Open Peer Review on Qeios

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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Funding: The author(s) received no specific funding for this work.

Potential competing interests: The author(s) declared that no potential competing interests exist.

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 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

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) 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).

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).

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[19]. 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.

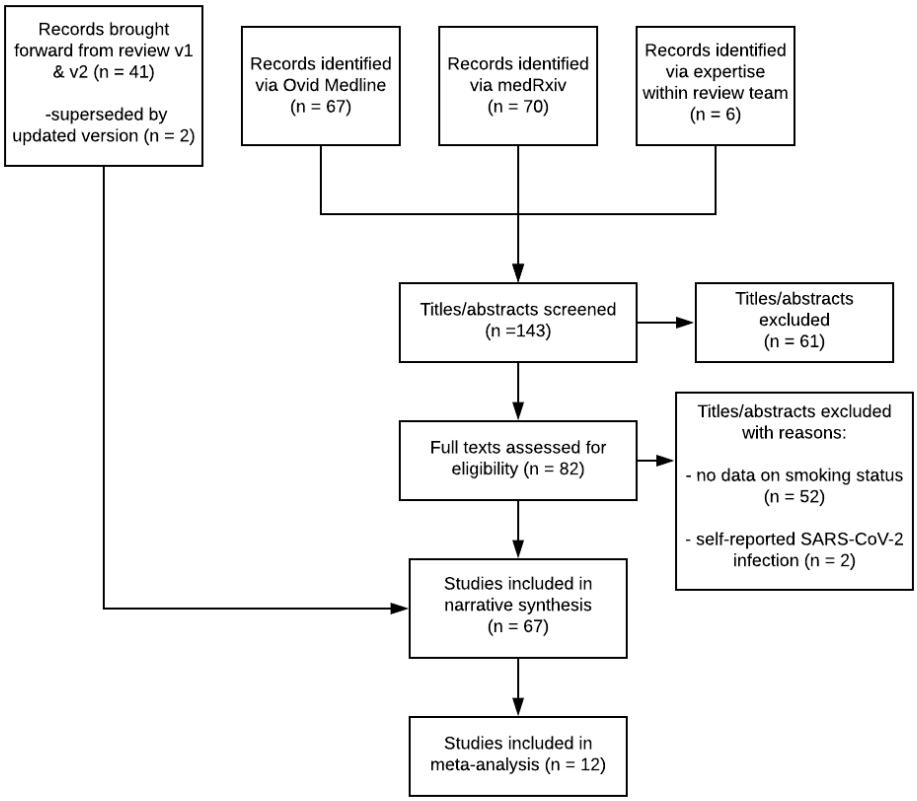
Evidence synthesis

A narrative synthesis was conducted. Where possible, data were pooled in R v.3.6.3[20] with

the Mantel-Haenszel 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

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[1,23,32–41,24,42–51,25–31], twelve in the US[52,53,62,63,54–61], six in the UK[64–69], four in France[70–73], three in Mexico[74–76], three in Spain[77–79], two multi-site international studies[80,81], two in Italy[82,83], and with one each from Iran[84], Israel[85], Korea[86], Kuwait[87] and Switzerland[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[26,41] 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[70] 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+	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
[35]	Liu, Ming	12/03/2020	China	41	Hospital	39 (30-48)	58.5%	Current smoker (9.8%) Not stated (90.2%)	Electronic health records
[32]	Huang, Yang	05/03/2020	China	36	Hospital	69 (60-78)	30.6%	Current/former smoker (11.1%) Not stated (88.9%)	Not stated
[37]	Xu	08/03/2020	China	53	Hospital	-'	47.2%	Current smoker (11.3%) Not stated (88.7%)	Electronic health records
[38]	Li	12/02/2020	China	17	Hospital	45 (33-57)	47.1%	Current smoker (17.6%) Not stated (82.4%)	Electronic health records

