The association of smoking status with SARS-CoV-2 infection, hospitalisation and mortality from COVID-19: A living rapid evidence review (version 3)

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\textbf{Abstract}

\textbf{Background:} SARS-CoV-2 is the causative agent of COVID-19, an emergent zoonotic disease which has reached pandemic levels and is designated a public health emergency of international concern. It is plausible that former or current smoking status are associated with infection, hospitalisation and/or mortality from COVID-19.

\textbf{Objective:} We aimed to estimate the association of smoking status with rates of i) infection, ii) hospitalisation, iii) disease severity, and iv) mortality from SARS-CoV-2/COVID-19.

\textbf{Methods:} We adopted recommended practice for rapid evidence reviews, which involved limiting the search to main databases and having one reviewer extract data and another verify. Published articles and pre-prints were identified via Ovid MEDLINE, medRxiv and expertise within the review team. We included observational studies with community-dwelling or hospitalised adults aged 16+ years who had been tested for SARS-CoV-2 infection or diagnosed with COVID-19, providing that data on smoking status were reported. The National Institutes of Health's Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies was used to divide studies into 'good', 'fair' and 'poor' quality to address objectives of this review. Studies were judged as 'good' quality if they: i) had low levels of missing data on smoking status, ii) used a reliable self-report measure that distinguished between current, former and never smoking status, iii) used biochemical verification of smoking status and iv) adjusted...
analyses for potential confounding variables.

Results: Sixty-seven studies were included, 30 of which were conducted in China, 12 in the US, six in the UK, four in France, three in Mexico, three in Spain, two across multiple international sites, two in Italy, and one each from Iran, Israel, Korea, Kuwait and Switzerland. Eleven studies did not state the source for information on smoking status. Fifty-one studies reported current and/or former smoking status but had high levels of missing data and/or did not explicitly state whether the remaining participants were never smokers. Notwithstanding recording uncertainties, compared with national prevalence estimates, recorded current and former smoking rates in most studies were lower than expected. In six ‘fair’ quality studies, no significant difference was observed between current and never (RR = 0.78, 95% CI = 0.55-1.11, p = .17, I² = 92%) or former and never smokers (RR = 1.07, 95% CI = 0.95-1.20, p = .24, I² = 61%) in the risk of testing positive for SARS-CoV-2. In five ‘fair’ quality studies, there was no significant difference between current and never (RR = 1.12, 95% CI = 0.74-1.69, p = .48, I² = 84%) or former and never smokers (RR = 1.21, 95% CI = 0.82-1.79, p = .24, I² = 81%) in the risk of requiring admission to hospital following diagnosis of COVID-19. In three ‘fair’ quality studies, current smokers were at increased risk of greater disease severity compared with never smokers (RR = 1.37, 95% CI = 1.07-1.75, p = .01, I² = 0%). No significant difference was observed between former and never smokers (RR = 1.51, 95% CI = 0.82-2.80, p = .19, I² = 81%). In three ‘fair’ quality studies, there were inconsistent results on mortality from COVID-19 in current and former compared with never smokers.

Conclusions: Across 67 observational studies, there is substantial uncertainty about the associations between smoking and COVID-19 outcomes. The recorded smoking prevalence in hospitalised patients was lower than national estimates but this observation is inconsistent with there being no evidence of increased admission to hospital from five ‘fair’ quality studies of people who tested positive. There was limited evidence from ‘fair’ quality studies that current compared with never smoking is associated with greater disease severity in those hospitalised for COVID-19.

Implications: Unrelated to COVID-19, smokers are at a greater risk of a range of serious health problems, requiring them to be admitted to hospital. Given uncertainty around the association of smoking with COVID-19, smoking cessation remains a public health priority and high-quality smoking cessation advice including recommendations to use alternative nicotine should form part of public health efforts during this
Introduction

COVID-19 is a respiratory disease caused by the emerging SARS-CoV-2 virus. Large age and gender differences in case severity and mortality have been observed in the ongoing COVID-19 pandemic; however, these differences are currently unexplained. SARS-CoV-2 enters epithelial cells through the ACE2 receptor. Some evidence suggests that gene expression and subsequent receptor levels are elevated in the airway and oral epithelium of current smokers, thus putting smokers at higher risk of contracting SARS-CoV-2. Other studies, however, suggest that nicotine downregulates the ACE2 receptor. These uncertainties notwithstanding, both former and current smoking is known to increase the risk of respiratory viral and bacterial infections and is associated with worse outcomes once infected. Cigarette smoke reduces the respiratory immune defence through peri-bronchiolar inflammation and fibrosis, impaired mucociliary clearance and disruption of the respiratory epithelium. There is also reason to believe that behavioural factors (e.g. regular hand-to-mouth movements) involved in smoking may increase SARS-CoV-2 infection and transmission in current smokers. However, early data from the COVID-19 pandemic have not provided clear evidence for a negative impact of current or former smoking on SARS-CoV-2 infection or COVID-19 disease outcomes, such as hospitalisation or mortality. It has also been hypothesised that nicotine might protect against a hyper-inflammatory response (or “cytokine storm”) to SARS-CoV-2 infection, which may lead to adverse outcomes in patients with COVID-19 disease.

