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

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Abstract

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.

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.

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. 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: Forty-one studies were included, 25 of which were conducted in China, seven

in the US, three in France, two across multiple international sites and one each in the UK, Korea, Mexico and Spain. Nine studies did not state the source for information on smoking status. Thirty-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 36 (5 'fair' and 31 'poor' quality) studies of hospitalised patients were generally lower than expected. In two 'fair' quality studies, current and former smokers appeared more likely to be tested for SARS-CoV-2 but there was no difference in the risk of testing positive in current (RR = 0.74, 95% CI = 0.31-1.73, p = .49) or former (RR = 1.18, 95% CI = 0.82-1.69, p = .37) compared with never smokers. In three 'fair' quality studies of people who tested positive in the community, there was no evidence for a decreased risk of hospitalisation among current (RR = 0.95, 95% CI = 0.76-1.18, p = .62) or former (RR = 1.04, 95% CI = 0.98-1.10, p = .26) smokers compared with never smokers. In three 'fair' quality studies, there was an increased risk of greater disease severity in hospitalised current (RR = 1.36, 95% CI = 1.07-1.74, p = .01) but not former (RR = 1.51, 95% CI = 0.86-2.65, p = .15) smokers compared with never smokers. Two 'poor' quality studies provided mixed evidence for the risk of death in current compared with former/never smokers.

Conclusions: Across 41 observational studies, there is substantial uncertainty about the associations between smoking and COVID-19 outcomes arising from the recording of smoking status. The recorded smoking prevalence in hospitalised patients across multiple settings was lower than national estimates but that observation is inconsistent with there being no evidence of increased admission to hospital from three 'fair' quality studies among people who tested positive in the community. 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 should form part of public health efforts during this pandemic.

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[1]; however, these differences are currently unexplained. SARS-CoV-2 enters epithelial cells through the ACE2 receptor[2]. Some evidence suggests that gene expression and subsequent receptor levels are elevated in the airway and oral epithelium of current smokers[3,4], thus putting smokers at higher risk of contracting SARS-CoV-2. Other studies, however, suggest that nicotine downregulates the ACE2 receptor[5]. These uncertainties notwithstanding, both former and current smoking is known to increase the risk of respiratory viral[6,7] and bacterial[8,9] 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[10]. 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[11]. 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[12].

There are several reviews that fall within the scope of smoking and COVID-19[11,13–17]. 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[18].

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) Involved as participants 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).

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

2. covid nicotine
3. covid vaping

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).

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 (19). 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.

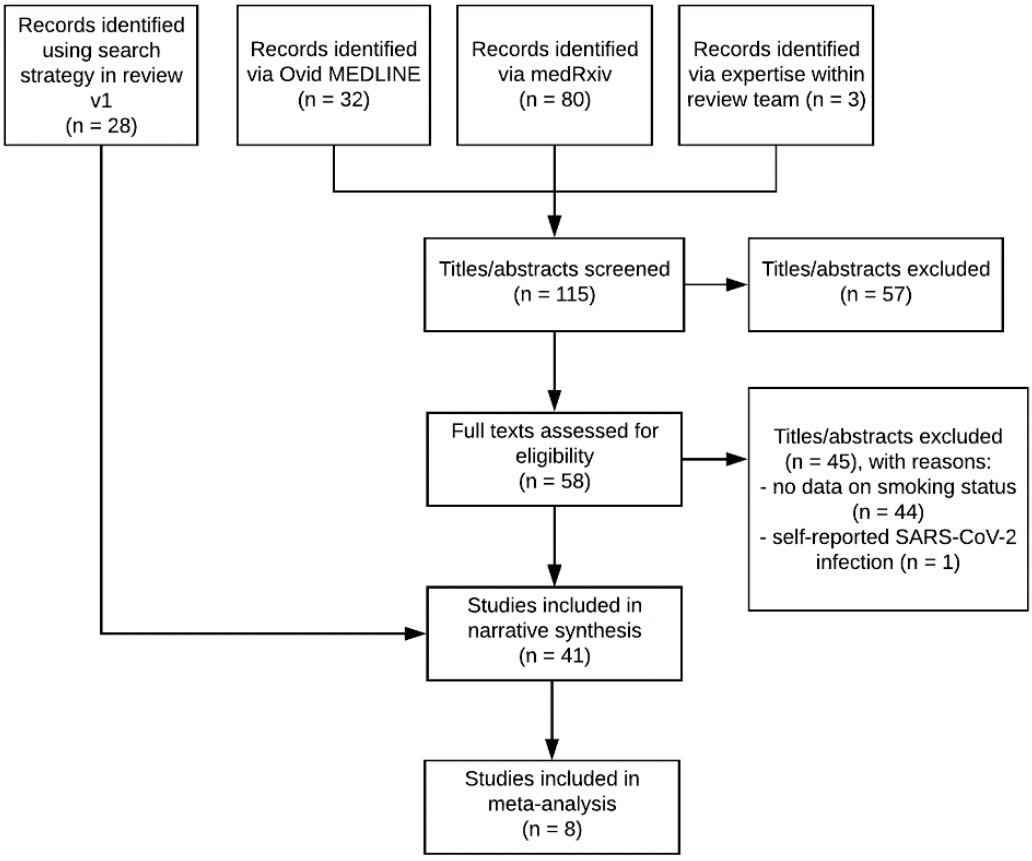
Evidence synthesis

A narrative synthesis was conducted. Where possible, data were pooled in RevMan

v.5.3[20] with the Mantel–Haenzel or inverse variance method using random or fixed effects, depending on heterogeneity, and presented as risk ratios (RRs)[21]. Heterogeneity between study outcomes was assessed using the I^2 statistic, suitable for smaller meta-analyses[22].