[32]	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
[39]	Hu	25/03/2020	China	323	Hospital	61 (23-91)^	48.6%	Current/former smoker (11.8%) Not stated (88.2%)	Not stated
[40]	Wang	24/03/2020	China	125	Hospital	41 (26-66)	43.2%	Current/former smoker (11.8%) Not stated (87.2%)	Electronic health records
[53]	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
[70]	Miyara	09/05/2020	France	479	Community/hospital	-'	44.7%	Current/occasional smoker (6.7%) Former smoker (31.7%) Never smoker (59.7%) Missing (1.8%)	Case report form
[41]	Dong	20/03/2020	China	9	Hospital	44 (30-46)	66.7%	Current smoker (11.1%)# Never smoker/unknown (88.9%)	Electronic health records
[86]	Kim	01/04/2020	Korea	28	Hospital	43 (30-56)	46.4%	Current smoker (18.5%) Never smoker/unknown (81.5%)	Electronic health records
[42]	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
[43]	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
[35]	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
[76]	Solis	25/04/2020	Mexico	650	Hospital	46^	42.1%	Current smoker (9.4%) Not stated (90.6%)	Electronic health records
[56]	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
[71]	Fontanet	23/04/2020	France	661	Community	37 (16-47)	62.0%	Current smoker (10.4%) Never smoker/unknown (89.6%)	Case report form
[44]	Zheng, Gao	19/04/2020	China	66	Hospital	47^	25.8%	Current smoker (12.1%) Not stated (87.9%)	Not stated
[45]	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
[77]	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
[57]	Magagnoli	16/04/2020	USA	368	Hospital	69 (59-75)	0.0%	Current/former smoker (14.1%) Not stated (85.9%)	Electronic health records
[46]	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
[72]	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
[64]	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
[38]	Gold (US CDC)	20/04/2020	USA	305	Hospital	-	-	Current smoker (5.1%) Not stated (94.9%)	Case report form
[80]	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
[81]	ISARIC	06/05/2020	Multiple	20,276	Hospital	72 (0-104)^	40.0%	Current/former smoker (4.8%) Never smoker (48.9%) Missing (46.3%)	Case report form
[47]	Yu, Cai	27/04/2020	China	95	Hospital	-'	44.2%	Current smoker (8.4%) Not stated (91.6%)	Electronic health records
[48]	Zheng, Xiong	30/04/2020	China	73	Hospital	43^	45.2%	Current/former smoker (11.0%) Never smoker (89.0%)	Not stated
[78]	de la Rica	11/05/2020	Spain	48	Hospital	66 (33-88)^	33%	Current/former smoker (20.8%) Not stated (79.2%)	Electronic health records
[49]	Yin, Yang	10/05/2020	China	106	Hospital	73 (67-79)	39.6%	Current/former smoker (17.0%) Not stated (83%)	Electronic health records
[82]	Gaibazzi	10/05/2020	Italy	441	Hospital	71 (62-80)	38%	Current smoker (4.8%) Former smoker (10%) Never smoker (85.3%)	Case report form
[39]	Shi, Zuo	10/05/2020	USA	96	Hospital	63 (54-74)^	41%	Current/former smoker (30.2%) Not stated (69.8%)	Not stated
[65]	Cho	11/05/2020	UK	1331	Community and Hospital	-'	49.2%	Current smoker (19%) Former smoker (27%) Never smoker (54%)	Case report form
[73]	Allenbach	08/05/2020	France	152	Hospital	77 (60-83)	31.1%	Current/former smoker (6.6%) Not stated (93.4%)	Electronic health records
[60]	Robilotti	08/05/2020	USA	423	Hospital	-'	50%	Current smoker (2.1%) Former smoker (37.6%) Never smoker (58.6%) Missing (1.7%)	Electronic health records
[66]	OpenSAFELY Collaborative	07/05/2020	UK	17,425,445	Community and Hospital	-'	50.1%	Current smoker (17.0%) Former smoker (32.9%) Never smoker (45.9%) Missing (4.2%)	Electronic health records
[79]	Borobia	06/05/2020	Spain	2226	Hospital	61 (46-78)	52%	Current smoker (7.1%) Not stated (92.9%)	Case report form
[83]	Giacomelli	06/05/2020	Italy	233	Hospital	61 (50-72)	31.9%	Current/former smoker (30%) Never smoker (70%)	Case report form