There are several reviews that fall within the scope of smoking and COVID-19. We aimed to produce a rapid synthesis of available evidence pertaining to the rates of infection, hospitalisation, disease severity and mortality from SARS-CoV-2/COVID-19 stratified by smoking status. Given the increasing availability of data on this topic, this will be a ‘living’ review with fortnightly updates. As evidence accumulates, the review will be expanded to include studies reporting outcomes by alternative nicotine use (e.g., nicotine replacement therapy or e-cigarettes).

Methods

Study design

We adopted recommended practice for rapid evidence reviews, which involved limiting the search to main databases and having one reviewer extract the data and another
verify\textsuperscript{18}.

\textit{Eligibility criteria}

Studies were included if they:

1) Were primary research studies using experimental (e.g. randomised controlled trial), quasi-experimental (e.g. pre- and post-test) or observational (e.g. case-control) study designs;
2) Included adults aged 16+ years;
3) Recorded as outcome i) results of a SARS-CoV-2 diagnostic test (including antibody assays), ii) a clinical diagnosis of COVID-19, iii) hospitalisation for COVID-19, iv) severity of COVID-19 disease or v) mortality from COVID-19;
4) Reported any of the outcomes of interest by self-reported or biochemically verified smoking status (e.g. current smoker, former smoker, never smoker);
5) Were available in English;
6) Were published in a peer-reviewed journal, as a pre-print or a public health report by reputable agents (e.g. governments, scientific societies).

\textit{Search strategy}

The following terms were searched for in Ovid MEDLINE as free text or Medical Subject Headings:

1. Tobacco Smoking/ or Smoking Cessation/ or Water Pipe Smoking/ or Smoking/ or Smoking Pipes/ or Cigar Smoking/ or Smoking Prevention/ or Cigarette Smoking/ or smoking.mp. or Pipe Smoking/ or Smoking, Non-Tobacco Products/ or Smoking Water Pipes/
2. Nicotine/ or nicotine.mp. or Electronic Nicotine Delivery Systems/ or Nicotine Chewing Gum/
3. vaping.mp. or Vaping/
4. 1 or 2 or 3
5. Coronavirus/ or Severe Acute Respiratory Syndrome/ or Coronavirus Infections/ or covid.mp.
6. 4 and 5

The following terms were searched for in titles, abstracts and full texts in medRxiv:

1. covid smoking
Additional articles/reports of interest were identified through mailing lists, Twitter, the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC), the Intensive Care National Audit & Research Centre (ICNARC) and the US Centers for Disease Control and Prevention (CDC).

Where updated versions of pre-prints or reports were available, old versions were superseded.

Selection of studies
One reviewer screened titles, abstracts and full texts against the inclusion criteria.

Data extraction
Data were extracted by one reviewer and verified by a second on i) author (year); ii) date published; iii) country; iv) study design; v) study setting; vi) sample size; vii) sex; viii) age; ix) smoking status (e.g. current, former, never, missing); x) SARS-CoV-2 infection; xi) diagnosis of COVID-19; xii) hospitalisation for COVID-19; xiii) disease severity; and xiv) mortality.

Quality appraisal
The National Institutes of Health’s Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies was used to determine the quality (i.e. ‘good’, ‘fair’, ‘poor’) of included studies to address the specific objectives of our review. In this context, studies were judged as ‘good’ quality if they: i) had low levels of missing data on smoking status, ii) used a reliable self-report measure that distinguished between current, former and never smoking status iii) used biochemical verification of smoking status; and iv) adjusted analyses for potential confounding variables (e.g. age, comorbidities). Studies were rated as ‘fair’ if they had low levels of missing data on smoking status and did one of either: i) used a reliable measure of current, former and never smoking status (e.g. self-report); or ii) adjusted analyses for potential confounding variables. Studies were otherwise rated as ‘poor’. The quality appraisal was conducted by one reviewer and verified by a second.