Results

A total of 115 records were identified, of which 58 full texts were screened, 41 studies were included in a narrative synthesis and 8 studies were included in meta-analysis (see Figure 1).



Study characteristics

Characteristics of included studies are presented in Table 1. Twenty-five studies were conducted in China[1,23,32–41,24,42–47,25–31], seven in the US[48–54], three in France[55–57], two multi-site international studies[58,59] and one each from the UK[60], Mexico[61], Korea[62] and Spain[63]. Thirty-five studies were conducted in hospital settings. Seven studies included a community component in addition to hospitalised patients[48,49,54–56,60]. Studies had a median of 368 (interquartile range = 66-1,000) participants. The total sample analysed in

the current review was 493,995 participants.

Smoking status

The levels used to categorise smoking status were heterogeneous (see Table 1). Nine studies did not report the source for information on smoking status. Notably, only six studies recorded current, former and never smoking status, with a further four studies reporting current or current/former and never smoking status. The remaining 31 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. Nine studies explicitly reported missing data on smoking status, which ranged from 1.3% to 92% (weighted mean = 33%). Smoking status was predominantly collected through routine electronic health records. Twelve studies used a bespoke case report form for COVID-19. None of the studies verified smoking status biochemically. Two studies[26,40] 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.

Smoking prevalence among those with SARS-CoV-2 infection or a COVID-19 diagnosis by country

In the included studies conducted in hospital settings across China, 3.8% to 17.6% were current smokers and 1.9% to 5.0% (missing = 1.2%-92.0%) were former smokers. However, current and former smoking prevalence in China was reported to be 50.5% and 8.4% respectively among men and 2.1% and 0.8% respectively among women in 2018[64], thus suggesting lower than expected proportions of current and former smokers in the included studies.

In the studies conducted in the US across community and hospital settings, 1.3% to 27.2% were current smokers and 2.3% to 30.6% (missing = 5.3%-96.4%) were former smokers. This compares with a prevalence of 13.8% current and 20.9% former smokers in the US in 2018[65].

In the studies conducted in France, 7.1% to 10.4% were current smokers and 18.0% to 59.1% (missing = 1.9%) were former smokers across community and hospital settings. This compares with a current and former smoking prevalence of 32.0% and 31.4%

respectively in France in 2018[66], thus suggesting a lower than expected proportion of current smokers in the included studies but a higher than expected proportion of former smokers in one study.

In one of the multi-site studies with participants predominantly from hospital settings in the UK, 4.7% were ever smokers (missing = 47.0%). In the study conducted in the UK, 10.0% were current smokers and 34.6% were former smokers (missing = 0.6%). This compares with a current and former smoking prevalence of 14.4% and 25.8% in England in 2018[67], thus suggesting a lower than expected proportion of current and former smokers in the multi-site study but a higher than expected proportion of former smokers in the UK only study.

In the study conducted within the healthcare service in Mexico, 9.4% were current smokers (missing = 90.6%). This compares with a national smoking prevalence of 16.6% in Mexico in 2015[68].

In the study conducted in a hospital setting in Spain, 42.9% were ever smokers (missing = 0.0%). This compares with a national ever smoking prevalence of 51.3% in Spain in 2008[69].

In the study conducted in a hospital setting in Korea, 18.5% were current smokers (missing = 82.1%). This compares with a national smoking prevalence of 19.3% in Korea in 2016[70].

Table 1. Characteristics of included studies.

