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 5)

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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 is 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 disease.

Methods: This is a living evidence review with frequent updates. 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 or experimental studies with community-dwelling or hospitalised adults aged 16+ years who had received a test for SARS-CoV-2 infection or a diagnosis of COVID-19, providing that data on smoking status were reported. Studies were judged as 'good' quality if they: i) had low levels of missing data on smoking status (i.e. <20%) and used a reliable self-report measure that distinguished between current, former and never smoking status; AND ii) used biochemical verification of smoking status and reported results from adjusted analyses; OR reported data from a representative/random sample. Studies were rated

as ‘fair’ if they fulfilled criterion i) only and were otherwise rated as ‘poor’.

Results: Version 5 with searches up to 23 June 2020 included 148 studies, 43 of which were conducted in China, 37 in the US, 15 in the UK, nine in Mexico, nine in Spain, eight in France, six in Italy, five across multiple international sites, two in Israel, and one each from 14 further countries. Thirty-two (21.6%) studies reported current, former and never smoking status. Twenty-six studies (17.6%) explicitly reported the proportion missing data on smoking status, which ranged from 0.08% to 96.4%. Notwithstanding recording uncertainties, compared with adult national prevalence estimates, recorded current and former smoking rates were generally lower than expected. In 12 ‘fair’ quality studies, current smokers were at reduced risk of testing positive for SARS-CoV-2 compared with never smokers (RR = 0.70, 95% CI = 0.55-0.88, p = .003, I2 = 90%). No significant difference was observed between former and never smokers (RR = 1.02, 95% CI = 0.92-1.12, p = .76, I2 = 72%). In seven ‘fair’ quality studies, there was no significant difference between current and never (RR = 1.06, 95% CI = 0.79-1.44, p = .63, I2 = 79%) or former and never smokers (RR = 1.20, 95% CI = 0.95-1.51, p = .10, I2 = 79%) in the risk of requiring admission to hospital with COVID-19 among those testing positive in the community. In six ‘fair’ quality studies, no significant difference in disease severity was observed between current and never smokers (RR = 1.22, 95% CI = 0.98-1.53, p = .08, I2 = 22%). Former smokers were at increased risk of greater disease severity compared with never smokers (RR = 1.58, 95% CI = 1.07-2.32, p = .02, I2 = 68%). In five ‘fair’ quality studies, current (RR = 1.70, 95% CI = 1.14-2.55, p = .01, I2 = 29%) and former smokers (RR = 2.00, 95% CI = 1.57-2.55, p < .0.001, I2 = 0%) were at increased risk of in-hospital death compared with never smokers.

Conclusions: Across 148 studies, there is substantial uncertainty about the associations of smoking with COVID-19 outcomes. The recorded smoking prevalence in the included studies was generally lower than overall adult national estimates. There was no evidence of reduced risk of admission to hospital for current compared with never smokers among those testing positive in the community. There was some evidence that current compared with never smoking is associated with reduced risk of testing positive in the community but also greater in-hospital mortality from COVID-19. There was some evidence that former compared with never smoking is associated with increased risk of greater disease severity and in-hospital mortality from COVID-19.

Implications: Unrelated to COVID-19, smokers are at a greater risk of a range of

serious health problems. Given uncertainty around the association of smoking with COVID-19 outcomes, smoking cessation remains a public health priority and high-quality smoking cessation advice including recommendations to use alternative nicotine products should form part of public health efforts during this pandemic. High quality, smoking-specific research is needed to resolve these mixed findings.

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 ACE-2 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 ACE-2 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 is a living review with regular updates. As evidence accumulates, the review will be expanded to include studies reporting COVID-19 outcomes by alternative nicotine use (e.g., nicotine replacement therapy or e-cigarettes).

Methods

Study design

This is a living evidence review which is updated as new evidence becomes available[18]. 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[19].

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, retrospective cohort, prospective cohort) 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) clinical diagnosis of COVID-19, iii) hospitalisation with COVID-19, iv) severity of COVID-19 disease in those hospitalised 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:

covid smoking
covid nicotine
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 public health 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, not stated, missing); x) SARS-CoV-2 infection; xi) diagnosis of COVID-19; xii) hospitalisation with COVID-19; xiii) disease severity in those hospitalised with COVID-19; and xiv) mortality.

Quality appraisal

In previous review versions, we used the National Institutes of Health's Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies to determine the quality of included studies[20]. However, we decided against applying the entire tool in the current review version. The appraisal is challenging to apply when studying an emerging disease with unknown pathology. For example, it is not possible to determine what

proportion of eligible participants/patients are included in the studied populations when the total number of infections in a given region/city is unknown. With a largely unknown disease process, it is also difficult to determine whether the time between the exposure and outcome is sufficient. We therefore focused on three of the 14 criteria to determine whether studies were of sufficient quality to warrant inclusion in meta-analysis. Studies were judged as 'good' quality if they: i) had low levels of missing data on smoking status (i.e. <20%) and used a reliable self-report measure that distinguished between current, former and never smoking status; AND ii) used biochemical verification of smoking status and reported results from adjusted analyses; OR reported data from a representative/random sample. Studies were rated as 'fair' if they fulfilled only criterion i) and 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[21] with the Mantel-Haenszel or inverse variance method using random or fixed effects, depending on heterogeneity, and presented as risk ratios (RRs)[22]. Heterogeneity between study outcomes was assessed using the I2 statistic, suitable for smaller meta-analyses[23].

To aid in the visualisation of smoking prevalence in the included studies, 95% bootstrap percentile confidence intervals were calculated for each study estimate. We performed 1,000 bootstrap replications, with the 2.5th and 97.5th percentiles of the empirical distribution forming the 95% bootstrap percentile confidence intervals[24]. It should be noted that prevalence estimates in the included studies were not adjusted for age, sex, socioeconomic position, or region within countries.

Results

In the current review version (v5), a total of 636 new records were identified, with 148 studies included in a narrative synthesis and 23 studies included in meta-analyses (see Figure 1).

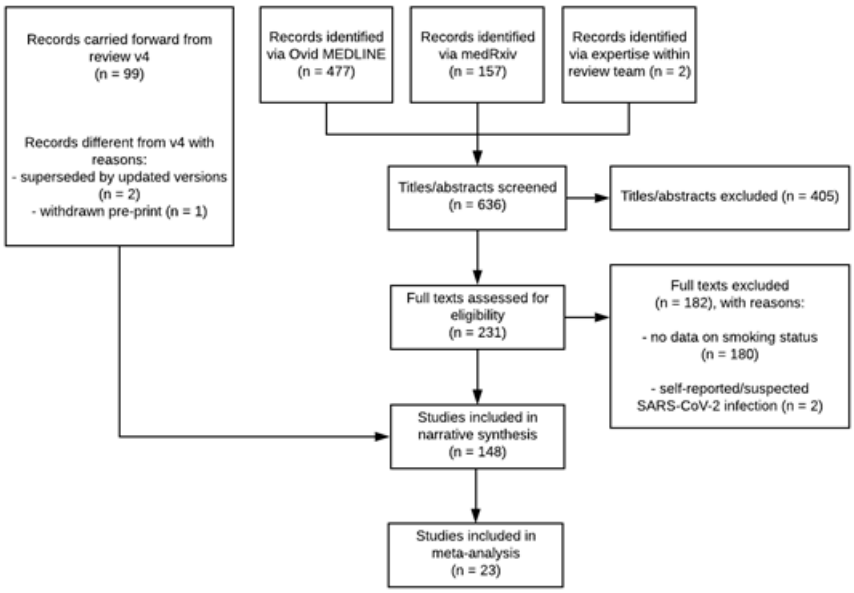

Figure 1. PRISMA flow diagram of included studies.

Study characteristics

Characteristics of included studies are presented in Table 1. Forty-three studies were conducted in China, 37 in the US, 15 in the UK, nine in Mexico, nine in Spain, eight in France, six in Italy, five across multiple international sites, two in Israel, and one each from Brazil, Chile, Denmark, Finland, Germany, India, Iran, South Korea, Kuwait, Poland, Portugal, Saudi Arabia, Switzerland and Turkey (see Figure 2). One-hundred-and-five studies were conducted in hospital settings. Thirty-four studies included a community component in addition to hospitalised patients. Seven studies were conducted exclusively in the community, one in a quarantine centre and one did not state the study setting. Studies had a median of 326 (interquartile range = 106-1,122) participants.

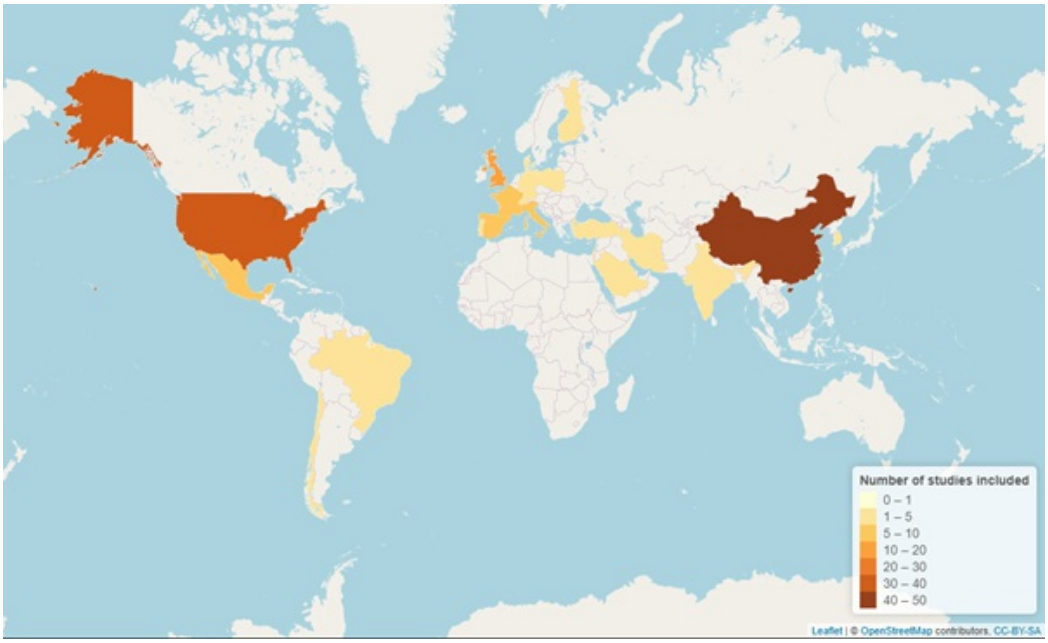

Figure 2. Map of countries where included studies were conducted. Five studies were performed in multiple countries and are hence not included here.