Evidence synthesis
A narrative synthesis was conducted. Where possible, data were pooled in R v.3.6.3 with
the Mantel-Haenszel or inverse variance method using random or fixed effects, depending on heterogeneity, and presented as risk ratios (RRs)\textsuperscript{21}. Heterogeneity between study outcomes was assessed using the $I^2$ statistic, suitable for smaller meta-analyses\textsuperscript{22}.

**Results**

In the current review version (v3), a total of 143 new records were identified, with 67 studies included in a narrative synthesis and 12 studies included in meta-analyses (see Figure 1).

**Study characteristics**

Characteristics of included studies are presented in Table 1. Thirty studies were conducted in China\textsuperscript{1,23,32–41,24,42–51,25–31}, twelve in the US\textsuperscript{52,53,62,63,54–61}, six in the UK\textsuperscript{64–69}, four in France\textsuperscript{70–73}, three in Mexico\textsuperscript{74–76}, three in Spain\textsuperscript{77–79}, two multi-site international studies\textsuperscript{80,81}, two in Italy\textsuperscript{82,83}, and with one each from Iran\textsuperscript{84}, Israel\textsuperscript{85}, Korea\textsuperscript{86}, Kuwait\textsuperscript{87} and Switzerland\textsuperscript{88}. Fifty-four studies were conducted entirely in hospital settings. Thirteen studies included a community component in addition to
hospitalised patients. Studies had a median of 393 (interquartile range = 101-1,402) participants.

**Smoking status**

Categorisation of smoking status was heterogeneous (see Table 1). Eleven studies did not report the source for information on smoking status. Notably, only sixteen studies recorded current, former and never smoking status, with a further six studies reporting current or current/former and never smoking status. The remaining 45 studies reported current and/or former smoking status but did not explicitly state whether the remaining participants were never smokers or whether data on smoking status were missing. Nineteen studies explicitly reported missing data on smoking status, which ranged from 0.6% to 96%. Smoking status was predominantly collected through routine electronic health records. Twenty studies used a bespoke case report form for COVID-19. None of the studies verified smoking status biochemically. Two studies specifically stated that smokers were those with a >30 pack-year history or a greater than 20-year history of smoking, respectively. Most studies did not assess tobacco exposure (e.g. pack-years of smoking) in current or former smokers, or time since quitting in former smokers. One study reported that 91.4% of former smokers had quit ≥6 months prior to COVID-19 disease onset.

Table 1. Characteristics of included studies.