Reference	Author	Date published	Country	Sample size	Setting	Median age (IQR)	% Female	Smoking status of those COVID+	Data source for smoking status
[1]	Guan, Ni	28/02/2020	China	1099	Hospital	47 (35-58)	41.9%	Current smoker (12.6%) Former smoker (1.9%) Never smoker (85.4%) Missing (1.3%)	Not stated
[23]	Guan, Liang	26/03/2020	China	1590	Hospital	49 (33-64)	42.7%	Current/former smoker (7.0%) Never smoker (93.0%)	Not stated
[24]	Lian	25/03/2020	China	788	Hospital	-'	38.5%	Current smoker (6.9%) Not stated (93.1%)	Not stated
[25]	Jin	24/03/2020	China	651	Hospital	46 (32-60)	49.2%	Current smoker (6.3%) Not stated (93.7%)	Not stated
[26]	Chen	26/03/2020	China	548	Hospital	62 (44-70)	37.6%	Current smoker (4.4%)* Former smoker (2.6%)* Not stated (93.1%)	Not stated
[27]	Zhou	11/03/2020	China	191	Hospital	56 (46-67)	38.0%	Current smoker (6.0%) Not stated (94.0%)	Not stated
[28]	Mo	16/03/2020	China	155	Hospital	54 (53-66)	44.5%	Current smoker (3.9%) Not stated (96.1%)	Case report form
[29]	Zhang, Dong	19/02/2020	China	140	Hospital	57 (25-87)^	46.3%	Current smoker (1.4%) Former smoker (5.0%) Not stated (93.6%)	Electronic health records
[30]	Wan	21/03/2020	China	135	Hospital	47 (36-55)	46.7%	Current smoker (6.7%) Not stated (93.3%)	Electronic health records
[31]	Liu, Tao	28/02/2020	China	78	Hospital	38 (33-57)	50.0%	Current/former smoker (6.4%) Not stated (93.6%)	Case report form
[32]	Huang, Wang	05/03/2020	China	41	Hospital	49 (41-58)	27.0%	Current smoker (7.3%) Not stated (92.7%)	Electronic health records
[33]	Zhang, Cai	20/03/2020	China	645	Hospital	-'	49.1%	Current smoker (6.4%) Not stated (93.5%)	Electronic health records
[34]	Guo	27/03/2020	China	187	Hospital	59 (45-73)	51.3%	Current smoker (9.6%) Not stated (90.4%)	Electronic health records
[45]	Liu, Ming	12/03/2020	China	41	Hospital	39 (30-48)	58.5%	Current smoker (9.8%) Not stated (90.2%)	Electronic health records
[52]	Huang, Yang	05/03/2020	China	36	Hospital	69 (60-78)	30.6%	Current/former smoker (11.1%) Not stated (88.9%)	Not stated
[36]	Xu	08/03/2020	China	53	Hospital	-'	47.2%	Current smoker (11.3%) Not stated (88.7%)	Electronic health records
[37]	Li	12/02/2020	China	17	Hospital	45 (33-57)	47.1%	Current smoker (17.6%) Not stated (82.4%)	Electronic health records

[48]	Rentsch~	14/04/2020	USA	3789	Community/hospital	66 (60-70)	4.6%	Current smoker (27.2%) Former smoker (30.6%) Never smoker (36.9%) Missing (5.3%)	Electronic health records
[38]	Hu	25/03/2020	China	323	Hospital	61 (23-91)^	48.6%	Current/former smoker (11.8%) Not stated (88.2%)	Not stated
[39]	Wang	24/03/2020	China	125	Hospital	41 (26-66)	43.2%	Current/former smoker (11.8%) Not stated (87.2%)	Electronic health records
[49]	Petrilli	11/04/2020	USA	4103	Community/hospital	52 (36-65)	47.9%	Current smoker (5.2%) Former smoker (16.2%) Never smoker/unknown (78.6%)	Electronic health records
[54]	Chow (US CDC)	31/03/2020	USA	7162	Community/hospital	-'	-	Current smoker (1.3%) Former smoker (2.3%) Missing (96.4%)	Case report form
[55]	Miyara	21/04/2020	France	482	Community/hospital	-'	43.0%	Current/occasional smoker (7.1%) Former smoker (59.1%) Never smoker (32%) Missing (1.8%)	Case report form
[40]	Dong	20/03/2020	China	9	Hospital	44 (30-46)	66.7%	Current smoker (11.1%)# Never smoker/unknown (88.9%)	Electronic health records
[62]	Kim	01/04/2020	Korea	28	Hospital	43 (30-56)	46.4%	Current smoker (18.5%) Never smoker/unknown (81.5%)	Electronic health records
[41]	Shi, Yu	18/03/2020	China	487	Hospital	46 (27-65)	46.8%	Current/former smoker (8.2%) Never smoker/unknown (89.1%)	Case report form
[47]	Yang, Yu	24/02/2020	China	52	Hospital	60 (47-73)	37.0%	Current smoker (3.8%) Never smoker/unknown (96.2%)	Case report form
[50]	Argenziano	22/04/2020	USA	1000	Hospital	63 (50-75)	40.4%	Current smoker (4.9%) Former smoker (17.9%) Never smoker (77.2%)	Case report form
[63]	Solis	25/04/2020	Mexico	650	Hospital	46^	42.1%	Current smoker (9.4%) Not stated (90.6%)	Electronic health records
[51]	Richardson	22/04/2020	USA	5700	Hospital	63 (52-75)	39.7%	Current/former smoker (9.8%) Never smoker (52.8%) Missing (37.4%)	Electronic health records
[56]	Fontanet	23/04/2020	France	661	Community	37 (16-47)	62.0%	Current smoker (10.4%) Never smoker/unknown (89.6%)	Case report form
[42]	Zheng, Gao	19/04/2020	China	66	Hospital	47^	25.8%	Current smoker (12.1%) Not stated (87.9%)	Not stated
[43]	Liao, Feng	24/04/2020	China	1848	Hospital	55 (48-61)	54.7%	Current/former smoker (0.4%) Not stated (7.6%) Missing (92.0%)	Electronic health records
[61]	Rodriguez-Cola	24/04/2020	Spain	7	Hospital	68 (34-75)	28.6%	Current/former smoker (42.9%) Never smoker (57.1%)	Electronic health records
[52]	Magagnoli	16/04/2020	USA	368	Hospital	69 (59-75)	0.0%	Current/former smoker (14.1%) Not stated (85.9%)	Electronic health records
[44]	Shi, Ren	23/04/2020	China	134	Hospital	46 (34-58)	51.5%	Current/former smoker (10.5%) Not stated (89.5%)	Case report form
[57]	Hadjadj	23/04/2020	France	50	Hospital	55 (50-63)	22.0%	Current smoker (2.0%) Former smoker (18.0%) Never smoker (80.0%)	Electronic health records
[60]	Niedzwiedz	30/04/2020	UK	428,225	Community and hospital	-'	-	Current smoker (10.0%) Former smoker (34.6%) Never smoker (55.4%)	Case report form
[53]	Gold (US CDC)	20/04/2020	USA	305	Hospital	-	-	Current smoker (5.1%) Not stated (94.9%)	Case report form
[58]	Mehra	01/05/2020	Multiple	8910	Hospital	49^	40.0%	Current smoker (5.5%) Former smoker (16.8%) Not stated (77.7%)	Case report form
[59]	ISARIC	27/04/2020	Multiple	19,463	Hospital	71 (0-104)^	37.0%	Current/former smoker (4.7%) Never smoker (48.3%) Missing (47.0%)	Case report form