Smoking status

Categorisation of smoking status was heterogeneous (see Table 1). Ninety-two studies collected data on smoking status through routine electronic health records, 35 studies used a bespoke case report form for COVID-19 and 21 studies did not state the source for information on smoking status. None of the studies verified smoking status biochemically. Notably, only 32 (21.6%) studies reported current, former and never smoking status, with a further 11 studies reporting current/former and never smoking status. The remaining 105 studies reported current, current/former or current and former smoking status but did not explicitly state whether remaining participants were never smokers or if data were missing on smoking status. Twenty-six studies explicitly reported the proportion with missing data on smoking status, which ranged from 0.08% to 96.4%.

Use of alternative nicotine products

Two studies recorded the use of alternative nicotine products in current and/or former smokers but did not report COVID-19 outcomes stratified by nicotine use[25,26].

Quality appraisal

Twenty-eight studies were rated as 'fair' quality due to having low levels of missing data and distinguishing between current, former and never smoking status (see Table 1). The remaining 120 studies were rated as 'poor' quality.

Table 1. Characteristics of included studies.

Reference	Lead author	Date published	Country	Sample size	Study setting	Median age (IQR)	Female %	Current smokers %	Current/former smokers %	Never smokers %	Never/unknown smokers %	Missing/not stated %	Overall rating
[1]	Guan, Ni	2020-02-28	China	1,099	Hospital	47 (35-58)	41.90	12.47	-	84.35	-	1.27	fair
[27]	Guan, Liang	2020-03-26	China	1,590	Hospital	49 (33-64)	42.70	-	6.98	93.02	-	0.00	poor
[28]	Lian	2020-03-25	China	788	Hospital	-	38.50	6.85	-	-	-	93.15	poor
[29]	Jin	2020-03-24	China	651	Hospital	46 (32-60)	49.20	6.30	-	-	-	93.70	poor
[30]	Chen	2020-03-26	China	548	Hospital	62 (44-70)	37.60	4.38	-	-	-	93.07	poor
[31]	Zhou, Yu	2020-03-11	China	191	Hospital	56 (46-67)	38.00	5.76	-	-	-	94.24	poor
[32]	Mo	2020-03-16	China	155	Hospital	54 (53-66)	44.50	3.87	-	-	-	96.13	poor
[33]	Zhang, Dong	2020-02-19	China	140	Hospital	57^ (25-87)	46.30	1.43	-	-	-	93.57	poor
[34]	Wan	2020-03-21	China	135	Hospital	47 (36-55)	46.70	6.67	-	-	-	93.33	poor
[35]	Liu, Tao	2020-02-28	China	78	Hospital	38 (33-57)	50.00	-	6.41	-	-	93.59	poor
[36]	Huang, Wang	2020-01-24	China	41	Hospital	49 (41-58)	27.00	7.32	-	-	-	92.68	poor
[37]	Zhang, Cai	2020-03-20	China	645	Hospital	-	49.10	6.36	-	-	-	93.64	poor
[38]	Guo	2020-03-27	China	187	Hospital	59 (45-73)	51.30	9.63	-	-	-	90.37	poor
[39]	Liu, Ming	2020-03-12	China	41	Hospital	39 (30-48)	58.50	9.76	-	-	-	90.24	poor
[36]	Huang, Yang	2020-03-05	China	36	Hospital	69 (60-78)	30.60	-	11.11	-	-	88.89	poor
[40]	Xu	2020-03-08	China	53	Hospital	-	47.20	11.32	-	-	-	88.68	poor
[41]	Li	2020-02-12	China	17	Hospital	45 (33-57)	47.10	17.65	-	-	-	82.35	poor
[42]	Rentsch	2020-04-14	USA	3,528	Community and Hospital	66 (60-70)	4.60	27.18	-	36.92	-	5.30	fair
[43]	Hu	2020-03-25	China	323	Hospital	61^ (23-91)	48.60	-	11.76	-	-	88.24	poor
[44]	Wang, Pan	2020-03-24	China	125	Hospital	41 (26-66)	43.20	-	12.80	-	-	87.20	poor
[45]	Petrilli	2020-04-11	USA	4,103	Community and Hospital	52 (36-65)	47.90	5.17	-	-	78.60	0.00	poor
[46]	Chow (US CDC)	2020-03-31	USA	7,162	Community and Hospital	-	-	1.34	-	-	-	96.36	poor
[47]	Dong, Cao	2020-03-20	China	9	Hospital	44 (30-46)	66.70	11.11	-	-	-	88.89	poor
[48]	Kim	2020-04-01	Korea	28	Hospital	43 (30-56)	46.40	17.86	-	-	-	82.14	poor
[49]	Shi, Yu	2020-03-18	China	487	Hospital	46 (27-65)	46.80	-	8.21	-	-	91.79	poor
[50]	Yang, Yu	2020-02-24	China	52	Hospital	60 (47-73)	37.00	3.85	-	-	-	96.15	poor
[51]	Argenziano	2020-04-22	USA	1,000	Hospital	63 (50-75)	40.40	4.90	-	77.20	-	0.00	fair
[52]	Solis	2020-04-25	Mexico	650	Hospital	46	42.10	9.38	-	-	-	90.62	poor
[53]	Richardson	2020-04-22	USA	5,700	Hospital	63 (52-75)	39.70	-	9.79	52.79	-	37.42	poor
[54]	Fontanet	2020-04-23	France	661	Community and Hospital	37 (16-47)	62.00	10.44	-	-	89.56	0.00	poor
[55]	Zheng, Gao	2020-04-19	China	66	Hospital	47^	25.80	12.12	-	-	-	87.88	poor
[56]	Liao, Feng	2020-04-24	China	1,848	Hospital	55 (48-61)	54.70	-	0.43	-	-	99.57	poor
[57]	Rodriguez-Cola	2020-04-24	Spain	7	Hospital	68 (34-75)	28.60	-	42.86	57.14	-	0.00	poor

[58]	Magagnoli	2020-04-16	USA	368	Hospital	69 (59-75)	0.00	-	14.13	-	-	85.87	poor
[59]	Shi, Ren	2020-04-23	China	134	Hospital	46 (34-58)	51.50	-	10.45	-	-	89.55	poor
[60]	Hadjadj	2020-04-23	France	50	Hospital	55 (50-63)	22.00	2.00	-	80.00	-	0.00	fair
[61]	Niedzwiedz	2020-04-30	UK	1,474	Community and Hospital	-	-	9.98	-	55.04	-	0.59	fair
[62]	Gold (US CDC)	2020-04-20	USA	305	Hospital	-	50.50	5.25	-	-	-	94.75	poor
[63]	Yu, Cai	2020-04-27	China	95	Hospital	-	44.21	8.42	-	-	-	91.58	poor
[64]	Zheng, Xiong	2020-04-30	China	73	Hospital	43^	45.20	-	10.96	89.04	-	0.00	poor
[65]	de la Rica	2020-05-11	Spain	48	Hospital	66^ (33-88)	33.00	-	20.83	-	-	79.17	poor
[66]	Yin, Yang	2020-05-10	China	106	Hospital	73 (61-85)	39.60	-	16.98	-	-	83.02	poor
[67]	Gaibazzi	2020-05-10	Italy	441	Hospital	71 (62-80)	38.00	4.76	-	85.26	-	0.00	poor
[68]	Shi, Zuo	2020-05-10	USA	96	Hospital	63^ (44-82)	41.00	-	30.21	-	-	69.79	fair
[69]	Cho	2020-05-11	UK	1,331	Community and Hospital	-	49.20	19.01	-	54.02	-	0.00	poor
[70]	Allenbach	2020-05-08	France	152	Hospital	77 (60-83)	31.10	-	6.58	-	-	93.42	fair
[71]	Robilotti	2020-05-08	USA	423	Hospital	-	50.00	2.13	-	58.63	-	1.65	fair
[72]	The Opensafely Collaborative	2020-05-07	UK	17,425,445	Community and Hospital	-	50.10	17.00	-	45.91	-	4.16	poor
[73]	Borobia	2020-05-06	Spain	2,226	Hospital	61 (46-78)	52.00	7.05	-	-	-	92.95	poor
[74]	Giacomelli	2020-05-06	Italy	233	Hospital	61 (50-72)	31.90	-	30.04	69.96	-	0.00	poor
[75]	Shah	2020-05-06	USA	316	Hospital	63 (43-72)	48.10	16.46	-	42.09	-	23.73	poor
[76]	Bello-Chavolla	2020-05-06	Mexico	62,489	Community and Hospital	-	49.40	-	9.94	-	-	90.06	fair
[77]	Kolin	2020-05-05	UK	1,474	Community and Hospital	58 (49-67)	46.60	14.45	-	44.57	-	0.81	poor
[78]	Lubetzky	2020-05-08	USA	54	Hospital	57 (29-83)	62.00	-	22.22	-	-	77.78	poor
[79]	Goyal	2020-04-17	USA	393	Hospital	62.2 (49-74)	39.30	5.09	-	-	-	94.91	poor
[80]	Feng	2020-04-10	China	476	Hospital	53 (40-64)	43.10	9.24	-	-	-	90.76	poor
[81]	Yao	2020-04-24	China	108	Hospital	52 (37-58)	60.20	3.70	-	-	-	96.30	poor
[82]	Sami	2020-05-15	Iran	490	Hospital	56.6 (41-71)	39.00	14.08	-	-	85.92	0.00	poor
[83]	Almazeedi	2020-05-15	Kuwait	1,096	Hospital	41 (25-57)	19.00	4.01	-	-	95.99	0.00	poor
[84]	Carrillo-Vega	2020-05-14	Mexico	10,544	Community and Hospital	46.5^ (30-62)	42.30	8.88	-	-	-	91.12	fair
[85]	Yanover	2020-05-13	Israel	4,353	Community and Hospital	35 (22-54)	44.50	11.81	-	85.23	-	0.00	fair
[86]	Hamer	2020-05-13	UK	387,109	Hospital	56.2 (48-64)	55.10	9.67	-	55.50	-	0.00	poor
[87]	Regina	2020-05-14	Switzerland	200	Hospital	70 (55-81)	40.00	4.50	-	-	-	95.50	fair
[88]	de Lusignan	2020-05-15	UK	3,802	Community	58 (34-73)	57.60	10.86	-	29.59	-	13.44	poor
[89]	Targher	2020-05-13	China	339	Hospital	48.4^	52.80	8.26	-	-	-	91.74	poor
[90]	Valenti	2020-05-18	Italy	789	Community	40.7^	34.98	25.86	-	-	-	74.14	fair
[91]	Feuth	2020-05-18	Finland	28	Hospital	56 (47-72)	46.00	10.71	-	60.71	-	0.00	poor
[92]	Ge	2020-05-18	China	51	Hospital	70 (58-79)	27.50	13.73	-	-	-	86.27	fair