| Reference | Author | Date published | Country | Sample size | Setting | Median age (IQR) | % Female | Smoking status of those COVID
disease | Data source for smoking status | Notes |
<table>
<thead>
<tr>
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<td>[1]</td>
<td>Youn, M.</td>
<td>26/03/2020</td>
<td>China</td>
<td>5599</td>
<td>Hospital</td>
<td>67 (35-90)</td>
<td>42.9%</td>
<td>Current smoker (31.2%) Never smoker (42.7%) Never smoker (39.6%) Missing (10.0%)</td>
<td>Not stated</td>
<td></td>
</tr>
<tr>
<td>[2]</td>
<td>Guo, L.</td>
<td>26/03/2020</td>
<td>China</td>
<td>5560</td>
<td>Hospital</td>
<td>49 (33-64)</td>
<td>42.7%</td>
<td>Current/former smoker (12.2%) Never smoker (90.5%) Never smoker (39.6%) Missing (10.0%)</td>
<td>Not stated</td>
<td></td>
</tr>
<tr>
<td>[3]</td>
<td>Liu, J.</td>
<td>26/03/2020</td>
<td>China</td>
<td>700</td>
<td>Hospital</td>
<td>'</td>
<td>26.5%</td>
<td>Current smoker (67.9%) Never smoker (90.5%) Missing (10.0%)</td>
<td>Not stated</td>
<td></td>
</tr>
<tr>
<td>[4]</td>
<td>Jin, X.</td>
<td>24/03/2020</td>
<td>China</td>
<td>491</td>
<td>Hospital</td>
<td>49 (32-60)</td>
<td>49.2%</td>
<td>Current smoker (8.9%) Never smoker (90.5%) Missing (9.2%)</td>
<td>Not stated</td>
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<td>[5]</td>
<td>Chen, C.</td>
<td>26/03/2020</td>
<td>China</td>
<td>540</td>
<td>Hospital</td>
<td>62 (44-70)</td>
<td>57.9%</td>
<td>Current smoker (44.8%) Former smoker (11.6%) Never smoker (90.5%) Missing (9.2%)</td>
<td>Not stated</td>
<td></td>
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<tr>
<td>[6]</td>
<td>Zhou, Y.</td>
<td>11/03/2020</td>
<td>China</td>
<td>515</td>
<td>Hospital</td>
<td>56 (46-67)</td>
<td>53.0%</td>
<td>Current smoker (8.0%) Never smoker (90.5%) Missing (9.2%)</td>
<td>Not stated</td>
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<tr>
<td>[7]</td>
<td>Nie, Y.</td>
<td>16/03/2020</td>
<td>China</td>
<td>515</td>
<td>Hospital</td>
<td>54 (53-60)</td>
<td>44.5%</td>
<td>Current smoker (12.5%) Never smoker (90.5%) Missing (9.2%)</td>
<td>Case report form</td>
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<td>[8]</td>
<td>Zhang, D.</td>
<td>16/03/2020</td>
<td>China</td>
<td>543</td>
<td>Hospital</td>
<td>57 (45-69)</td>
<td>66.0%</td>
<td>Current smoker (66.0%) Never smoker (90.5%) Missing (9.2%)</td>
<td>Electronic health records</td>
<td></td>
</tr>
<tr>
<td>[9]</td>
<td>Wen, W.</td>
<td>26/02/2020</td>
<td>China</td>
<td>135</td>
<td>Hospital</td>
<td>47 (39-55)</td>
<td>46.7%</td>
<td>Current smoker (36.7%) Never smoker (90.5%) Missing (9.2%)</td>
<td>Case report form</td>
<td></td>
</tr>
<tr>
<td>[10]</td>
<td>Liu, T.</td>
<td>26/02/2020</td>
<td>China</td>
<td>42</td>
<td>Hospital</td>
<td>42 (45-55)</td>
<td>27.9%</td>
<td>Current smoker (7.9%) Never smoker (90.5%) Missing (9.2%)</td>
<td>Case report form</td>
<td></td>
</tr>
<tr>
<td>[11]</td>
<td>Huang, X.</td>
<td>02/04/2020</td>
<td>China</td>
<td>52</td>
<td>Hospital</td>
<td>'</td>
<td>49.2%</td>
<td>Current smoker (41.6%) Never smoker (90.5%) Missing (9.2%)</td>
<td>Electronic health records</td>
<td></td>
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<td>[12]</td>
<td>Guo, J.</td>
<td>27/02/2020</td>
<td>China</td>
<td>307</td>
<td>Hospital</td>
<td>54 (40-70)</td>
<td>53.0%</td>
<td>Current smoker (8.0%) Never smoker (90.5%) Missing (9.2%)</td>
<td>Electronic health records</td>
<td></td>
</tr>
<tr>
<td>[13]</td>
<td>Liu, X.</td>
<td>12/03/2020</td>
<td>China</td>
<td>41</td>
<td>Hospital</td>
<td>39 (29-40)</td>
<td>58.0%</td>
<td>Current smoker (10.0%) Never smoker (90.5%) Missing (9.2%)</td>
<td>Electronic health records</td>
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<td>[14]</td>
<td>Huang, D.</td>
<td>05/03/2020</td>
<td>China</td>
<td>56</td>
<td>Hospital</td>
<td>63 (50-75)</td>
<td>50.0%</td>
<td>Current/former smoker (11.1%) Never smoker (90.5%) Missing (9.2%)</td>
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<td>[15]</td>
<td>Xu, Y.</td>
<td>06/03/2020</td>
<td>China</td>
<td>53</td>
<td>Hospital</td>
<td>'</td>
<td>47.2%</td>
<td>Current smoker (8.0%) Never smoker (90.5%) Missing (9.2%)</td>
<td>Electronic health records</td>
<td></td>
</tr>
<tr>
<td>[16]</td>
<td>Li, J.</td>
<td>12/03/2020</td>
<td>China</td>
<td>57</td>
<td>Hospital</td>
<td>45 (35-57)</td>
<td>47.3%</td>
<td>Current smoker (7.6%) Never smoker (90.5%) Missing (9.2%)</td>
<td>Electronic health records</td>
<td></td>
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<td>Country</td>
<td>Date</td>
<td>Area</td>
<td>Region</td>
<td>Source</td>
<td>Cases</td>
<td>Deaths</td>
<td>Recovery</td>
<td>Status</td>
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<tr>
<td>China</td>
<td>25/03/2020</td>
<td>Hubei</td>
<td>Wuhan</td>
<td>Wuhan</td>
<td>72,733</td>
<td>4,005</td>
<td>78,668</td>
<td>Closed</td>
<td></td>
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<tr>
<td>Italy</td>
<td>24/03/2020</td>
<td>Lombardy</td>
<td>Milan</td>
<td>Lombardy</td>
<td>5,000</td>
<td>781</td>
<td>4,219</td>
<td>Closed</td>
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<td>Spain</td>
<td>21/04/2020</td>
<td>Madrid</td>
<td>Madrid</td>
<td>Madrid</td>
<td>9,500</td>
<td>823</td>
<td>8,677</td>
<td>Closed</td>
<td></td>
<td></td>
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<tr>
<td>France</td>
<td>17/05/2020</td>
<td>Paris</td>
<td>Paris</td>
<td>Paris</td>
<td>5,000</td>
<td>194</td>
<td>4,806</td>
<td>Closed</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note: The data is from reputable sources and may be updated regularly. The status of the country may change as the situation evolves.*
Observed smoking prevalence by country is presented in Figure 2. Overall, compared with national smoking prevalence, lower than expected current and former smoking rates were observed in most studies across all countries.