Note. -' Age not provided for unstratified sample; * Current and former smoker defined as 30 pack-years of smoking; ^ Denotes range (as opposed to IQR); ~ Includes participants with negative and positive SARS-CoV-2 tests; # Current smoker defined as >20 years of smoking.

SARS-CoV-2 infection by smoking status

One 'poor' and two 'fair' quality studies provided data on SARS-CoV-2 test results for people meeting local testing criteria by smoking status (see Table 2). In the 'poor' quality study with data from high school students, school-based staff, parents and siblings in France[56], current smokers (7.2%) were less likely to test positive than never smokers (28.0%) (RR = 0.26, 95% CI = 0.11-0.61, p < .002).

In a cohort study of US military veterans aged 54-75[48], current smokers were more likely to receive a test: 42.3% (1,603/3,789) of the sample were current smokers compared with 23.8% of all veterans aged 50+ years using any tobacco product between 2010-201571. Current smokers (RR = 0.48, 95% CI = 0.40-0.58, p < .001) but not former smokers (RR = 0.98, 95% CI = 0.82-1.17, p = .80) had a significantly reduced risk of testing

positive compared with never smokers.

In the UK Biobank cohort[60], former smokers (RR = 1.29, 95% CI = 1.14-1.45, p < .001) and current smokers (RR = 1.44, 95% CI = 1.20-1.71, p < .001) were more likely to be tested compared with never smokers in a multivariable analysis. However, former smokers (RR = 1.42, 95% CI = 1.18-1.70, p < .001) but not current smokers (RR = 1.15, 95% CI = 0.86-1.54, p > .05) had greater risk of testing positive compared with never smokers.

Meta-analyses were performed for the two 'fair' quality studies. No significant difference was observed between current and never smokers (RR = 0.74, 95% CI = 0.31-1.73, p = .49) or former and never smokers (RR = 1.18, 95% CI = 0.82-1.69, p = .37) in the risk of testing positive for SARS-CoV-2 (see Figure 2 and 3, respectively).

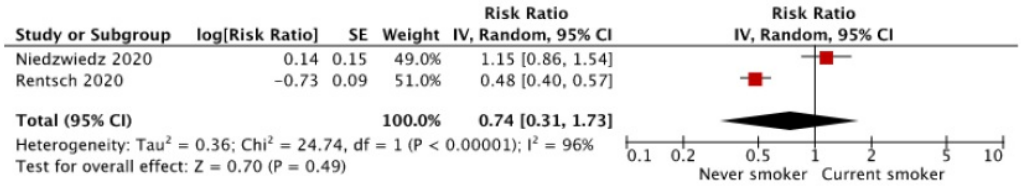


Figure 2. Forest plot for risk of testing positive for SARS-CoV-2 in current vs. never smokers

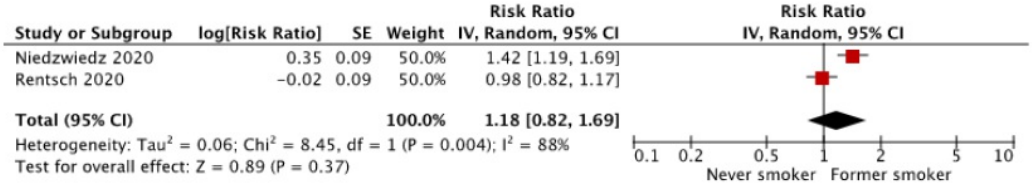


Figure 3. Forest plot for risk of testing positive for SARS-CoV-2 in former vs. never smokers.