[93]	Parrotta	2020-05-18	USA	76	Community and Hospital	44.9 (13-71)	61.80	2.63	-	68.42	-	2.63	poor
[94]	Shekhar	2020-05-18	USA	50	Hospital	55.5 (20-85)	54.00	48.00	-	-	-	52.00	poor
[95]	Mejia-Vilet	2020-05-16	Mexico	329	Hospital	49 (41-60)	36.00	-	6.99	-	-	93.01	poor
[96]	Chen, Jiang	2020-05-16	China	135	Hospital	-	42.20	-	9.63	-	-	90.37	poor
[97]	Li	2020-05-16	China	1,008	Hospital	55 (44-65)	43.60	5.65	-	-	-	94.35	poor
[26]	Rimland	2020-05-19	USA	11	Hospital	59 (48-65)	18.20	9.09	-	-	-	81.82	poor
[98]	Palaiodimos	2020-05-15	USA	200	Hospital	64 (50-73.5)	51.00	-	32.50	67.50	-	0.00	fair
[99]	Ip	2020-05-25	USA	2,512	Hospital	64 (52-76)	37.62	3.07	-	64.49	-	14.61	poor
[100]	Heili-Frades	2020-05-25	Spain	4,712	Hospital	62 (47-77)	50.50	4.94	-	-	66.49	11.16	poor
[101]	Vaquero-Roncero	2020-05-24	Spain	146	Hospital	66^ (59-72)	32.20	-	6.85	-	-	93.15	poor
[102]	Kim, Garg	2020-05-22	USA	2,491	Hospital	62 (50-75)	46.80	6.02	-	-	68.13	0.08	poor
[103]	Wu	2020-05-21	Italy	174	Hospital	61.2^ (50-71)	30.46	-	33.33	-	-	66.67	poor
[104]	Shi, Zhao	2020-05-20	China	101	Hospital	71 (59-80)	40.60	-	4.95	-	-	95.05	poor
[105]	Kimmig	2020-05-20	USA	60	Hospital	64 (50-68)	41.67	-	36.67	-	-	63.33	fair
[106]	Al-Hindawi	2020-05-20	UK	31	Hospital	61	12.90	3.23	-	25.81	-	0.00	poor
[107]	Basse	2020-05-19	France	141	Hospital	62 (52-72)	72.00	17.73	-	-	-	82.27	poor
[108]	Freites	2020-05-19	Spain	123	Hospital	59.88^ (44-74)	69.92	3.25	-	-	-	96.75	poor
[109]	Alshami	2020-05-19	Saudi Arabia	128	Quarantine Centre	39.6^ (24-55)	53.90	15.62	-	-	-	82.03	poor
[110]	Berumen	2020-05-26	Mexico	102,875	Hospital	-	49.08	-	9.64	-	90.36	0.00	poor
[111]	Gianfrancesco	2020-05-29	Multiple	600	Community and Hospital	56 (45-67)	71.00	-	21.50	64.83	-	13.67	poor
[112]	Li, Long	2020-05-28	China	145	Not Stated	49^ (13-80)	61.00	-	5.52	-	-	94.48	poor
[113]	Batty	2020-06-01	UK	908	Hospital	57.27^ (48-66)	44.27	11.23	-	-	-	88.77	fair
[114]	Israel	2020-06-01	Israel	24,087	Community and Hospital	43.4^ (24-62)	48.70	17.08	-	69.88	-	0.00	poor
[115]	del Valle	2020-05-30	USA	1,484	Hospital	62 (52-72)	40.60	5.53	-	-	-	71.16	poor
[116]	Zuo, Zuo	2020-05-29	USA	44	Hospital	57^ (45-69)	18.18	-	27.27	-	-	72.73	poor
[117]	Chaudhry	2020-05-29	USA	40	Community and Hospital	52 (45.5-61)	60.00	-	15.00	-	-	85.00	poor
[118]	Louis	2020-06-28	USA	22	Hospital	66.5^ (55-77)	36.40	-	45.45	-	-	54.55	poor
[119]	Soto-Mota	2020-05-27	Mexico	400	Hospital	-	30.00	-	12.00	-	-	88.00	poor
[120]	Patel	2020-05-26	USA	104	Hospital	60.66^ (47-74)	47.00	41.35	-	-	49.04	9.62	poor
[121]	Garibaldi	2020-05-26	USA	832	Hospital	63 (49-75)	47.00	5.53	-	-	-	71.88	poor
[122]	Docherty	2020-05-22	Multiple	20,133	Hospital	72.9 (58-82)	40.00	4.23	-	44.54	-	29.55	poor
[123]	Boulware	2020-03-06	Multiple	821	Community	40 (33-50)	51.60	3.29	-	-	-	96.71	fair
[124]	Kuderer	2020-05-28	Multiple	928	Community and Hospital	66 (57-76)	50.0	4.6	-	50.5	-	9.70	fair
[125]	Romao	2020-06-08	Portugal	34	Community	41^ (26-66)	67.7	-	26.5	-	-	73.53	poor
[126]	Giannouchos	2020-06-07	Mexico	236,439	Community and Hospital	42.5^ (25-59)	49.1	9.1	-	-	90.9	0.00	poor