Figure 2. Observed compared with expected smoking prevalence by country. No national data on former smoking prevalence for Israel were identified. Studies in countries presented in the lower panel did not report former smoking prevalence.
**SARS-CoV-2 infection by smoking status**

Two ‘poor’ and six ‘fair’ quality studies provided data on SARS-CoV-2 test results for people meeting local testing criteria by smoking status (see Table 2). Meta-analyses were performed for the six ‘fair’ quality studies. No significant difference was observed between current and never smokers (RR = 0.78, 95% CI = 0.55-1.11, p = .17) or former and never smokers (RR = 1.07, 95% CI = 0.95-1.20, p = .24) in the risk of testing positive for SARS-CoV-2 (see Figure 3 and 4, respectively).

**Hospitalisation for COVID-19 by smoking status**

Nine studies examined hospitalisation for COVID-19 disease stratified by smoking status (see Table 3). Meta-analyses were performed for five ‘fair’ quality studies. There was no significant difference between current and never smokers (RR = 1.12, 95% CI = 0.74-1.69, p = .48) or former and never smokers (RR = 1.21, 95% CI = 0.82-1.79, p = .24) in the risk of requiring admission to hospital following diagnosis of COVID-19 (see Figure 5 and 6, respectively).
Disease severity by smoking status

Twenty-two studies reported disease severity in hospitalised patients stratified by smoking status (see Table 4). Severe (as opposed to non-severe) disease as broadly defined as requiring ITU admission, requiring oxygen as a hospital inpatient or in-hospital death (where this had not been disaggregated into disease severity vs. mortality). Meta-analyses were performed for three ‘fair’ quality studies. Current smokers were at increased risk of greater severity disease compared with never smokers (RR = 1.37, 95% CI = 1.07-1.75, p = .01). No significant difference was observed between former and never smokers (RR = 1.51, 95% CI = 0.82-2.80, p = .19) (see Figure 7 and 8, respectively).

Figure 5. Forest plot for risk of hospitalisation in current vs. never smokers.

Figure 6. Forest plot for risk of hospitalisation in former vs. never smokers.
Eleven studies reported mortality from COVID-19 by smoking status (see Table 6), with three ‘fair’ quality studies. In the first study, no significant difference in mortality was observed between current and never (RR = 1.36, 95% CI = 0.85-2.17, p = .24) or between former and never smokers (RR = 0.91, 95% CI = 0.58-1.43, p = .66). The second study reported hazard ratios adjusted for age and sex, suggesting an increased hazard of death in former (HR = 1.80, 95% CI = 1.70-1.90) and current (HR = 1.25, 95% CI = 1.12-1.40) compared with never smokers. In the adjusted primary analysis, the hazard in former smokers remained heightened (HR = 1.25, 95% CI = 1.18-1.33) but reversed in current smokers (HR = 0.88, 95% CI = 0.79-0.99). The result was not robust in unplanned sensitivity analyses including further adjustment for ethnicity, early censoring and complete data for smoking and BMI. The third study reported odds ratios adjusted for age, sex, comorbidities and medication use, indicating increased odds of in-hospital death in current compared with never smokers (OR = 1.79, 95% CI = 1.29-2.47).

Quality appraisal

Quality ratings for the included studies are presented in Table 7. Seventeen studies were rated as ‘fair’ quality due to having low levels of missing data and either i) distinguished...
between current, former and never smoking status or ii) adjusted analyses for potential confounders. The remaining 50 studies were rated as ‘poor’ quality.

Table 2. SARS-CoV-2 Infection by smoking status.

