviews[12][13]. Subjects in face-to-face interviews may be unwilling to admit socially undesirable behavior and attitudes under direct questioning[14]. In contrast to face-to-face interviews, government agencies and academic researchers find no evidence for strong social desirability bias in self-reported surveys of smoking behavior[15][16][17]. Considering the conditions under which COVID-19 patients may be interviewed during hospital admission, there are justifiable reasons to suspect the accuracy of smoking histories obtained from these interviews. COVID-19 patients may be quite ill with severe respiratory symptoms, including coughing, trouble breathing, and shortness of breath. They are probably wearing a mask and will likely encounter health care professionals who are themselves masked, gloved, and wearing face protection, impeding both verbal and visual doctor-patient communication. Patients may find it difficult to answer questions, wish to hurry through the interview process, and downplay potentially risky behaviors such as smoking. Even well-intentioned health care professionals may not conduct thorough interviews because of stress and overwork. For example, in a large Chinese study (Table 3 of [18]), patients with unknown smoking status were lumped together with non-smokers in a single non-smoking category (Never/unknown). Thus, failure to correctly identify active and previous smokers at the time of hospital admission could reduce estimates of smoking prevalence among COVID-19 patients, relative to the general population.

A second alternative explanation is "reverse causation". Patients hospitalized with COVID-19 may be simply less prone to use tobacco. A potentially robust "reverse causation" hypothesis for reduced prevalence of smokers in the COVID-19 population is the enrichment of patients in that population with serious comorbidities that motivates them to quit, or avoid, smoking. That is, COVID-19 patients with comorbidities could be less prone to smoke.We call this explanation the "smoking cessation" hypothesis. Antismoking campaigns have effectively reduced smoking in recent decades. The smoking rate among American adults was 42-45% in the mid-20th Century. It is now ~ 14% [19]. Antismoking campaigns emphasize that individuals with underlying medical conditions exacerbated by smoking—diabetes, cardiovascular disease, obesity, cancer--should quit. Consequently, individuals with these conditions may smoke less (perhaps by several fold) or cease smoking all together. Several important risk factors for tobacco-related disease—hypertension, obesity, and diabetes--overlap substantially with COVID-19 risk factors. It seems likely that such high-risk individuals have altered their behavior to smoke less or quit altogether. If so, this population presents a lower smoking prevalence than the general population. If individuals who quit smoking because of tobacco-related disease contract COVID-19 and become hospitalized, their low smoking prevalence is expected to reduce that of COVID-19 patients in general because patients with such comorbidities comprise a major fraction of the COVID-19 population [20]. In other words, we suggest that successful intervention in the high-risk groups during the pre-COVID-19 years, by antismoking campaigns, medical providers, and family members, has reduced smoking prevalence in the COVID-19 population. Also, many nursing homes prohibit smoking. Nursing facilities contribute large numbers of patients to the COVID-19 population. We judge that the "smoking cessation" mechanism may account for a significant fraction of the reduced prevalence of smokers in the COVID-19 population. Testing this hypothesis will require a focused research program. Our judgement that "protection" is unlikely derives, in part, from considering the history of research on the negative correlation between smoking history and the lifetime risk of Parkinson's disease (PD, see Note 1). Despite repeated attempts, there are no reports of successful efforts to ameliorate Parkinson's disease with nicotine patches or other nicotine replacement therapy.

Testing the "Smoking Cessation" vs "Protection" Hypotheses

Medical histories and records taken during hospital admission provide the currently available epidemiological data. Oral histories of patient lifestyle are likely to be rushed or incomplete during a pandemic. In contrast, smoking data from smoking prevention and cessation programs collected by

health maintenance organizations (HMOs) are reliable[21]. Subjects typically enter these programs because they have a high risk of tobacco-related disease and wish to reduce their risk by smoking cessation[22][23][24]. In many cases, the programs follow patients for twelve months or more and classify them as "successful" and "unsuccessful" quitters. Smoking status and participation in smoking cessation programs are now part of electronic medical records, which allow HMOs to routinely determine whether subjects have become COVID-19 patients.