[127]	Ramlall	2020-06-06	USA	11,116	Community and Hospital	52 (34.7-69.5)	55.2	-	26.8	73.2	-	0.00	poor
[128]	Wang, Oekelen	2020-06-05	USA	58	Community and Hospital	67	48.0	-	36.2	-	-	63.79	poor
[129]	Perrone	2020-06-05	Italy	1,189	Hospital	-	21.2	-	21.9	-	-	78.13	poor
[130]	Sharma	2020-06-05	India	501	Hospital	35.1^ (18-51)	36.0	-	4.2	-	-	95.81	poor
[131]	Eugen-Olsen	2020-06-02	Denmark	407	Hospital	64 (47-77)	57.7	20.6	-	39.6	-	2.95	fair
[132]	Martinez-Portilla	2020-06-02	Mexico	224	Community and Hospital	29 (26-33)	100.0	-	3.1	-	-	96.88	poor
[133]	Raisi-Estabragh	2020-06-02	UK	4,510	Hospital	-	48.8	-	51.8	-	-	48.20	poor
[134]	Luo	2020-06-02	China	625	Hospital	46	47.7	3.0	-	-	-	96.96	poor
[135]	Houlihan	2020-06-09	UK	200	Community	34 (29-44)	61.0	11.0	-	66.5	-	6.00	fair
[136]	Cen	2020-06-08	China	1,007	Hospital	61 (49-68)	51.0	-	8.7	-	-	91.26	poor
[137]	Klang	2020-05-23	USA	3,406	Hospital	-	61.8	-	23.3	-	-	76.72	poor
[138]	Maraschini	2020-06-12	Italy	146	Hospital	32.5^ (27-38)	100.0	-	-	80.8	-	9.59	poor
[139]	Wang, Zhong	2020-06-12	USA	7,592	Community and Hospital	-	45.1	3.6	-	51.9	-	27.42	poor
[140]	McQueenie	2020-06-12	UK	428,199	Community and Hospital	-	54.9	-	44.4	55.0	-	0.59	poor
[25]	Miyara	2020-06-12	France	479	Community and Hospital	-	44.7	6.7	-	59.7	-	1.88	fair
[141]	Apea	2020-06-12	UK	1,737	Hospital	63.4^	30.4	-	10.0	-	-	90.04	poor
[142]	Woolford	2020-06-11	UK	4,510	Community and Hospital	70.5	51.2	13.0	-	48.1	-	0.80	fair
[143]	Hultcrantz	2020-06-11	USA	127	Community and Hospital	68 (41-91)	46.0	-	26.8	72.4	-	0.79	poor
[144]	Cepelowicz	2020-06-10	USA	280	Hospital	59.6^ (41-77)	45.5	5.7	-	74.6	-	8.93	fair
[145]	Lan	2020-06-09	USA	104	Community	49^ (34-63)	47.1	-	24.0	-	-	75.96	poor
[146]	Russell, Moss	2020-06-09	UK	156	Community and Hospital	65.18^ (50-79)	42.3	7.1	-	37.8	-	30.13	poor
[147]	Zeng	2020-06-16	China	1,031	Hospital	60.3^ (46-74)	47.8	-	10.2	-	-	89.82	poor
[148]	Suleyman	2020-06-16	USA	463	Hospital	57.5^ (40-74)	55.9	-	34.6	-	-	65.44	poor
[149]	Chen, Yu	2020-06-16	China	1,859	Hospital	59 (45-68)	50.0	2.4	-	94.0	-	0.00	fair
[150]	Garassino	2020-06-12	Multiple	200	Community and Hospital	68 (61.8-75)	30.0	24.0	-	18.5	-	2.00	fair
[151]	Hernandez, Garduno	2020-06-11	Mexico	32,583	Community and Hospital	45 (34-56)	48.7	-	11.0	-	88.8	0.15	poor
[152]	Govind	2020-06-20	UK	6,309	Community and Hospital	46.5^ (31-61)	38.3	66.3	-	5.5	-	1.49	fair
[153]	Siso-Almirall	2020-06-20	Spain	322	Community and Hospital	56.7^ (38-74)	50.0	-	25.2	-	-	74.84	poor
[154]	Gu	2020-06-18	USA	5,698	Community and Hospital	47^ (26-67)	62.0	7.0	-	50.8	-	17.53	fair
[155]	Kibler	2020-06-16	France	702	Community and Hospital	82^ (75-88)	56.0	3.7	-	-	-	96.30	poor
[156]	Ikitimur	2020-06-03	Turkey	81	Hospital	55^ (38-72)	44.0	-	28.4	-	-	71.60	poor
[157]	Sierpinski	2020-06-03	Poland	1,942	Community	50 (-)	60.0	6.3	-	-	49.7	44.03	poor

[158]	Zhou, He	2020-06-10	China	238	Hospital	55.5 (35-67)	57.0	2.9	-	-	-	97.06	poor
[159]	Crovetto	2020-06-19	Spain	874	Community and Hospital	33.7^ (28-38)	100.0	1.1	-	-	13.2	85.70	poor
[160]	Veras	2020-06-09	Brazil	32	Hospital	58.9^ (40-77)	47.0	-	25.0	-	-	75.00	poor
[161]	Sterlin	2020-06-11	France	135	Hospital	61 (50-72)	41.0	3.7	-	57.8	-	0.00	fair
[162]	Rossi	2020-06-09	France	246	Hospital	68^ (53-83)	39.0	-	25.2	-	-	74.80	poor
[163]	Duan	2020-06-22	China	616	Hospital	64 (53-70)	57.5	3.7	-	-	-	96.27	poor
[164]	Martin-Jiminez	2020-06-09	Spain	339	Hospital	81.6 (72-87)	39.5	-	30.7	-	-	69.32	poor
[165]	Elezkurtaj	2020-06-17	Germany	26	Hospital	70 (61.8-78.3)	34.6	-	19.2	-	-	80.77	poor
[166]	Lenka	2020-06-22	USA	32	Hospital	62.2^ (51-73)	37.5	-	50.0	-	-	50.00	poor
[167]	Olivares	2020-06-16	Chile	21	Hospital	61^ (26-85)	76.2	-	9.5	-	-	90.48	poor
[168]	Salton	2020-06-20	Italy	173	Hospital	64.4^	34.9	-	29.5	-	-	70.52	poor
[169]	Wei	2020-06-18	USA	147	Hospital	52^ (34-70)	41.0	14.3	-	-	-	85.71	poor
[170]	Zuo, Estes	2020-06-17	China	172	Hospital	61^ (25-95)	44.0	-	26.2	-	-	73.84	poor
[171]	Killerby	2020-06-17	USA	531	Community and Hospital	51.6 (38-62)	57.1	-	17.1	71.4	-	11.49	poor

Note. – Age not provided for total sample; ^ Denotes mean (SD).

Smoking prevalence by country

Unadjusted smoking prevalence compared with overall estimates for national adult smoking prevalence split by country and study setting is presented in Figure 3a and 3b. Lower than expected current and former smoking prevalence was generally observed. Large variability in prevalence estimates was observed across studies conducted in the US.

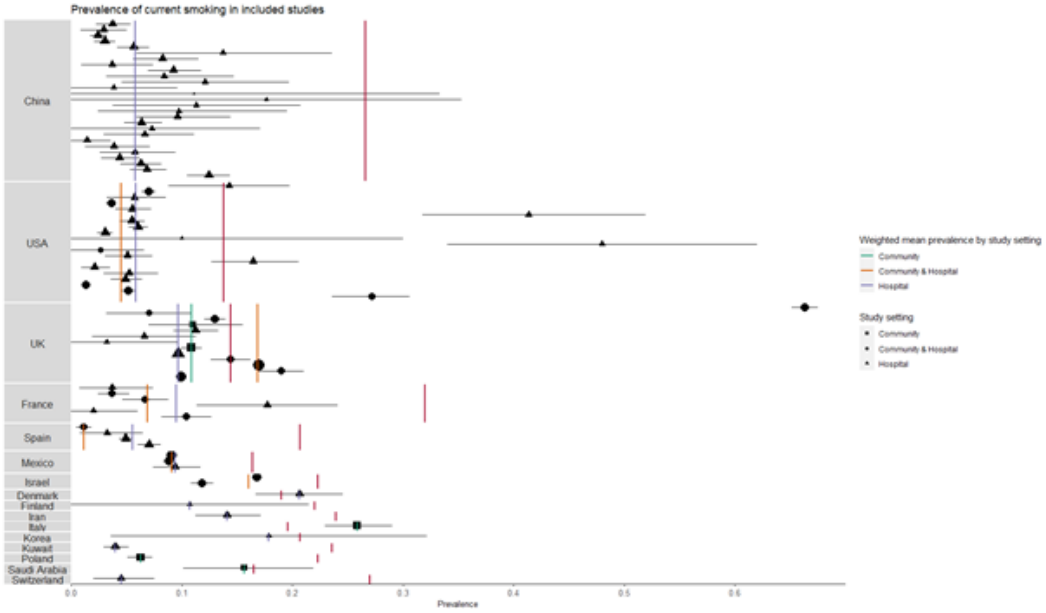

Figure 3a. Weighted mean prevalence of current smoking in included studies with 95% bootstrap confidence intervals compared with national current smoking prevalence (solid red lines), split by country. Shape corresponds to study setting (community, community and hospital, hospital) and shape size corresponds to relative study sample size.

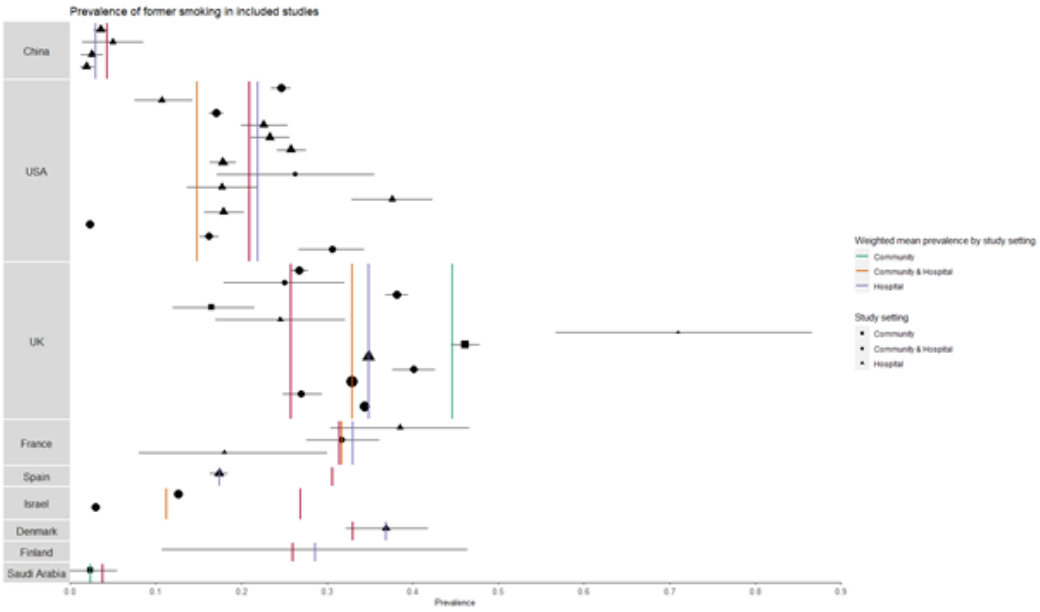

Figure 3b. Weighted mean prevalence of former smoking in included studies (where this was reported) with 95% bootstrap confidence intervals compared with national former smoking prevalence (solid red lines), split by country. Shape corresponds to study setting (community, community and hospital, hospital) and shape size corresponds to relative study sample size.