[61]	Shah	06/05/2020	USA	316	Hospital	63 (43-72)	48.1%	Current smoker (16.5%) Former smoker (17.7%) Never smoker (42.1%) Missing (23.7%)	Case report form
[75]	Bello-Chavolla	06/05/2020	Mexico	62,489	Community and Hospital	-'	49.4%	Current/former smoker (9.9%) Not stated (90.1%)	Electronic health records
[67]	Kolin	05/05/2020	UK	1474	Community and Hospital	58 (54-62)	46.6%	Current smoker (14.5%) Former smoker (40.2%) Never smoker (44.6%) Missing (0.8%)	Electronic health records
[62]	Lubetzky	08/05/2020	USA	54	Hospital	57 (29-83)^	62%	Current/former smoker (22.2%) Not stated (77.8%)	Electronic health records
[63]	Goyal	17/04/2020	USA	393	Hospital	62 (49-74)	39.3%	Current smoker (5.1%) Not stated (94.9%)	Electronic health records
[50]	Feng	10/04/2020	China	476	Hospital	53 (40-64)	43.1%	Current smoker (6.5%) Former smoker (2.7%) Never smoker (86.1%) Missing (4.6%)	Electronic health records
[51]	Yao	24/04/2020	China	108	Hospital	52 (37-58)	60.2%	Current smoker (3.7%) Not stated (96.3%)	Electronic health records
[64]	Sami	15/05/2020	Iran	490	Hospital	57 (49-64)	39%	Current smoker (14.1%) Never/unknown smoker (85.9%)	Case report form
[87]	Almazeedi	15/05/2020	Kuwait	1096	Hospital	41 (25-57)	19%	Current smoker (4%) Never smokers (96%)	Case report form
[76]	Carrillo-Vega	14/05/2020	Mexico	10,544	Community and Hospital	47 (39-55)	42.3%	Current smoker (8.9%) Not stated (91.1%)	Electronic health records
[65]	Yanover	13/05/2020	Israel	4353	Community and Hospital	35 (22-54)	44.5%	Current smoker (11.8%) Former smoker (3%) Never smoker (85.2%)	Electronic health records
[68]	Hamer	13/05/2020	UK	387,109	Hospital	56 (52-60)	55.1%	Current smoker (9.7%) Former smoker (34.8%) Never smoker (55.5%)	Electronic health records
[88]	Regina	14/05/2020	Switzerland	200	Hospital	70 (55-81)	40%	Current smoker (4.5%) Not stated (95.5%)	Electronic health records
[69]	de Lusignan	15/05/2020	UK	3802	Community and Hospital	58 (34-73)	57.6%	Current smoker (10.9%) Former smoker (46.1%) Never smoker (29.6%) Missing (13.4%)	Electronic health records

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.

Smoking prevalence by country

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.

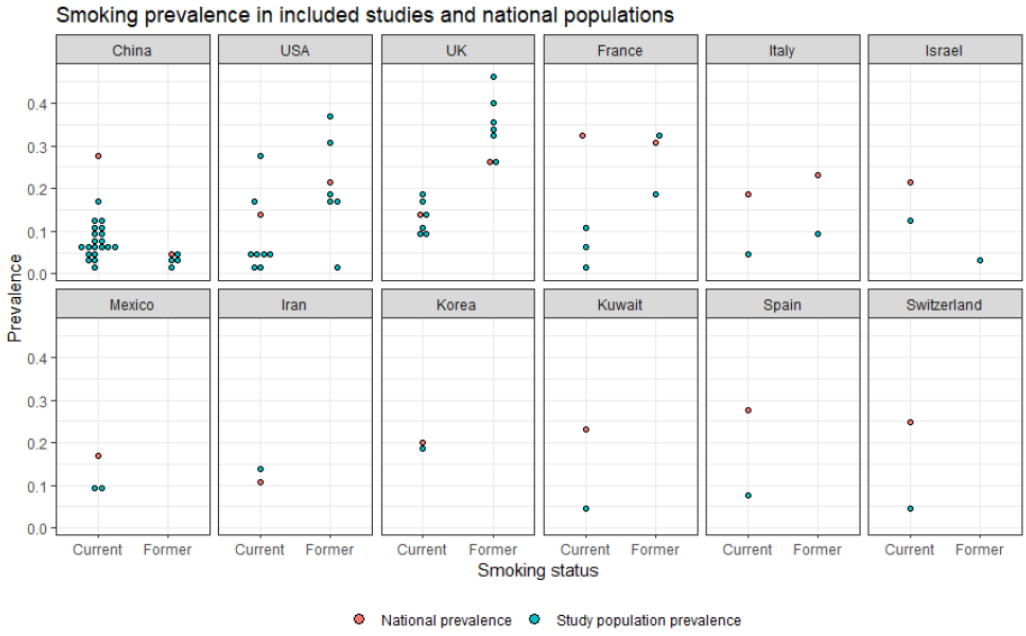


Figure 2. Observed compared with expected smoking prevalence by country. No national data on former smoking prevalence for Israel were identified. Studies in countries presented in the lower panel did not report former smoking prevalence.