Hospitalisation for COVID-19 by smoking status

Five studies examined hospitalisation for COVID-19 disease stratified by smoking status (see Table 3). Meta-analyses were performed for three 'fair' quality studies. There was no significant difference between current and never smokers (RR = 0.95, 95% CI = 0.76-1.18, p = .62) or former and never smokers (RR = 1.04, 95% CI = 0.98-1.10, p = .26) in the risk of requiring admission to hospital following diagnosis of COVID-19 (see Figure 4 and 5, respectively).

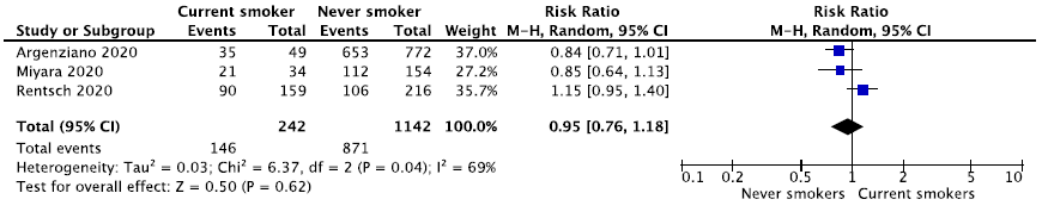


Figure 4. Forest plot for risk of hospitalisation in current vs. never smokers.

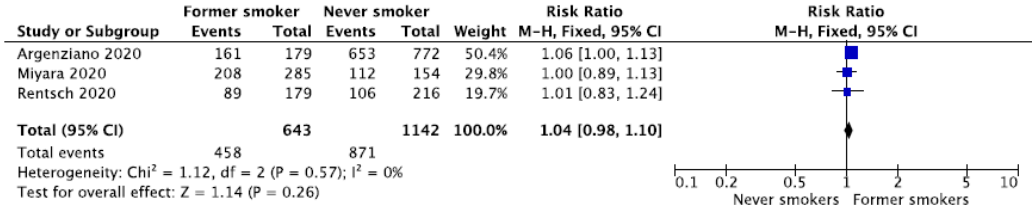


Figure 5. Forest plot for risk of hospitalisation in former vs. never smokers.

Disease severity by smoking status

Thirteen studies reported disease severity in hospitalised patients stratified by smoking status (see Table 4). Severe (as opposed to non-severe) disease was 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 = 1.36, 95% CI = 1.07-1.74, p = .01). No significant difference was observed between former and never smokers (RR = 1.51, 95% CI = 0.86-2.65, p = .15) (see Figure 6 and 7, respectively).

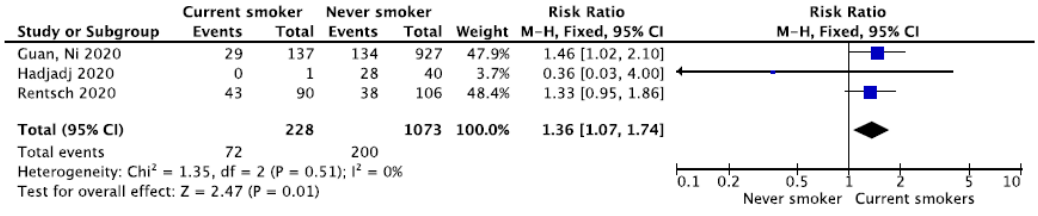


Figure 6. Forest plot for the risk of severe disease in current vs. never smokers.

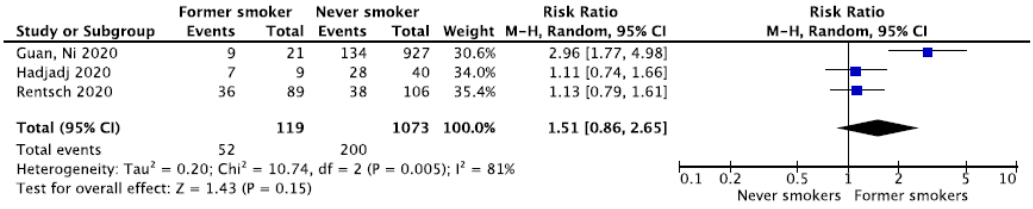


Figure 7. Forest plot for the risk of severe disease in former vs. never smokers.

Mortality by smoking status

Five studies reported mortality from COVID-19 by smoking status (see Table 5), with two 'poor' quality studies reporting multivariable analyses[58,63]. One reported increased odds of in-hospital death in current compared with former/never/unknown smokers (OR = 1.79, 95% CI = 1.29-2.47, p < .001) and the other reported no significant difference in mortality between current and former/never/unknown smokers (HR = 1.05, 95% CI = 0.79-1.39, p = 0.74).

Quality appraisal

Quality ratings for the included studies are presented in Table 6. Seven 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 34 studies were rated as 'poor' quality.