SARS-CoV-2 infection by smoking status

Twenty-five 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 12 'fair' quality studies (see Figure 4 and 5). Current smokers were at reduced risk of testing positive for SARS-CoV-2 compared with never smokers (RR = 0.70, 95% CI = 0.55-0.88, p = .003, I^2 = 90%). No significant difference was observed between former and never smokers (RR = 1.02, 95% CI = 0.92-1.12, p = .76, I^2 = 72%).

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

		SARS-CoV-2 negative						SARS-CoV-2 positive					
Author	Total population tested	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* (84.30%)	1444 (48.55%)	704 (23.67%)	-	826 (27.77%)	-	554* (15.70%)	159 (28.70%)	179 (32.31%)	-	216 (38.99%)	-
Fontanet	661	490 (74.13%)	64 (13.06%)	-	-	426 (86.94%)	-	171 (25.87%)	5 (2.92%)	-	-	166 (97.08%)	-
Cho	1331	793 (59.58%)	142 (17.91%)	214 (26.99%)	-	437 (55.11%)	-	538 (40.42%)	111 (20.63%)	145 (26.95%)	-	282 (52.42%)	-
Shah	243**	212 (87.24%)	52 (24.53%)	47 (22.17%)	-	113 (53.30%)	-	29 (11.93%)	0 (0.00%)	9 (31.03%)	-	20 (68.97%)	-
Bello-Chavolla	62489	46960 (75.15%)	-	-	4835 (10.30%)	-	42125 (89.70%)	15529 (24.85%)	-	-	1374 (8.85%)	-	14155 (91.15%)
Kolin	1474***	805 (54.61%)	141 (17.52%)	307 (38.14%)	-	354 (43.98%)	3 (0.37%)	669 (45.39%)	72 (10.76%)	285 (42.60%)	-	303 (45.29%)	9 (1.35%)
de Lusignan	3291^	2740 (83.26%)	366 (13.36%)	1450 (52.92%)	-	924 (33.72%)	-	551 (16.74%)	47 (8.53%)	303 (54.99%)	-	201 (36.48%)	-
Valenti	789	689 (87.33%)	197 (28.59%)	-	-	-	492 (71.41%)	40 (5.07%)	7 (17.50%)	-	-	-	33 (82.50%)
Parrotta	76	39 (51.32%)	1 (2.56%)	10 (25.64%)	-	27 (69.23%)	1 (2.56%)	37 (48.68%)	1 (2.70%)	10 (27.03%)	-	25 (67.57%)	1 (2.70%)
Berumen	102875	71353 (69.36%)	-	-	7173 (10.05%)	64180 (89.95%)	-	31522 (30.64%)	-	-	2748 (8.72%)	28774 (91.28%)	-
Israel	24087	20076 (83.35%)	3711 (18.48%)	2670 (13.30%)	-	13695 (68.22%)	-	4011 (16.65%)	403 (10.05%)	471 (11.74%)	-	3137 (78.21%)	-
del Valle	1108`	143 (12.91%)	27 (18.88%)	53 (37.06%)	-	-	63 (44.06%)	965 (87.09%)	55 (5.70%)	293 (30.36%)	-	-	617 (63.94%)
Romao	34	20 (58.82%)	-	-	5 (25.00%)	-	15 (75.00%)	14 (41.18%)	-	-	4 (28.57%)	-	10 (71.43%)
Ramlall	11116	4723 (42.49%)	-	-	-	-	-	6393 (57.51%)	-	-	1643.001 (25.70%)	4749.999 (74.30%)	-
Sharma	501	267 (53.29%)	-	-	1 (0.37%)	-	266 (99.63%)	234 (46.71%)	-	-	20 (8.55%)	-	214 (91.45%)

		SARS-CoV-2 negative						SARS-CoV-2 positive					
Author	Total population tested	N (%)	Current smoker (%)	Former smoker (%)	Current/former smoker (%)	Never smoker (%)	Not stated (%)	N (%)	Current smoker (%)	Former smoker (%)	Current/former smoker (%)	Never smoker (%)	Not stated (%)
Eugen-Olsen	407	290 (71.25%)	76 (26.21%)	104 (35.86%)	-	102 (35.17%)	-	117 (28.75%)	8 (6.84%)	46 (39.32%)	-	59 (50.43%)	-
Raisi-Estabragh	4510	3184 (70.60%)	-	-	1653 (51.92%)	-	1531 (48.08%)	1326 (29.40%)	-	-	683 (51.51%)	-	643 (48.49%)
Houlihan	177	97 (54.80%)	14 (14.43%)	14 (14.43%)	-	69 (71.13%)	-	80 (45.20%)	7 (8.75%)	19 (23.75%)	-	54 (67.50%)	-
McQueenie	428199	424355 (99.10%)	-	-	189299 (44.61%)	235056 (55.39%)	-	1311 (0.31%)	-	-	669 (51.03%)	642 (48.97%)	-
Woolford	4474	3161 (70.65%)	441 (13.95%)	1194 (37.77%)	-	1526 (48.28%)	-	1313 (29.35%)	145 (11.04%)	525 (39.98%)	-	643 (48.97%)	-
Lan	104	83 (79.81%)	-	-	24 (28.92%)	-	59 (71.08%)	21 (20.19%)	-	-	1 (4.76%)	-	20 (95.24%)
Hernandez-Garduno	32583	20279 (62.24%)	-	-	2399 (11.83%)	17861 (88.08%)	-	12304 (37.76%)	-	-	1191 (9.68%)	11083 (90.08%)	-
Govind	6215	6207 (99.87%)	4104 (66.12%)	1669 (26.89%)	-	342 (5.51%)	-	102 (1.64%)	78 (76.47%)	20 (19.61%)	-	2 (1.96%)	-
Gu	4699	3815 (81.19%)	360 (9.44%)	1142 (29.93%)	-	2313 (60.63%)	-	884 (18.81%)	40 (4.52%)	264 (29.86%)	-	580 (65.61%)	-
Kibler	702	680 (96.87%)	25 (3.68%)	-	-	-	655 (96.32%)	22 (3.13%)	1 (4.55%)	-	-	-	21 (95.45%)

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; ^ Data on smoking status were missing for 511 participants; ` Data on smoking status were missing for 376 participants.

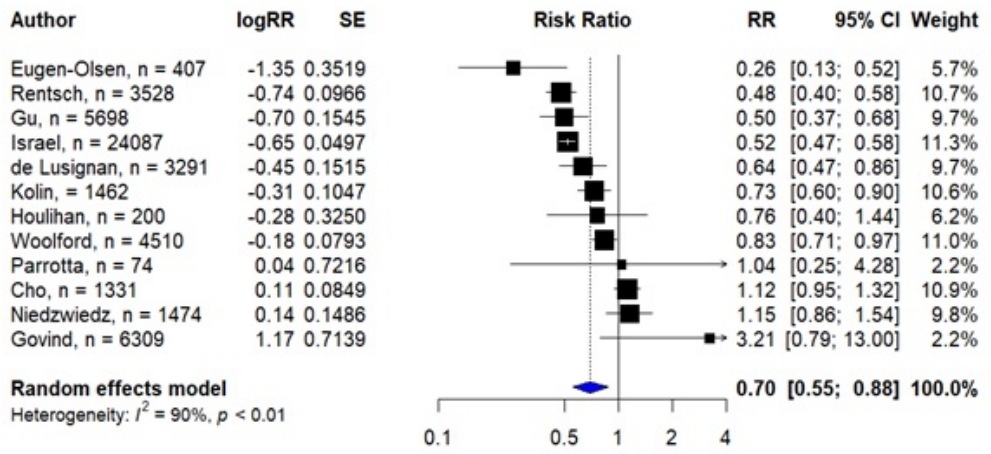

Figure 4. Forest plot for risk of testing positive for SARS-CoV-2 in current vs. never smokers.

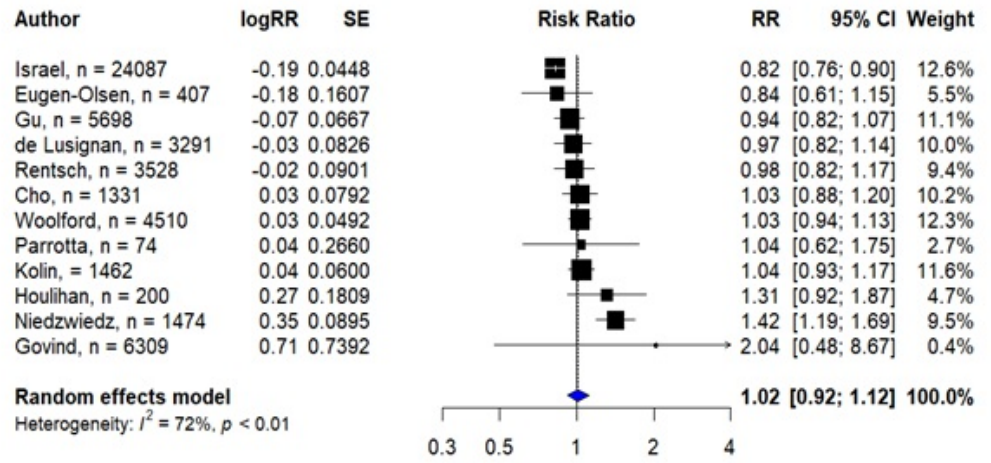

Figure 5. Forest plot for risk of testing positive for SARS-CoV-2 in former vs. never smokers.