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).

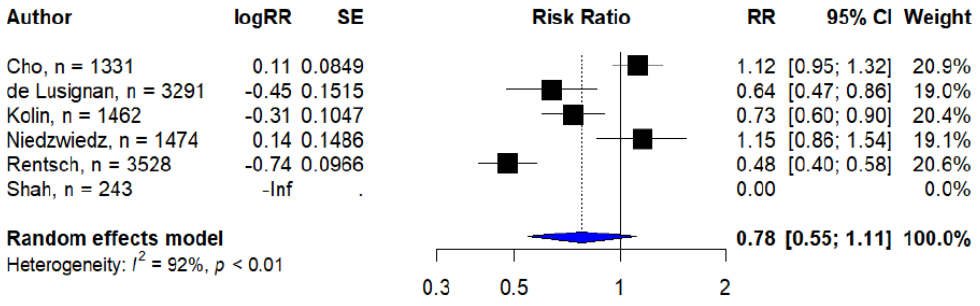


Figure 3. Forest plot for risk of testing positive for SARS-CoV-2 in current vs. never smokers.

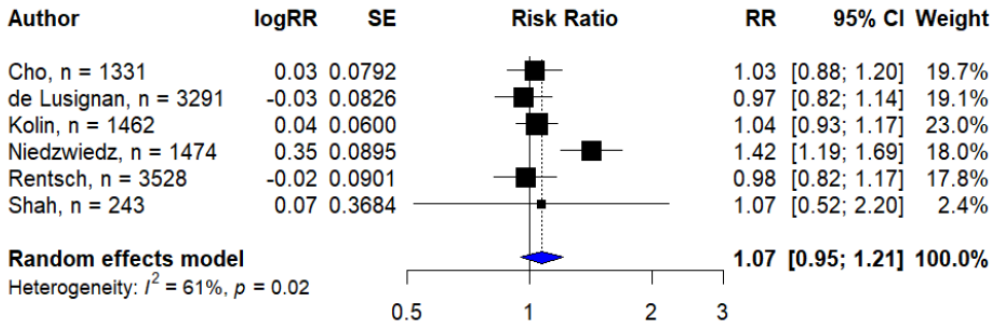


Figure 4. Forest plot for risk of testing positive for SARS-CoV-2 in former vs. never smokers.

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).

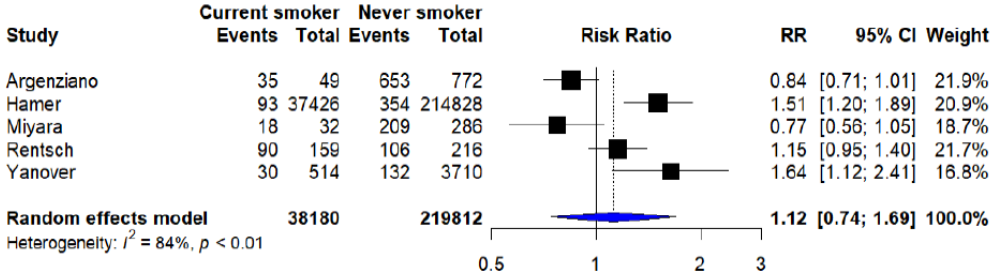


Figure 5. Forest plot for risk of hospitalisation in current vs. never smokers.

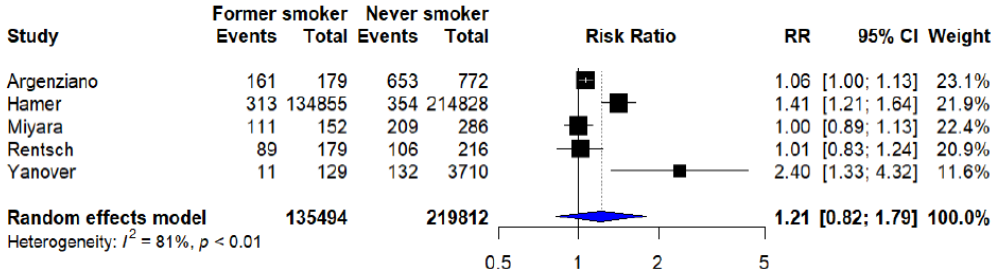


Figure 6. Forest plot for risk of hospitalisation in former vs. never smokers.

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).