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

	Total population tested	SARS-CoV-2 negative				SARS-CoV-2 positive			
Author	N	N	Current smoker	Former smoker	Never smoker	N	Current smoker	Former smoker	Never smoker
Rentsch	3528*	2974* (84.3%)	1444 (48.6%)	704 (23.6%)	826 (27.8%)	554* (15.7%)	159 (28.7%)	179 (32.3%)	216 (39.0%)
Fontanet	661	490 (74.1%)	64 (13.1%)	0 (0%)	426 (86.4%)	171 (25.9%)	5 (2.9%)	0 (0%)	166 (97.1%)

Note. Niedzwiedz 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.

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

	COVID +ve sample*	Community						Hospitalised					
Author	N	N	Current smoker	Former smoker	Never smoker	Never/unknown	Not stated	N	Current smoker	Former smoker	Never smoker	Never/unknown	Not stated
Rentsch	554*	269 (48.6%)	69 (25.7%)	90 (33.5%)	110 (40.8%)	-	-	285 (51.4%)	90 (31.6%)	89 (31.2%)	106 (37.2%)	-	-
Petrilli	4103	2104 (51.3%)	108 (5.1%)	250 (11.9%)	-	1746 (83.0%)	-	1999 (48.7%)	104 (5.2%)	416 (20.8%)	-	1479 (74.0%)	-
Chow (US CDC)	6637'	5143 (77.5%)	61 (1.2%)	80 (1.6%)	-	-	5002 (97.3%)	1494 (22.5%)	27 (1.8%)	78 (5.2%)	-	-	1389 (93.0%)
Miyara	482**	139 (28.8%)	13 (9.4%)	77 (55.4%)	42 (30.2%)	-	-	343 (71.1%)	21 (6.1%)	208 (60.6%)	112 (32.7%)	-	-
Argenziano	1000	151^ (15.1%)	14 (9.3%)	18 (11.9%)	119 (78.8%)	-	-	849 (84.9%)	35 (4.1%)	161 (19.0%)	653 (76.9%)	-	-

Note. * Data on smoking status were missing for 31 participants; ** Data on smoking status were missing for 9 participants; ^ 22 individuals died in the emergency department and were thus not hospitalised but are included in the community sample; ' Data on outcomes were missing for 525 participants.

Table 4. Disease severity by smoking status.

	Sample size	Non-severe disease							Severe disease						
Author	N	n	Current smoker	Former smoker	Current/former smoker	Never smoker	Never smoker/unknown	Not stated	n	Current smoker	Former smoker	Current/former smoker	Never smoker	Never smoker/unknown	Not stated
Guan, Ni	1085[a]	913 (84.1%)	108 (11.8%)	12 (1.3%)	-	793 (86.9%)	-	-	172 (15.9%)	29 (16.9%)	9 (5.2%)	-	134 (77.9%)	-	-
Zhang, Dong	9[b]	3 (33.3%)	0 (0.0%)	3 (100.0%)	-	-	-	-	6 (66.7%)	2 (33.3%)	4 (66.7%)	-	-	-	-
Wan	9[c]	8 (88.9%)	8 (100.0%)	-	-	-	-	-	1 (11.1%)	1 (100.0%)	-	-	-	-	-
Huang, Wang	3[d]	3 (100.0%)	3 (100.0%)	-	-	-	-	-	0 (0.0%)	0 (0.0%)	-	-	-	-	-
Rentsch	285	168 (58.9%)*	47 (28.0%)	53 (31.5%)	-	68 (40.4%)	-	-	117 (21.1%)	43 (36.8%)	36 (30.8%)	-	38 (32.5%)	-	-
Hu	323	151 (46.7%)	-	-	12 (7.9%)	-	-	139 (92.1%)	172 (53.3%)	-	-	26 (15.1%)	-	-	146 (84.9%)
Wang, Pan	125	100 (80.0%)	-	-	9 (9.0%)	-	-	91 (91.0%)	25 (20.0%)	-	-	7 (28.0%)	-	-	18 (72.0%)
Petrilli	4103	932 (22.7%)*	62 (6.7%)	175 (18.8%)	-	-	695 (74.6%)	-	650 (15.8%)	28 (4.3%)	145 (22.3%)	-	-	477 (73.4%)	-
Kim	27[f]	21 (81.5%)	3 (60.0%)	-	-	-	18 (82.6%)	-	6 (22.2%)	2 (40.0%)	-	-	-	4 (17.4%)	-
Shi, Yu	474*	425 (89.7%)	-	-	34 (7.8%)	-	391 (89.3%)	-	49 (10.3%)	-	-	6 (12.2%)	-	43 (87.8%)	-
Liao, Feng	148[g]	92 (62.2%)	-	-	5 (5.4%)	-	-	87 (94.6%)	56 (37.8%)	3 (5.4%)	-	-	-	-	53 (94.6%)
Shi, Ren	134	88 (65.7%)	-	8 (9.1%)	-	-	-	80 (90.9%)	46 (34.3%)	-	-	6 (13.0%)	-	-	40 (87.0%)
Hadjadj	50	15 (30.0%)	1 (6.7%)	2 (13.3%)	-	12 (80.0%)	-	-	35 (70.0%)	0 (0.0%)	7 (20.0%)	-	28 (80%)	-	-

Note. [a] Data on smoking status were missing for 14 participants; [b] Data on smoking status were missing for 131 participants; [c] Data on smoking status were missing for 126 participants; [d] Data on smoking status were missing for 38 participants; [e] Data on smoking status were missing for 13 participants; [f] Data on smoking status were missing for 1 participant; [g] Data on 1700 participants were not presented; * Patients with disease requiring hospital (but not ITU) admission.