Hospitalisation for COVID-19 by smoking status

Twenty-one studies examined hospitalisation for COVID-19 disease stratified by smoking status (see Table 3). Meta-analyses were performed for seven 'fair' quality studies (see Figure 6 and 7). There was no significant difference between current and never (RR = 1.06, 95% CI = 0.79-1.44, p = .63, I^2 = 79%) or former and never smokers (RR = 1.20, 95% CI = 0.95-1.51, p = .10, I^2 = 79%) in the risk of requiring admission to hospital with COVID-19.

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

		Community							Hospitalised						
Author	Population with outcome	N (%)	Current smoker (%)	Former smoker (%)	Current/former smoker (%)	Never smoker (%)	Never/unknown smoker (%)	Not stated (%)	N (%)	Current smoker (%)	Former smoker (%)	Current/former smoker (%)	Never smoker (%)	Never/unknown smoker (%)	Not stated (%)
Rentsch	554	269 (48%)	69 (25.65%)	90 (33.46%)	-	110 (40.89%)	-	-	285 (51%)	90 (31.58%)	89 (31.23%)	-	106 (37.19%)	-	-
Petrilli	4103	2104 (51%)	108 (5.13%)	250 (11.88%)	-	-	1746 (82.98%)	-	1999 (48%)	104 (5.20%)	416 (20.81%)	-	-	1479 (73.99%)	-
Chow (US CDC)	6637	5143 (77%)	61 (1.19%)	80 (1.56%)	-	-	-	5002 (97.26%)	1494 (22%)	27 (1.81%)	78 (5.22%)	-	-	-	1389 (92.97%)
Argenziano	1000	151 (15%)	14 (9.27%)	18 (11.92%)	-	119 (78.81%)	-	-	849 (84%)	35 (4.12%)	161 (18.96%)	-	653 (76.91%)	-	-
Miyara	470	139 (29%)	14 (10.07%)	41 (29.50%)	-	77 (55.40%)	-	7 (5.04%)	340 (72%)	18 (5.29%)	111 (32.65%)	-	209 (61.47%)	-	2 (0.59%)
Lubetzky	54	15 (27%)	-	-	4 (26.67%)	-	-	11 (73.33%)	39 (72%)	-	-	8 (20.51%)	-	-	31 (79.49%)
Carrillo-Vega	9946	3922 (39%)	408 (10.40%)	-	-	-	-	3514 (89.60%)	6024 (60%)	486 (8.07%)	-	-	-	-	5538 (91.93%)
Yanover	4353	4180 (96%)	484 (11.58%)	118 (2.82%)	-	3578 (85.60%)	-	-	173 (3%)	30 (17.34%)	11 (6.36%)	-	132 (76.30%)	-	-
Hamer	387109	386349 (99%)	37333 (9.66%)	134542 (34.82%)	-	214474 (55.51%)	-	-	760 (0%)	93 (12.24%)	313 (41.18%)	-	354 (46.58%)	-	-
Heili-Frades	4712	1973 (41%)	121 (6.13%)	222 (11.25%)	-	-	1630 (82.62%)	1630 (82.62%)	2739 (58%)	112 (4.09%)	598 (21.83%)	-	-	2029 (74.08%)	-
Freites	123	69 (56%)	1 (1.45%)	-	-	-	-	68 (98.55%)	54 (43%)	3 (5.56%)	-	-	-	-	51 (94.44%)
Berumen	102875	18832 (18%)	-	-	1546 (8.21%)	-	17286 (91.79%)	-	12690 (12%)	-	-	1202 (9.47%)	-	11488 (90.53%)	-
Gianfrancesco	600	323 (53%)	-	-	61 (18.89%)	-	-	262 (81.11%)	277 (46%)	-	-	68 (24.55%)	-	-	209 (75.45%)
Chaudhry	40	19 (47%)	-	-	0 (0.00%)	-	-	19 (100.00%)	21 (52%)	-	-	6 (28.57%)	-	-	15 (71.43%)
Giannouchos	89756	58485 (65%)	4679 (8.00%)	-	-	-	53806 (92.00%)	-	31271 (34%)	2721 (8.70%)	-	-	-	28550 (91.30%)	-
Bo, Wang	57	22 (38%)	-	-	6 (27.27%)	-	-	16 (72.73%)	36 (63%)	-	-	15 (41.67%)	-	-	20 (55.56%)
Miyara	470	132 (28%)	14 (10.61%)	41 (31.06%)	-	77 (58.33%)	-	-	338 (71%)	18 (5.33%)	111 (32.84%)	-	209 (61.83%)	-	-
Suleyman	463	108 (23%)	-	-	23 (21.30%)	-	-	85 (78.70%)	355 (76%)	-	-	137 (38.59%)	-	-	218 (61.41%)
Garassino	196	48 (24%)	10 (20.83%)	27 (56.25%)	-	11 (22.92%)	-	-	152 (77%)	38 (25.00%)	84 (55.26%)	-	26 (17.11%)	-	-
Siso-Almirall	260	119 (45%)	-	-	31 (26.05%)	-	-	88 (73.95%)	141 (54%)	-	-	50 (35.46%)	-	-	91 (64.54%)
Gu	884	511 (57%)	30 (5.87%)	126 (24.66%)	-	355 (69.47%)	-	-	373 (42%)	10 (2.68%)	138 (37.00%)	-	225 (60.32%)	-	-
Killerby	531	311 (58%)	-	-	37 (11.90%)	222 (71.38%)	-	52 (16.72%)	220 (41%)	-	-	54 (24.55%)	157 (71.36%)	-	9 (4.09%)

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.

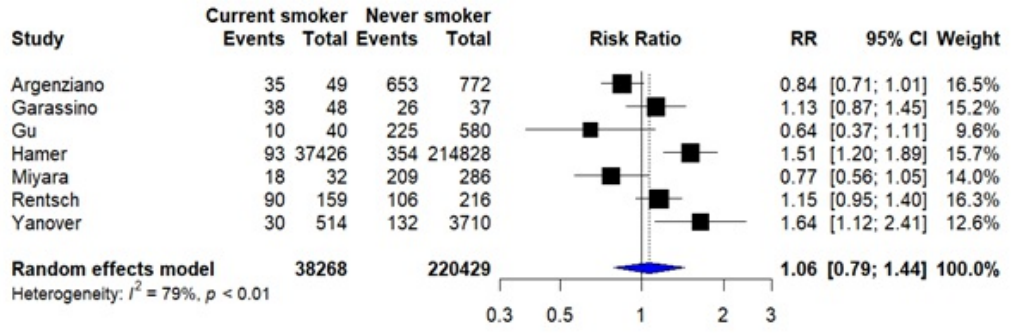

Figure 6. Forest plot for risk of hospitalisation in current vs. never smokers.

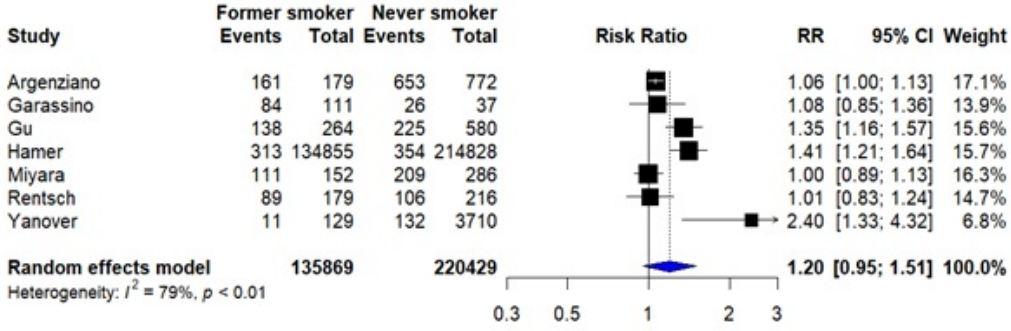

Figure 7. Forest plot for risk of hospitalisation in former vs. never smokers.

Disease severity by smoking status

Forty 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. Meta-analyses were performed for six 'fair' quality studies (see Figure 8 and 9). No significant difference was observed between current and never smokers (RR = 1.22, 95% CI = 0.98-1.53, p = .08, I^2 = 22%). Former smokers were at increased risk of greater disease severity compared with never smokers (RR = 1.58, 95% CI = 1.07-2.32, p = .02, I^2 = 68%).

Table 4. Disease severity by smoking status.