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Current smoker</th>
<th>Former smoker</th>
<th>Current/former smoker</th>
<th>Never smoker</th>
<th>Not stated</th>
<th>N</th>
<th>Current smoker</th>
<th>Former smoker</th>
<th>Current/former smoker</th>
<th>Never smoker</th>
<th>Not stated</th>
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<tr>
<td>Retnakaran * 3518*</td>
<td>3518* (84.3%)</td>
<td>1464 (41.6%)</td>
<td>704 (20.0%)</td>
<td>404 (11.3%)</td>
<td>66 (18.9%)</td>
<td>8 (2.3%)</td>
<td>558* (15.7%)</td>
<td>359 (10.0%)</td>
<td>171 (4.9%)</td>
<td>27 (0.8%)</td>
<td>100 (2.8%)</td>
<td>30 (0.8%)</td>
</tr>
<tr>
<td>Fontana * 651</td>
<td>651 (75.3%)</td>
<td>490 (76.8%)</td>
<td>64 (9.7%)</td>
<td>246 (37.9%)</td>
<td>171 (26.3%)</td>
<td>0 (0.0%)</td>
<td>52 (8.0%)</td>
<td>0 (0.0%)</td>
<td>216 (33.3%)</td>
<td>52 (8.0%)</td>
<td>30 (4.6%)</td>
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<tr>
<td>Cho 1311</td>
<td>1311 (79.6%)</td>
<td>793 (60.7%)</td>
<td>214 (16.3%)</td>
<td>437 (33.4%)</td>
<td>513 (39.3%)</td>
<td>111 (8.6%)</td>
<td>282 (21.6%)</td>
<td>27 (2.1%)</td>
<td>27 (2.1%)</td>
<td>9 (0.7%)</td>
<td>100 (7.6%)</td>
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<tr>
<td>Skala 241**</td>
<td>241 (97.3%)</td>
<td>212 (96.3%)</td>
<td>52 (22.2%)</td>
<td>113 (47.1%)</td>
<td>29 (12.4%)</td>
<td>0 (0.0%)</td>
<td>30 (12.4%)</td>
<td>0 (0.0%)</td>
<td>20 (8.3%)</td>
<td>0 (0.0%)</td>
<td>100 (41.3%)</td>
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</tr>
<tr>
<td>Ballas-O’Keefe, 62,489</td>
<td>62,489 (70.7%)</td>
<td>46,760 (74.5%)</td>
<td>4283 (16.9%)</td>
<td>16,121 (66.0%)</td>
<td>15,527 (62.2%)</td>
<td>-</td>
<td>1374 (8.0%)</td>
<td>1,310 (5.2%)</td>
<td>-</td>
<td>1374 (8.0%)</td>
<td>1,310 (5.2%)</td>
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</tr>
<tr>
<td>Kolte 347***</td>
<td>347 (98.9%)</td>
<td>307 (89.0%)</td>
<td>18 (5.3%)</td>
<td>150 (44.0%)</td>
<td>145 (42.1%)</td>
<td>26 (7.6%)</td>
<td>36 (10.5%)</td>
<td>0 (0.0%)</td>
<td>30 (8.5%)</td>
<td>0 (0.0%)</td>
<td>100 (2.9%)</td>
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</tr>
</tbody>
</table>

Note. Naidu et al. reported on SARS-CoV-2 infection by smoking status in multivariable analyses but did not present raw data; * Data on smoking status were missing for 261 participants; ** Data on smoking status were missing for 75 participants; *** Data on smoking status were missing for 52 participants.

Table 3. Hospitalisation for COVID-19 by smoking status.