Table 5. Mortality by smoking status.

	Sample size	Death						Recovery					
Author	N	n	Current smoker	Former smoker	Never smoker	Never smoker/unknown	Not stated	n	Current smoker	Former smoker	Never smoker	Never smoker/unknown	Not stated
Chen	274*	113 (41.2%)	7 (6.2%)	2 (1.8%)	-	-	104 (92.0%)^	161 (58.8)	5 (3.1%)	-	-	-	156 (96.9%)
Zhou	191	54 (28.3%)	5 (9.3%)	-	-	-	49 (90.7%)	137 (71.7%)	6 (4.4%)	-	-	-	131 (95.6%)
Yang, Yu	52	32 (61.5%)	0 (0.0%)	-	-	32 (100.0%)	-	20 (38.5%)	2 (10.0%)	-	-	18 (90.0%)	-
Mehra	8910	515 (5.8%)	46 (8.9%)	83 (16.1%)	-	-	386 (4.3	8395 (94.2%)	445 (5.3%)	1410 (16.8%)	-	-	6540 (77.9%)

Note. Solis et al. reported on mortality by smoking status in a multivariable analysis but did not present raw data; * Data on mortality were missing for 274 participants; ^ No smoking history defined as <30 pack-years of smoking.

Table 6. Quality ratings of included studies.

Author	1. Research question clearly stated	2. Study population clearly specified/defined	3. Participation rate of eligible persons at least 50%	4. All subjects recruited from the same or similar populations	5. Sample size justification provided	6. Exposure of interest measured prior to outcome(s)	7. Timeframe sufficient to see an association between exposure and outcome if it existed	8. Examined different levels of the exposure as related to the outcome	9. Exposure measure clearly defined, valid and reliable	10. Exposure assessed more than once over time	11. Outcome measure(s) clearly defined, valid and reliable	12. Outcome assessors blinded to exposure status	13. Loss to follow-up after baseline 20% or less	14. Key potential confounding variables measured and statistically adjusted for	Overall rating
Guan, Ni	Yes	No	No	Cannot determine	No	Yes	Cannot determine	Yes	No	Cannot determine	Yes	No	Not applicable	No	Poor
Guan, Liang	Yes	No	No	Cannot determine	No	Yes	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	Yes	Fair
Lian	Yes	No	Cannot determine	Cannot determine	No	Yes	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	No	Poor
Jin	Yes	Yes	Cannot determine	Cannot determine	No	Yes	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	No	Poor
Chen	Yes	Yes	Cannot determine	Yes	No	Yes	Cannot determine	Yes	No	Cannot determine	Yes	No	Not applicable	No	Poor
Zhou, Yu	Yes	Yes	Yes	Yes	No	Yes	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	No	Poor
Mo	Yes	Yes	Cannot determine	Yes	No	Yes	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	No	Poor
Zhang, Dong	Yes	Yes	Yes	Yes	No	Yes	Cannot determine	Yes	No	Cannot determine	Yes	No	Not applicable	No	Poor
Wan	Yes	No	Cannot determine	Cannot determine	No	Yes	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	No	Poor
Liu, Tao	Yes	Yes	Yes	Yes	No	Cannot determine	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	No	Poor
Huang, Wang	Yes	Yes	Yes	Yes	No	Yes	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	No	Poor
Zhang, Cai	Yes	No	Cannot determine	Yes	No	Cannot determine	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	No	Poor
Guo	Yes	Yes	Yes	Yes	No	Yes	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	No	Poor
Liu, Ming	Yes	Yes	Yes	Yes	No	Yes	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	No	Poor
Huang, Yang	Yes	Yes	Cannot determine	Cannot determine	No	Yes	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	No	Poor
Xu	Yes	Yes	Yes	Yes	No	Yes	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	No	Poor
Li	Yes	No	Cannot determine	Cannot determine	No	Yes	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	No	Poor
Rentsch	Yes	Yes	Yes	Yes	No	Yes	Cannot determine	Yes	No	Cannot determine	Yes	No	Not applicable	Yes	Fair
Hu	Yes	No	Cannot determine	Cannot determine	No	Yes	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	Yes	Fair
Wang, Pan	Yes	No	Cannot determine	Cannot determine	No	Yes	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	No	Poor
Petrilli	Yes	Yes	Yes	Yes	No	Yes	Cannot determine	Yes	No	Cannot determine	Yes	No	Not applicable	Yes	Fair

