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Commentary: Smoking, nicotine and COVID-19 outcomes: unprecedented challenges to epidemiologists

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Very important research questions

Amid the COVID-19 pandemic, epidemiologists have been conducting numerous studies on questions related to COVID-19. Smoking impairs lung function and causes upper and lower respiratory infection, chronic obstructive pulmonary diseases, cardiovascular diseases and many cancers. Whether smoking alters the risk of COVID-19 infection and its outcomes is an important question which has motivated many epidemiologists to investigate and share their emerging findings as quickly as possible. In a context where health systems are under enormous pressure and the pandemic itself is rapidly evolving, the challenge of minimizing error in such investigations is particularly pronounced. The study by Gao *et al*. is one of the earliest investigations of COVID-19, conducted using linked primary care and hospitalization and death registration records from a 3-month period (24 January to 30 April 2020) coinciding with the first wave of the pandemic in England.[1] Its major strengths were: (i) the prospective analysis with smoking data collected before outcomes; (ii) the very large community sample of 7 869 534 people from 1205 general practices, representing 20% of English practices; and (iii) the use of several methods to address confounding.

The authors reported that current smokers showed lower risks of severe COVID outcomes—hospitalization, intensive care unit admission and death—attributed to COVID-19, by one-third, two-thirds and one-fifth, respectively, compared with never smokers, but the hazard ratios (HRs) showed no trend by number of cigarettes. The HRs in former smokers were small (1.01–1.17). The HRs were non-significantly increased (1.04–1.12) for electric cigarette (e-cigarette) use without smoking. However, in current and former smokers, higher risks of all-cause mortality (HR, 1.42 and 1.11, respectively) were observed.

Despite the above strengths, there are substantive challenges in interpreting the results of this and similar studies. These are addressed here under two broad headings:

methodological problems (relating to the potential for errors in this particular study), and challenges in interpreting the wider evidence base (including other studies on the link between smoking and COVID-19).

Methodological problems

In general, the major challenge when using data from record linkage is that subjects were not selected and recruited, and exposure, outcome and confounder data were not collected specifically for the research questions. This leads, potentially, to selection and misclassification biases. For example, the cohort of Gao *et al.*[1] was limited to people registered with a general practitioner (GP). This could result in selection bias if groups with lower general practice registration rates (e.g. those with greater residential mobility) also had a higher prevalence of smoking. Such bias might distort the observed HRs if these groups were also at higher risk of serious COVID-19 outcomes, for instance, due to higher levels of comorbidity. The potential for exposure misclassification is illustrated by the much lower prevalence of e-cigarette use reported in the study cohort than in contemporaneous survey estimates of national prevalence (0.8% vs 5%),[1] suggesting under-recording of e-cigarette use in general practice records.

The risks of selection and information bias were likely heightened during the first wave of COVID-19. During the study period of *Gao et al.*,[1] the risk of information and classification errors of COVID-19 outcomes could be high, given the limited availability of COVID-19 tests in England. Population testing was not available, and testing in hospitals was not yet comprehensive.

During explosive COVID-19 outbreaks, the health care systems of many countries were severely tested. Primary and ambulatory care, COVID-19 testing, diagnosis and treatments (including intensive care) were not always readily available, and decision making might not have been consistent across different settings. These factors could have affected the accuracy and completeness of record keeping, including clinical and cause-of-death data. The potential for misclassification with respect to COVID-19 diagnosis would have been exacerbated where COVID-19 tests were in short supply, as was the case in England during the study period.

The authors note that around a fifth of deaths in their cohort occurred in people who were never admitted to hospital. Non-random outcome misclassification could be substantial if current smokers with COVID-19 were less likely to be hospitalized, tested and diagnosed than never smokers.

Whether the observed results were substantially biased towards or away from null by each of the methodological problems of exposures and outcomes individually, and by the combination of different problems together, could not be ascertained.

In contrast to COVID-specific estimates, all-cause mortality is less vulnerable to misclassification arising from a lack of comprehensive testing. We might therefore have more confidence in the finding of Gao *et al.* that current smokers had higher all-cause mortality than either former or never smokers.[1]

Interpreting the wider evidence base

Many of the above limitations are also reflected in the wider evidence base. The most up-to-date rapid living evidence review by Simons *et al.* (13 August 2021, Version 12),[2] cited by Gao *et al.*,[1] concluded that 'current smokers appear to be at reduced risk of SARS-CoV-2 infection and increased risk of greater in-hospital disease severity, while former smokers appear to be at increased risk of in-hospital disease severity and mortality from COVID-19. However, it is uncertain whether these associations are causal'. Note that, of the 547 studies included, only 87 rated as of good or fair quality were included in the meta-analysis. Nevertheless, a recent meta-analysis of observational studies showed that current and former smokers had higher risk of COVID-19 death.[3]

Gao *et al.* cited the study by Clift *et al.*[4] (not included by Simons *et al.*[3]) combining observational analysis and Mendelian randomization using the UK Biobank cohort, which reported that current smoking was associated with elevated risk of severe COVID-19. Gao *et al.* stated that 'the conflicting results are hard to reconcile'.[1] However, in another recent Mendelian randomization study using summary statistics from genome-wide association studies (GWAS), FinnGen and UK Biobank showed 'genetic evidence that smoking probably increases the risk of severe COVID-19 and possibly also milder forms of COVID-19'.[5] Moreover, a meta-analysis found six Mendelian randomization studies which consistently demonstrated 'strong associations of smoking traits, including smoking initiation, smoking heaviness and lifetime smoking index (which combined smoking initiation, duration, heaviness and cessation), in the risk of COVID-19 severity, hospitalzation and mortality', and the authors suggested that the mechanism may be 'an increased expression of ACE2, a receptor for SARS-CoV-2 in the airway epithelium' in smokers.[6]

The quality of evidence would be strengthened by including more population-based studies with longer follow-up and taking account of potential effects from different pandemic waves and SARS-Cov-2 variants, changes in infection control measures, and varying health system

factors (including changes in COVID-19 treatment). The relationship between smoking and long COVID should also be studied as an important outcome.

Given the robustness of Mendelian randomization studies and the fact that the findings are consistent with two meta-analyses of conventional observational studies, the total weight of evidence favours the conclusion that smoking increases the risk of COVID-19 morbidity and mortality, in my view. Amid the pandemic and beyond, the most urgent public health advice to smokers is to quit completely.

Ethics approval

Not applicable.

Data availability

Not applicable.

Conflict of interest

None declared.

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