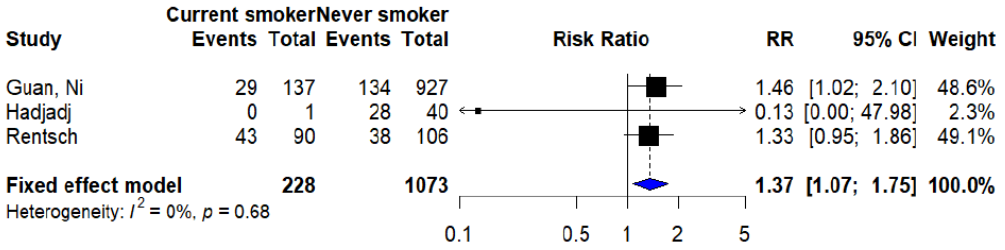


Figure 7. Forest plot for the risk of severe disease in current vs. never smokers.

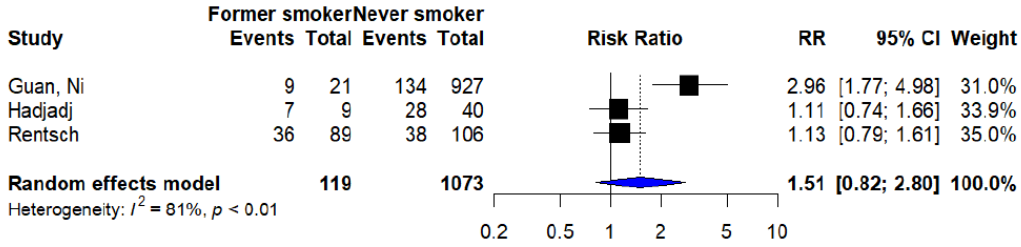


Figure 8. Forest plot for the risk of severe disease in former vs. never smokers.

Mortality by smoking status

Eleven studies reported mortality from COVID-19 by smoking status (see Table 6), with three 'fair' quality studies[66,80,82]. In the first study[82], 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[66] 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[80] 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.

	Total population tested	SARS-CoV-2 negative						SARS-CoV-2 positive					
Author	**N**	**N**	**Current smoker**	**Former smoker**	**Current/former smoker**	**Never smoker**	**Not stated**	**N**	**Current smoker**	**Former smoker**	**Current/former smoker**	**Never smoker**	**Not stated**
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%)	-
Fontanet	661	490 (74.1%)	64 (13.1%)	0 (0%)	-	426 (86.4%)	-	171 (25.9%)	5 (2.9%)	0 (0%)	-	166 (97.1%)	-
Cho	1331	793 (59.6%)	142 (17.9%)	214 (27%)	-	437 (55.1%)	-	538 (40.4%)	111 (20.6%)	145 (27%)	-	282 (52.4%)	-
Shah	243**	212 (87.2%)	52 (24.5%)	47 (22.2%)	-	113 (53.3%)	-	29 (10.4%)	0 (0%)	9 (31%)	-	20 (69%)	-
Bello-Chavollo	62,489	46,960 (75.2%)	-	-	4831 (10.3%)	-	42,125 (89.7%)	15,529 (24.9%)	-	-	1374 (8.8%)	-	14,155 (91.2%)
Kolin	1474***	805 (54.6%)	141 (17.5%)	307 (38.1%)	-	354 (44%)	-	669 (45.4%)	72 (10.8%)	285 (42.6%)	-	303 (45.3%)	-

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; ** Data on smoking status were missing for 75 participants; *** Data on smoking status were missing for 12 participants.

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

COVID +ve sample*		Community							Hospitalised						
Author	**N**	**N**	**Current smoker**	**Former smoker**	**Current/former smoker**	**Never smoker**	**Never/unknown**	**Not stated**	**N**	**Current smoker**	**Former smoker**	**Current/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 (29.6%)	14 (10.1%)	41 (29.5%)	-	77 (55.4%)	-	7 (5%)	340 (72.3%)	18 (5.3%)	111 (32.6%)	-	209 (61.5%)	-	2 (0.6%)
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%)	-	-
Lubetzky	54	15 (27.8%)	-	-	4 (26.7%)	-	-	11 (73.3%)	39 (72.2%)	-	-	8 (20.5%)	-	-	31 (79.5%)
Carrillo-Vega	9946	3922 (39.4%)	408 (10.4%)	-	-	-	-	3514 (89.6%)	6024 (60.6%)	486 (8.1%)	-	-	-	-	5538 (91.9%)
Yanover	4353	4180 (96%)	484 (11.6%)	118 (2.8%)	-	3578 (85.6%)	-	-	173 (4%)	30 (17.3%)	11 (6.4%)	-	132 (76.3%)	-	-
Hamer	387,109	386,349 (99.8%)	37,333 (9.7%)	134,542 (34.8%)	-	214,474 (55.6%)	-	-	760 (0.2%)	93 (12.2%)	313 (41.2%)	-	354 (46.6%)	-	-