Chow (US CDC)	Yes	No	No	No	No	Yes	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	No	Poor
Miyara	Yes	Yes	Yes	Yes	No	Yes	Cannot determine	Yes	No	Cannot determine	Yes	No	Not applicable	No	Fair
Dong, Cao	No	No	Cannot determine	Cannot determine	No	Yes	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	No	Poor
Kim	Yes	Yes	Yes	Yes	No	Yes	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	No	Poor
Shi, Yu	Yes	Yes	Yes	Yes	No	Yes	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	No	Poor
Yang, Yu	Yes	Yes	Yes	Yes	No	Yes	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	No	Poor
Argenziano	Yes	Yes	Yes	Yes	No	Yes	Cannot determine	Yes	No	Cannot determine	Yes	No	Not applicable	No	Fair
Solís	Yes	No	Cannot determine	Cannot determine	No	Yes	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	Yes	Poor
Richardson	Yes	Yes	Yes	Yes	No	Yes	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	No	Poor
Fontanet	Yes	Yes	Yes	Yes	No	No	Cannot determine	No	No	No	Yes	No	Not applicable	No	Poor
Zheng, Gao	Yes	Yes	Yes	Yes	No	Cannot determine	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	No	Poor
Liao, Feng	Yes	Yes	Yes	Yes	No	Cannot determine	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	No	Poor
Rodríguez	Yes	Yes	Yes	Yes	No	Yes	Cannot determine	No	No	Cannot determine	Yes	No	Yes	No	Poor
Magagnoli	Yes	Yes	Yes	Yes	No	Yes	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	No	Poor
Shi, Ren	Yes	No	Cannot determine	Cannot determine	No	Yes	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	No	Poor
Hadjadj	Yes	No	Cannot determine	Cannot determine	No	Cannot determine	Cannot determine	Yes	No	Cannot determine	Yes	No	Not applicable	No	Poor
Niedzwiedz	Yes	Yes	Yes	Yes	No	Yes	Cannot determine	Yes	No	Cannot determine	Yes	No	Not applicable	Yes	Fair
ISARIC	No	No	Cannot determine	Cannot determine	No	Cannot determine	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	No	Poor
Gold (US CDC)	Yes	Yes	Yes	Yes	No	Yes	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	No	Poor
Mehra	Yes	No	Cannot determine	Cannot determine	No	Yes	Cannot determine	Yes	No	Cannot determine	Yes	No	Not applicable	Yes	Poor

Discussion

This rapid review of 41 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 36 studies of hospitalised patients (of which five were of 'fair' quality) were generally 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.

Infection by smoking status

Current and former smokers in the community appear more likely to receive a test. It should be noted that 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 and increased sputum production. However, there was no difference in the risk of testing positive in current or former compared with never smokers.

Hospitalisation and disease severity by smoking status

As reported elsewhere, smoking prevalence among multiple hospital cohorts was

consistently lower than national estimates[16]. 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.

However, these early studies are limited by several factors. First, most studies relied on electronic health records (EHRs) as the source of information on smoking status. Research shows large discrepancies between EHRs and actual behaviour[72]. Known failings of EHRs include implausible longitudinal changes, such as former smokers being recorded as never smokers at subsequent hospital visits[72]. 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[73]. It is hence likely that substantial under-reporting of current and former smoking status has occurred across the included studies. Second, individuals with severe symptoms from COVID-19 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). Third, smokers with COVID-19 may be less likely to present to hospital because of lack of access to healthcare and more likely to die in the community from sudden complications (i.e. self-selection). Taken together, these may explain the observation that smoking prevalence has been consistently lower than expected in hospitalised cohorts, without invoking a protective effect of smoking. In contrast, it is not clear how these biases could lead to the associations between under-reported smoking status and greater disease severity among those hospitalised. If there is a true negative effect and the 'missing smokers' arise from biases, then the observed association among those hospitalised would be deflated by those people being classified as never smokers or missing from hospital. On the other hand, if there is a protective effect of nicotine, then abrupt nicotine withdrawal upon hospitalisation may lead to worse outcomes[12]. Fourth, it should also be noted that smoking is a risk factor for both hypertension and diabetes, two diseases associated with worse outcomes from COVID-19, which suggests that current and former smoking may be both directly and indirectly implicated in COVID-19 outcomes. Last, 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.

Mortality by smoking status

Two 'poor' quality studies provided mixed evidence for the risk of death in current compared with former/never smokers. It should also be noted that these early studies have not followed all patients for a sufficient period of time to report such an outcome.

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 not including at least two large population surveys due to their reliance on self-reported SARS-CoV-2 infection (which hence means they are not currently meeting our eligibility criteria)[74,75]. 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.

Implications for research, policy and practice

Further research is needed to resolve the mixed findings summarised in our review. A priority study would be a large, representative 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[76]. GPs and other healthcare providers can play a crucial role – brief, high-quality and free online training is available at NCSCT.

Conclusion

Across 41 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.

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Conflicts of interest

DS and OP report no conflicts of interest. LS has received a research grant and honoraria for a talk and travel expenses from manufacturers of smoking cessation medications (Pfizer and Johnson & Johnson). JB has received unrestricted research funding from Pfizer to study smoking cessation.

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