		Non severe disease							Severe disease						
Author	Population with severity	N (%)	Current smoker (%)	Former smoker (%)	Current/former smoker (%)	Never smoker (%)	Never/unknown smoker (%)	Not stated (%)	N (%)	Current smoker (%)	Former smoker (%)	Current/former smoker (%)	Never smoker (%)	Never/unknown smoker (%)	Not stated (%)
Guan, Ni	1085	913 (84%)	108 (11.83%)	12 (1.31%)	-	793 (86.86%)	-	-	172 (15%)	29 (16.86%)	9 (5.23%)	-	134 (77.91%)	-	-
Zhang, Dong	9	3 (33%)	0 (0.00%)	3 (100.00%)	-	0 (0.00%)	-	-	6 (66%)	2 (33.33%)	4 (66.67%)	-	0 (0.00%)	-	-
Wan	9	8 (88%)	8 (100.00%)	0 (0.00%)	-	0 (0.00%)	-	-	1 (11%)	1 (100.00%)	0 (0.00%)	-	0 (0.00%)	-	-
Huang, Wang	3	3 (100%)	3 (100.00%)	0 (0.00%)	-	0 (0.00%)	-	-	0 (0%)	0 (-)	0 (-)	-	0 (-)	-	-
Rentsch	285	168 (58%)	47 (27.98%)	53 (31.55%)	-	68 (40.48%)	-	-	117 (41%)	43 (36.75%)	36 (30.77%)	-	38 (32.48%)	-	-
Hu	323	151 (46%)	-	-	12 (7.95%)	-	139 (92.05%)	-	172 (53%)	-	-	26 (15.12%)	-	146 (84.88%)	-
Wang, Pan	125	100 (80%)	-	-	9 (9.00%)	-	91 (91.00%)	-	25 (20%)	-	-	7 (28.00%)	-	18 (72.00%)	-
Petrilli	1278	932 (72%)	62 (6.65%)	175 (18.78%)	-	-	391 (41.95%)	-	650 (50%)	28 (4.31%)	145 (22.31%)	-	-	477 (73.38%)	-
Kim	27	21 (77%)	3 (14.29%)	-	-	-	18 (85.71%)	-	6 (22%)	2 (33.33%)	0 (0.00%)	-	-	4 (66.67%)	-
Shi, Yu	474	425 (89%)	-	-	34 (8.00%)	-	391 (92.00%)	-	49 (10%)	-	-	6 (12.24%)	-	43 (87.76%)	-
Liao, Feng	148	92 (62%)	-	-	5 (5.43%)	-	-	87 (94.57%)	56 (37%)	3 (5.36%)	-	-	-	-	53 (94.64%)
Shi, Ren	134	88 (65%)	-	-	8 (9.09%)	-	-	80 (90.91%)	46 (34%)	-	-	6 (13.04%)	-	-	40 (86.96%)
Hadjadj	50	15 (30%)	1 (6.67%)	2 (13.33%)	-	12 (80.00%)	-	-	35 (70%)	0 (0.00%)	7 (20.00%)	-	28 (80.00%)	-	-

Zheng, Xiong	73	43 (58%)	-	-	6 (13.95%)	37 (86.05%)	-	-	30 (41%)	-	-	2 (6.67%)	28 (93.33%)	-	-
de la Rica	48	26 (54%)	-	-	6 (23.08%)	-	-	20 (76.92%)	20 (41%)	-	-	4 (20.00%)	-	-	16 (80.00%)
Yin, Yang	106	47 (44%)	-	-	6 (12.77%)	-	-	41 (87.23%)	59 (55%)	-	-	12 (20.34%)	-	-	47 (79.66%)
Allenbach	147	100 (68%)	-	-	9 (9.00%)	-	-	91 (91.00%)	47 (31%)	-	-	0 (0.00%)	-	-	47 (100.00%)
Goyal	393	263 (66%)	14 (5.32%)	-	-	-	-	249 (94.68%)	130 (33%)	6 (4.62%)	-	-	-	-	124 (95.38%)
Feng	454	333 (73%)	27 (8.11%)	-	-	-	-	306 (91.89%)	121 (26%)	17 (14.05%)	-	-	-	-	104 (85.95%)
Yao	108	83 (76%)	1 (1.20%)	-	-	-	-	82 (98.80%)	25 (23%)	3 (12.00%)	-	-	-	-	22 (88.00%)
Sami	490	400 (81%)	53 (13.25%)	-	-	-	-	347 (86.75%)	90 (18%)	16 (17.78%)	-	-	-	-	74 (82.22%)
Regina	200	163 (81%)	9 (5.52%)	-	-	-	-	154 (94.48%)	37 (18%)	0 (0.00%)	-	-	-	-	37 (100.00%)
Feuth	28	21 (75%)	1 (4.76%)	7 (33.33%)	-	13 (61.90%)	-	-	7 (25%)	2 (28.57%)	1 (14.29%)	-	4 (57.14%)	-	-
Mejia-Vilet	329	214 (65%)	-	-	13 (6.07%)	-	-	201 (93.93%)	115 (34%)	-	-	10 (8.70%)	-	-	105 (91.30%)
Chen, Jiang	135	54 (40%)	-	-	4 (7.41%)	-	-	50 (92.59%)	81 (60%)	-	-	9 (11.11%)	-	-	72 (88.89%)
Vaquero-Roncero	146	75 (51%)	-	-	4 (5.33%)	-	-	71 (94.67%)	71 (48%)	-	-	6 (8.45%)	-	-	65 (91.55%)
Kim, Garg	2490	1692 (67%)	112 (6.62%)	395 (23.35%)	-	-	1185 (70.04%)	-	798 (32%)	38 (4.76%)	247 (30.95%)	-	-	512 (64.16%)	-
Wu	174	92 (52%)	-	-	47 (51.09%)	-	45 (48.91%)	-	82 (47%)	11 (13.41%)	-	-	-	71 (86.59%)	-
Zuo, Zuo	-	- (-%)	-	-	-	-	-	-	- (-%)	-	-	-	-	-	-
Chaudhry	40	34 (85%)	-	-	5 (14.71%)	-	-	29 (85.29%)	6 (15%)	-	-	1 (16.67%)	-	-	5 (83.33%)
Patel	104	67 (64%)	25 (37.31%)	-	-	-	36 (53.73%)	6 (8.96%)	37 (35%)	18 (48.65%)	-	-	-	15 (40.54%)	4 (10.81%)
Garibaldi	832	532 (63%)	25 (4.70%)	107 (20.11%)	-	-	-	400 (75.19%)	300 (36%)	21 (7.00%)	81 (27.00%)	-	-	-	198 (66.00%)
Kuderer	928	686 (73%)	35 (5.10%)	210 (30.61%)	-	370 (53.94%)	-	29 (4.23%)	242 (26%)	8 (3.31%)	116 (47.93%)	-	99 (40.91%)	15 (6.20%)	4 (1.65%)
Romao	14	14 (100%)	-	-	4 (28.57%)	-	-	10 (71.43%)	0 (0%)	-	-	-	-	-	-
Giannouchos	89756	78050 (86%)	6322 (8.10%)	-	-	-	71728 (91.90%)	-	11706 (13%)	1089 (9.30%)	-	-	-	10617 (90.70%)	-
Cen	1007	720 (71%)	-	-	70 (9.72%)	-	-	650 (90.28%)	287 (28%)	-	-	18 (6.27%)	-	-	269 (93.73%)
Maraschini	132	89 (67%)	-	11 (12.36%)	-	78 (87.64%)	-	-	43 (32%)	-	3 (6.98%)	-	40 (93.02%)	-	-
Russell, Moss	156	128 (82%)	9 (7.03%)	31 (24.22%)	-	51 (39.84%)	-	37 (28.91%)	28 (17%)	2 (7.14%)	8 (28.57%)	-	8 (28.57%)	-	10 (35.71%)
Siso-Almirall	260	212 (81%)	-	-	60 (28.30%)	-	-	152 (71.70%)	48 (18%)	-	-	21 (43.75%)	-	-	27 (56.25%)
Gu	884	511 (57%)	30 (5.87%)	126 (24.66%)	-	355 (69.47%)	-	-	134 (15%)	3 (2.24%)	61 (45.52%)	-	70 (52.24%)	-	-

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 1 participant; [f] Data on smoking status were missing for 13 participants; [g] Data on smoking status were missing for 1700 participants; [h] Data on smoking status were missing for 5 participants; [i] Data on smoking status were missing for 21 participants; [j] Data on smoking status were missing for 1 participant; * Patients with disease requiring hospital (but not ITU) admission.

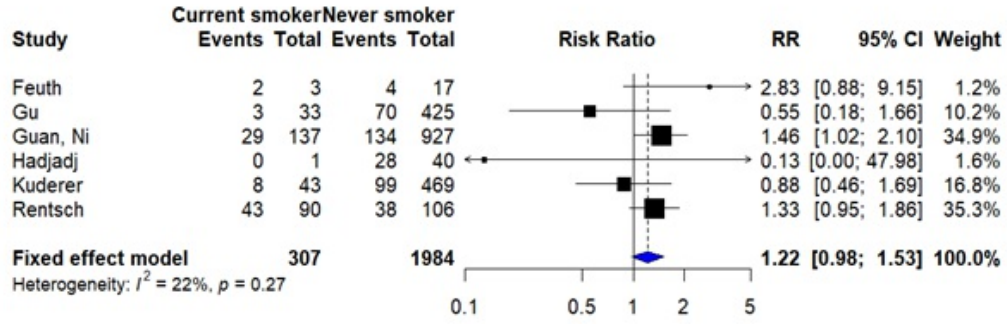

Figure 8. Forest plot for the risk of severe disease in current vs. never smokers.

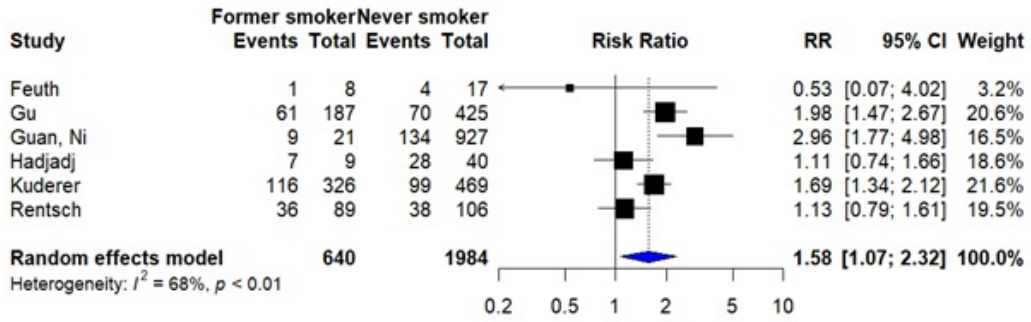

Figure 9. Forest plot for the risk of severe disease in former vs. never smokers.