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[e]	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%)	-	-
Zheng, Xiong	73	43 (58.9%)	-	-	6 (14%)	37 (86%)	-	-	30 (41.1%)	-	-	2 (6.7%)	28 (93.3%)	-	-
de la Rica	48	26 (54.2%)	-	-	6 (23.1%)	-	-	20 (76.9%)	20 (41.7%)	-	-	4 (20%)	-	-	16 (80%)
Yin, Yang	106	47 (44.3%)	-	-	6 (12.8%)	-	-	41 (87.2%)	59 (55.7%)	-	-	12 (20.3%)	-	-	47 (79.7%)
Allenbach	147	100 (68%)	-	-	9 (9%)	-	-	91 (91%)	47 (32%)	-	-	0 (0%)	-	-	47 (100%)
Goyal	393	263 (67%)	14 (5.3%)	-	-	-	-	249 (94.7%)	130 (33.1%)	6 (4.6%)	-	-	-	-	124 (95.4%)
Feng	471	352 (74.7%)	27 (7.7%)	-	-	-	-	325 (92.3%)	124 (26.3%)	17 (13.7%)	-	-	-	-	107 (86.3%)
Yao	108	83 (76.9%)	1 (1.2%)	-	-	-	-	82 (98.8%)	25 (23.1%)	3 (12%)	-	-	-	-	22 (88%)
Sami	490	400 (81.6%)	53 (13.3%)	-	-	-	-	347 (86.8%)	90 (18.4%)	16 (17.8%)	-	-	-	-	74 (82.2%)
Regina	200	163 (81.5%)	9 (5.5%)	-	-	-	-	154 (94.5%)	37 (18.5%)	0 (0%)	-	-	-	-	37 (100%)

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	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
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%)
Gaibazzi	441	156 (35.4%)	10 (6.4%)	14 (9%)	-	132 (84.6%)	-	-	285 (64.6%)	11 (3.9%)	30 (10.5%)	-	244 (85.6%)	-	-
Borobia	2226	460 (20.7%)	77 (9.6%)	-	-	-	-	416 (90.4%)	1766 (79.3%)	113 (6.4%)	-	-	-	-	1653 (93.6%)
Giacomelli	233	48 (20.6%)	-	-	17 (35.4%)	31 (64.6%)	-	-	185 (79.4%)	-	-	53 (28.6%)	132 (71.4%)	-	
Yao	108	12 (11.1%)	3 (25%)	-	-	-	-	9 (75%)	96 (88.9%)	1 (1%)	-	-	-	-	95 (99%)
Carrillo-Vega	9946	963 (9.7%)	99 (10.3%)	-	-	-	-	864 (89.7%)	8983 (90.3%)	795 (8.9%)	-	-	-	-	8188 (91.1%)

Note. Solis et al. and the OpenSAFELY Collaborative reported on mortality by smoking status in a multivariable analysis but did not present raw data on both exposure and outcome; * 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	Fair
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
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	Fair
Yu, Cai	Yes	Yes	Cannot determine	Cannot determine	No	Cannot determine	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	No	Poor
Zheng, Xiong	Yes	No	Cannot determine	Cannot determine	No	Cannot determine	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	Yes	Poor
Miyara	Yes	Yes	Yes	Yes	No	Yes	Cannot determine	Yes	No	Cannot determine	Yes	No	Not applicable	No	Fair
de la Rica	Yes	Yes	Yes	Yes	No	Yes	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	No	Poor
Yin, Yang	Yes	Yes	Cannot determine	Yes	No	Cannot determine	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	No	Poor
Gaibazzi	Yes	Yes	Cannot determine	Cannot determine	No	Cannot determine	Cannot determine	Yes	No	Cannot determine	Yes	No	Not applicable	Yes	Fair
Shi, Zuo	Yes	Yes	Cannot determine	Yes	No	Cannot determine	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	No	Poor