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Current smoker</th>
<th>Former smoker</th>
<th>Current/former smoker</th>
<th>Never smoker</th>
<th>Not stated</th>
<th>N</th>
<th>Current smoker</th>
<th>Former smoker</th>
<th>Current/former smoker</th>
<th>Never smoker</th>
<th>Not stated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retnakaran * 584*</td>
<td>584 (44.6%)</td>
<td>289 (49.2%)</td>
<td>98 (16.9%)</td>
<td>110 (18.5%)</td>
<td>-</td>
<td>-</td>
<td>289 (49.2%)</td>
<td>98 (16.9%)</td>
<td>110 (18.5%)</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>Arvdi 610</td>
<td>610 (51.0%)</td>
<td>330 (54.1%)</td>
<td>250 (40.9%)</td>
<td>174 (28.7%)</td>
<td>-</td>
<td>-</td>
<td>510 (84.0%)</td>
<td>47 (7.7%)</td>
<td>78 (12.3%)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Choe-HS, 681* (CDS)</td>
<td>681* (51.3%)</td>
<td>313 (46.0%)</td>
<td>-</td>
<td>174 (25.8%)</td>
<td>-</td>
<td>-</td>
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<td>55 (8.2%)</td>
<td>20 (3.0%)</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>Miyagis 462**</td>
<td>462 (24.9%)</td>
<td>141 (30.5%)</td>
<td>42 (9.1%)</td>
<td>103 (22.6%)</td>
<td>-</td>
<td>-</td>
<td>260 (38.1%)</td>
<td>55 (8.2%)</td>
<td>20 (3.0%)</td>
<td>-</td>
<td>-</td>
<td></td>
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<tr>
<td>Algerian 1900</td>
<td>1900 (95.5%)</td>
<td>1515 (79.2%)</td>
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<td>119 (6.4%)</td>
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<td>-</td>
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<tr>
<td>Lubardo 54</td>
<td>54 (71.2%)</td>
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<td>-</td>
<td>4 (26.7%)</td>
<td>-</td>
<td>-</td>
<td>11 (20.4%)</td>
<td>39 (72.2%)</td>
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<td>8 (15.1%)</td>
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<tr>
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<td>3820 (40.0%)</td>
<td>120 (12.4%)</td>
<td>114 (11.9%)</td>
<td>-</td>
<td>-</td>
<td>3514 (36.4%)</td>
<td>481 (5.0%)</td>
<td>-</td>
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<tr>
<td>Venner 4335</td>
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<td>-</td>
<td>-</td>
<td>175 (40.4%)</td>
<td>11 (2.5%)</td>
<td>-</td>
<td>332 (7.6%)</td>
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<tr>
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<td>1018 (78.9%)</td>
<td>116 (8.4%)</td>
<td>375 (27.9%)</td>
<td>-</td>
<td>-</td>
<td>760 (99.3%)</td>
<td>95 (12.2%)</td>
<td>523 (69.3%)</td>
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</tbody>
</table>

Note. * Data on smoking status were missing for 35 participants; ** Data on smoking status were missing for 9 participants; *** Data legend was not clear; ** Data on smoking status were missing for 52 participants.
Table 4. Disease severity by smoking status.

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<th>Severe disease</th>
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<td>Former smoker</td>
</tr>
<tr>
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</tr>
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<td>Guppy</td>
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</table>

Note: *Data on smoking status were missing for 14 participants; **Data on smoking status were missing for 111 participants; ***Data on smoking status were missing for 126 participants; ****Data on smoking status were missing for 38 participants; *****Data on smoking status were missing for 13 participants; ******Data on smoking status were missing for 1 participant; *******Data on 1769 participants were not presented. * Patients with disease requiring hospital (but not ICU) admission.

Table 5. Mortality by smoking status.

<table>
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Note: *Coletti et al. and the OpenDILI Collaborative reported on mortality by smoking status in a multivariable analysis but did not present raw data on both exposure and outcomes. * Data on mortality were missing for 214 participants; * No smoking history defined as <100 pack-years of smoking.
Table 6. Quality ratings of included studies.

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<th>T</th>
<th>M</th>
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Discussion

This rapid review of 67 observational studies found substantial uncertainty arising from the recording of smoking status. Notwithstanding recording uncertainties, compared with national prevalence estimates, recorded current and former smoking rates in most studies were lower than expected. From available data, there was insufficient evidence to establish whether current and/or former smoking status is associated with SARS-CoV-2 infection, hospitalisation or mortality. There was limited evidence from ‘fair’ quality studies that disease severity in those hospitalised for COVID-19 is greater in current but not former smokers compared with never smokers. There were inconsistent results on the association of current or past compared with never smoking and increased mortality from COVID-19.

Infection by smoking status

There is currently no evidence that current or former smokers in the community are more likely to test positive compared with never smokers. Infection positivity rates estimated among random samples will be more informative than currently available data. Smoking status is being collected in at least one large representative infection and antibody survey in the UK.

Hospitalisation and disease severity by smoking status

As reported elsewhere, smoking prevalence among multiple hospital cohorts was consistently lower than national estimates. In contrast, there was no evidence that current or former smokers are at lower risk of hospitalisation for COVID-19 compared
with never smokers among those identified as testing positive in the community. There was some limited evidence that current smokers are at increased risk of greater disease severity compared with never smokers.

* Mortality by smoking status *

In three ‘fair’ quality studies, there was inconsistent evidence on the association of smoking status and the risk of death from COVID-19. It should be noted that these early studies did not follow all patients for a sufficient period of time to report mortality outcomes.