Smoking could both increase the probability of COVID-19 hospitalization by exacerbating smoking-related diseases and exert a protective effect by a still unidentified mechanism. Mindful of this complication, preliminary studies could test the contrasting predictions made by the "smoking cessation" and "protection" hypotheses. For individuals without pre-existing medical conditions (such as hypertension, chronic obstructive pulmonary disease (COPD), or diabetes) prior to hospitalization with COVID-19, the predictions are straightforward. The "smoking cessation" hypothesis predicts that successful (ex-smokers) and unsuccessful quitters (active smokers) will present a similar incidence of COVID-19 hospitalizations during the pandemic. In contrast, the "protection" hypothesis predicts that, in general, active smokers will present a lower incidence. The predictions become more complicated for individuals with smoking-related diseases prior to COVID-19 hospitalization because continued smoking is expected to exacerbate these diseases. For individuals with smoking-related diseases, the "smoking cessation" hypothesis predicts that successful quitters will present a similar, or lower, incidence of COVID-19 hospitalization compared to unsuccessful ones because failure to quit could exacerbate COVID-19 comorbidities. Predictions for the "protection" hypothesis depend on whether the deleterious effects of continued smoking on COVID-19 comorbidities outweigh its protective effects. Thus, predictions in this case are difficult to make *a priori.* Such an analysis will make an important contribution to mechanistic discussions about the low smoking prevalence of COVID-19 patients.

Predictions are also less clear for patients who have stopped smoking because they take varenicline—a nicotinic partial agonist—or because they use ENDSs. Data on these subjects will increase the interest of the studies. Confounding variables include the possibility that smokers put their hand near their mouths more often than non-smokers, increasing the likelihood of infection.

Finally, it will also be important to know how many COVID-19 patients stopped smoking when they felt the irritation of initial COVID-19 symptoms. As HMOs treat more COVID-19 patients, and increasingly test members for SARS-CoV-2 infection and antibodies, their databases will become troves of information about the interactions between lifestyle choices, such as smoking, and COVID-19. It will eventually be

possible to query all tested members, including those who have not been hospitalized and those who stopped smoking voluntarily.

This commentary emphasizes the knowledge to be gained by analyzing smoking behavior in depth before and during the COVID-19 pandemic. If, over the upcoming years, the "smoking cessation" hypothesis increases support for health maintenance organizations, their antismoking campaigns deserve congratulations. Their successful efforts at prevention and cessation will have mitigated harm among individuals at risk for tobacco-related disease and possibly COVID-19.

Declaration of Interests

None declared.

Note 1.

More than 70 studies, beginning in 1959[25], report a negative correlation between smoking and PD. These studies are both case-control and cohort. The overall average odds ratio for the PD effect is ~2; the odds of finding smokers in the PD patient population are half that of finding them in the PD-free controls.

Data with animal models and cultured dopaminergic neurons further suggest that nicotine may underlie this negative correlation[26]. A plausible biological mechanism proposes that the interaction between

nicotine and nicotinic acetylcholine receptors in the endoplasmic reticulum (ER) reduces ER stress and the unfolded protein response[27] which, in turn, reduce the risk of PD.

Alternatively, "reverse causality" could explain this negative correlation. Anecdotally, neurologists report that early-stage PD patients stop smoking, even though they display few or no minor motor symptoms. Mechanistically, this tendency could be explained by damage to dopaminergic neurons during the prodromal stage, so that the prodromal patient derives less reward from activation of the nicotinic receptors on those neurons[28][29]. Regardless of the "reverse causality" mechanism, the result is that, several years later, when patients are diagnosed with PD, the PD population has a dearth of smokers and the non-PD population is comparatively enriched in smokers. This hypothesis postulates that the apparent neuroprotective effect of smoking occurs because PD patients are less likely to smoke—not because smokers are protected.

A "reverse causality" mechanism for COVID-19 based on patient behavior (COVID-19 patients with severe co-morbidities smoke less, rather than that smokers are protected) is analogous to that for PD.

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Declarations