Cho	Yes	Yes	Cannot determine	Yes	No	Yes	Cannot determine	Yes	Yes	Cannot determine	Yes	No	Not applicable	Yes	Fair
Allenbach	Yes	Yes	Cannot determine	Yes	No	No	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	No	Poor
Robilotti	Yes	No	Yes	Cannot determine	No	Cannot determine	Cannot determine	Yes	Yes	Cannot determine	Yes	No	Not applicable	No	Poor
OpenSAFELY Collaborative	Yes	No	Yes	Cannot determine	No	Cannot determine	Cannot determine	Yes	No	Cannot determine	Yes	Yes	Not applicable	Yes	Fair
Borobia	Yes	Yes	Yes	Cannot determine	No	No	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	No	Poor
Giacomelli	Yes	Yes	Cannot determine	Yes	No	Cannot determine	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	No	Poor
Shah	Yes	Yes	Cannot determine	Yes	No	Cannot determine	Cannot determine	Yes	Yes	Cannot determine	Yes	Yes	Not applicable	No	Fair
Bello-Chavolla	Yes	Yes	Cannot determine	Yes	No	Cannot determine	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	No	Poor
Kolin	Yes	Yes	Cannot determine	Yes	No	Cannot determine	Cannot determine	Yes	Yes	Cannot determine	Yes	No	Not applicable	No	Fair
Lubetzky	Yes	Yes	Cannot determine	Yes	No	Cannot determine	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	No	Poor
Goyal	Yes	Yes	Yes	Cannot determine	No	Cannot determine	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	No	Poor
Feng	Yes	Yes	Yes	Cannot determine	No	Cannot determine	Cannot determine	Yes	No	Cannot determine	Yes	No	Not applicable	No	Poor
Yao	Yes	Yes	Yes	Cannot determine	No	Cannot determine	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	No	Poor
Sami	Yes	Yes	Cannot determine	Cannot determine	No	Cannot determine	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	No	Poor
Almazeedi	Yes	Yes	Yes	Yes	No	Cannot determine	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	Yes	Poor
Carillo-Vega	Yes	Yes	Yes	Cannot determine	No	Cannot determine	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	Yes	Poor
Yanover	Yes	Yes	Yes	Yes	No	Cannot determine	Cannot determine	Yes	No	Cannot determine	Yes	No	Not applicable	Yes	Fair
Hamer	Yes	No	Cannot determine	Yes	No	Cannot determine	Cannot determine	Yes	No	Cannot determine	No	No	Not applicable	No	Fair
Regina	Yes	Yes	Cannot determine	Yes	No	Cannot determine	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	Yes	Poor
ISARIC	No	No	Cannot determine	Cannot determine	No	Cannot determine	Cannot determine	No	No	Cannot determine	Yes	No	Not applicable	No	Poor

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[89].

Hospitalisation and disease severity by smoking status

As reported elsewhere, smoking prevalence among multiple hospital cohorts was consistently lower than national estimates16. 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[90]. Known failings of EHRs include implausible longitudinal changes, such as former smokers being recorded as never smokers at subsequent hospital visits[90]. 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[91]. 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[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)[92].

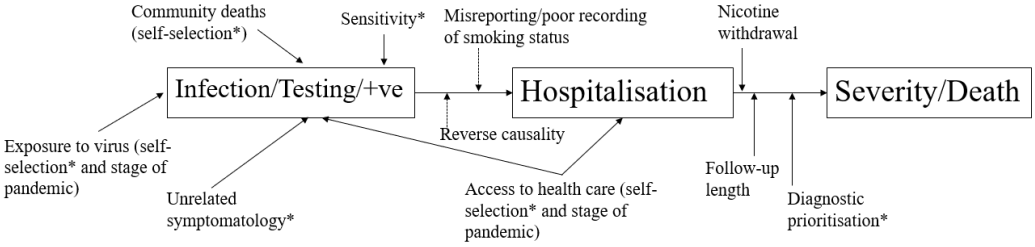


Figure 9. A schematic of some interpretation issues for the association of smoking and SARS-CoV-2/COVID-19. * indicates potential confounding with smoking status

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)[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.

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

An original short review for the Royal College of Physicians was converted to an extended living review after a request by Martin Dockrell, Tobacco Control Lead, Public Health England. All scientific decisions were made by the authors independently of funders and external organisations. The authors would also like to thank Rosemary Koper for her assistance in running the electronic searches.

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