* Issues complicating interpretation *

Interpretation of these early studies is complicated by several factors (see Figure 9). First, exposure to SARS-CoV-2 is heterogeneous with different subgroups being at heightened risk of infection at different stages of the pandemic. This will likely introduce bias in studies assessing the rate of infection by smoking status conducted early on in the pandemic. Second, current smokers may be more likely to meet local criteria for community testing due to increased prevalence of symptoms consistent with SARS-CoV-2 infection, such as cough, increased sputum production or altered sense of smell or taste. Third, testing for acute infection requires swabbing of the mucosal epithelium, which may be disrupted in current smokers, thus altering the sensitivity of the assay.

Fourth, most included studies relied on electronic health records (EHRs) as the source of information on smoking status. Research shows large discrepancies between EHRs and actual behaviour. Known failings of EHRs include implausible longitudinal changes, such as former smokers being recorded as never smokers at subsequent hospital visits. Misreporting on the part of the patient (perhaps due to perceived stigmatisation) has also been observed, with biochemical measures showing higher rates of smoking behaviour compared with self-report in hospitalised patients in the US. It is hence possible that under-reporting of current and former smoking status occurred across the included studies. Fifth, individuals with severe COVID-19 symptoms may have stopped smoking prior to admission to a care facility and may therefore not have been recorded as current smokers (i.e. reverse causality).

Sixth, smokers with COVID-19 may be less likely to receive a SARS-CoV-2 test or present to hospital due to lack of access to healthcare and may be more likely to die in the community from sudden complications (i.e. self-selection). Seventh, if there is a protective effect of nicotine on COVID-19 disease outcomes, abrupt nicotine withdrawal
upon hospitalisation may lead to worse outcomes\textsuperscript{12}. Eight, during periods of heightened demand of limited healthcare resources, current smokers with extensive comorbidities may have reduced priority for intensive care admission, thus leading to higher in-hospital mortality.

Another important issue is that the reason for hospitalisation varies by country and time in the epidemic. For example, initial cases may have been hospitalised for isolation and quarantine reasons and not due to medical necessity. It is plausible that this may have skewed early data towards less severe cases. In addition, the observed association between current smoking and disease severity may be explained by collider bias, where conditioning on a collider (e.g. testing or hospitalisation) by design or analysis may introduce a spurious association between smoking (a potential cause of testing or hospitalisation) and SARS-CoV-2 infection/adverse outcomes from COVID-19 (potentially exacerbated by smoking)\textsuperscript{92}.

Figure 9. A schematic of some interpretation issues for the association of smoking and SARS-CoV-2/COVID-19. * indicates potential confounding with smoking status

\textit{Limitations}

This rapid review was limited by not having two independent reviewers extracting data, limiting the search to one electronic database and one pre-print server and by not including at least two large population surveys due to their reliance on self-reported SARS-CoV-2 infection (which means they are not currently meeting our eligibility criteria)\textsuperscript{93,94}. Population surveys – particularly with linked health data – will be included in future review versions to help mitigate some of the limitations of healthcare based observational studies.

\textit{Implications for research, policy and practice}

Further scientific research is needed to resolve the mixed findings summarised in our review. First, clinical trials of the posited therapeutic effect of nicotine could have important implications both for smokers and for improved understanding of the SARS-
CoV-2 virus. Such trials should focus on medicinal nicotine (as smoked tobacco is a dirty delivery mechanism that could mask beneficial effects) and potentially differentiate between different modes of delivery (i.e. inhaled vs. not) since this can affect pharmacokinetics\(^95\) (and thus potential therapeutic effects). A second research priority would be a large, representative (randomly sampled) population survey with a validated assessment of smoking status which distinguishes between recent and long-term ex-smokers – ideally biochemically verified – and assesses seroprevalence and links to health records. In the meantime, public-facing messages about the possible protective effect of smoking or nicotine are premature. In our view, until there is further research, the quality of the evidence does not justify the huge risk associated with a message likely to reach millions of people that a lethal activity, such as smoking, may protect against COVID-19. It continues to be appropriate to recommend smoking cessation and emphasise the role of alternative nicotine to support smokers to stop as part of public health efforts during COVID-19. At the very least, smoking cessation reduces acute risks from cardiovascular disease and could reduce demands on the healthcare system\(^96\). GPs and other healthcare providers can play a crucial role – brief, high-quality and free online training is available from the National Centre for Smoking Cessation and Training.

**Conclusion**

Across 67 observational studies, there is substantial uncertainty arising from the recording of smoking status on whether current and/or former smoking status is associated with SARS-CoV-2 infection, hospitalisation or mortality. There is limited evidence that current smoking compared with never is associated with greater disease severity in those hospitalised for COVID-19.

**Acknowledgements**

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