Mortality by smoking status

Thirty studies reported mortality from COVID-19 by smoking status (see Table 5), with five 'fair' quality studies included in meta-analyses (see Figure 10 and 11). Current (RR = 1.70, 95% CI = 1.14-2.55, p = .01, I^2 = 29%) and former (RR = 2.00, 95% CI = 1.57-2.55, p < .0.001, I^2 = 0%) smokers were at increased risk of in-hospital mortality from COVID-19 compared with never smokers.

Table 5. Mortality by smoking status.

		Recovered							Died						
Author	Population with mortality	N (%)	Current smoker (%)	Former smoker (%)	Current/former smoker (%)	Never smoker (%)	Never/unknown smoker (%)	Not stated (%)	N (%)	Current smoker (%)	Former smoker (%)	Current/former smoker (%)	Never smoker (%)	Never/unknown smoker (%)	Not stated (%)
Chen	274	161 (58%)	5 (3.11%)	5 (3.11%)	-	-	-	151 (93.79%)	113 (41%)	7 (6.19%)	2 (1.77%)	-	-	-	104 (92.04%)
Zhou, Yu	191	137 (71%)	6 (4.38%)	-	-	-	-	131 (95.62%)	54 (28%)	5 (9.26%)	-	-	-	-	49 (90.74%)
Yang, Yu	52	20 (38%)	2 (10.00%)	-	-	-	18 (90.00%)	-	32 (61%)	-	-	-	-	32 (100.00%)	-
Borobia	2226	1766 (79%)	113 (6.40%)	-	-	-	-	1653 (93.60%)	460 (20%)	44 (9.57%)	-	-	-	-	416 (90.43%)
Giacomelli	233	185 (79%)	-	-	53 (28.65%)	132 (71.35%)	-	-	48 (20%)	-	-	17 (35.42%)	31 (64.58%)	-	0 (0.00%)
Yao	108	96 (88%)	1 (1.04%)	-	-	-	-	95 (98.96%)	12 (11%)	3 (25.00%)	-	-	-	-	9 (75.00%)
Carillo-Vega	9946	8983 (90%)	795 (8.85%)	-	-	-	-	8188 (91.15%)	963 (9%)	99 (10.28%)	-	-	-	-	864 (89.72%)
Heng	51	39 (76%)	6 (15.38%)	-	-	-	-	33 (84.62%)	12 (23%)	1 (8.33%)	-	-	-	-	11 (91.67%)
Chen, Jiang	135	- (-%)	-	-	-	-	-	-	31 (22%)	-	-	4 (12.90%)	-	-	27 (87.10%)
Heili-Frades	4712	4086 (86%)	210 (5.14%)	659 (16.13%)	-	-	3217 (78.73%)	-	626 (13%)	23 (3.67%)	161 (25.72%)	-	-	442 (70.61%)	-
Kim, Garg	2490	2070 (83%)	128 (6.18%)	481 (23.24%)	-	-	1461 (70.58%)	-	420 (16%)	22 (5.24%)	161 (38.33%)	-	-	236 (56.19%)	-
Al-Hindawi	31	15 (48%)	0 (0.00%)	10 (66.67%)	-	5 (33.33%)	-	-	16 (51%)	1 (6.25%)	12 (75.00%)	-	3 (18.75%)	-	-
Louis	22	16 (72%)	-	-	7 (43.75%)	-	-	9 (56.25%)	6 (27%)	-	-	3 (50.00%)	-	-	3 (50.00%)
Soto-Mota	400	200 (50%)	-	-	23 (11.50%)	-	-	177 (88.50%)	200 (50%)	-	-	25 (12.50%)	-	-	175 (87.50%)
Garibaldi	747	634 (84%)	36 (5.68%)	129 (20.35%)	-	-	-	469 (73.97%)	113 (15%)	6 (5.31%)	36 (31.86%)	-	-	-	71 (62.83%)

Docherty	13364	8199 (61%)	370 (4.51%)	1832 (22.34%)	-	4179 (50.97%)	-	1818 (22.17%)	5165 (38%)	214 (4.14%)	1350 (26.14%)	-	2105 (40.76%)	-	1496 (28.96%)
Kuderer	928	807 (86%)	38 (4.71%)	262 (32.47%)	-	425 (52.66%)	-	31 (3.84%)	121 (13%)	5 (4.13%)	64 (52.89%)	-	44 (36.36%)	-	2 (1.65%)
Ramlall	11116	10498 (94%)	-	-	2771 (26.40%)	7727 (73.60%)	-	-	618 (5%)	-	-	208 (33.66%)	410 (66.34%)	-	-
Wang, Oekelen	57	43 (75%)	-	-	14 (32.56%)	-	-	29 (67.44%)	14 (24%)	-	-	7 (50.00%)	-	-	7 (50.00%)
Martinez-Portilla	224	217 (96%)	-	-	7 (3.23%)	-	-	210 (96.77%)	7 (3%)	-	-	0 (0.00%)	-	-	7 (100.00%)
Cen	1007	964 (95%)	-	-	87 (9.02%)	-	-	877 (90.98%)	43 (4%)	-	-	1 (2.33%)	-	-	42 (97.67%)
Klang	3406	2270 (66%)	-	-	492 (21.67%)	-	-	1778 (78.33%)	1136 (33%)	-	-	301 (26.50%)	-	-	835 (73.50%)
Wang, Zhong	5510	4874 (88%)	247 (5.07%)	1083 (22.22%)	-	3544 (72.71%)	-	-	636 (11%)	28 (4.40%)	214 (33.65%)	-	394 (61.95%)	-	-
Miyara	338	211 (62%)	13 (6.16%)	58 (27.49%)	-	141 (66.82%)	-	-	46 (13%)	1 (2.17%)	23 (50.00%)	-	21 (45.65%)	-	-
Cepelowicz	255	209 (81%)	-	-	28 (13.40%)	181 (86.60%)	-	-	53 (20%)	-	-	18 (33.96%)	28 (52.83%)	-	-
Zeng	1031	866 (84%)	-	-	69 (7.97%)	-	-	797 (92.03%)	165 (16%)	-	-	36 (21.82%)	-	-	129 (78.18%)
Chen, Yu	1859	1651 (88%)	32 (1.94%)	54 (3.27%)	-	1565 (94.79%)	-	-	208 (11%)	13 (6.25%)	12 (5.77%)	-	183 (87.98%)	-	-
Garassino	190	124 (65%)	-	-	92 (74.19%)	32 (25.81%)	-	-	66 (34%)	-	61 (92.42%)	-	5 (7.58%)	-	-
Gu	884	864 (97%)	40 (4.63%)	250 (28.94%)	-	219 (25.35%)	-	-	20 (2%)	0 (0.00%)	14 (70.00%)	-	6 (30.00%)	-	-

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 smoking status were missing for 274 participants; ** Data on smoking status were missing for 598 participants; *** Data on smoking status were missing for 85 participants; ` Data on smoking status were missing for 6769 participants; ^ No smoking history defined as <30 pack-years of smoking.

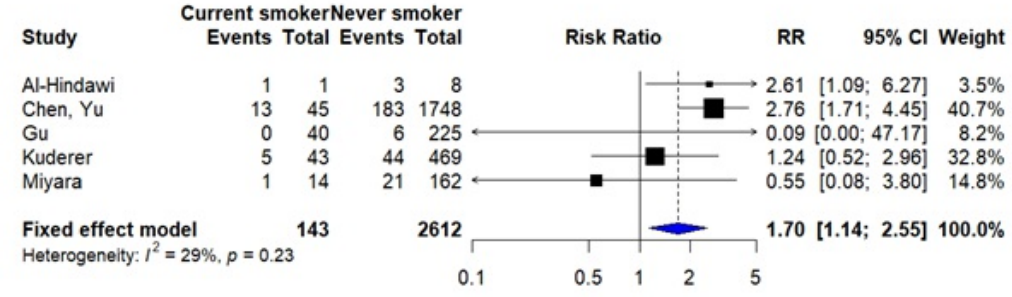

Figure 10. Forest plot for the risk of mortality in current vs. never smokers.

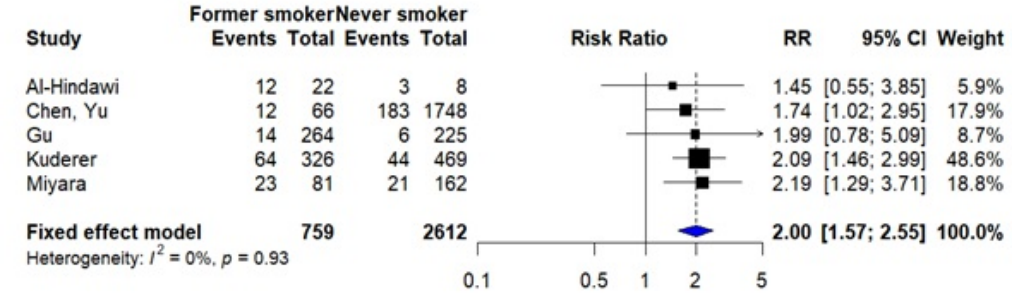

Figure 11. Forest plot for the risk of mortality in former vs. never smokers.

Discussion

This rapid review of 148 studies found substantial uncertainty arising from the recording of smoking status. Notwithstanding these uncertainties, compared with overall adult

national prevalence estimates, recorded current and former smoking rates in most countries were lower than expected. From available data, there was insufficient evidence to conclude that current and/or former smoking status is associated with hospitalisation. There was some evidence from 'fair' quality studies that the risk of SARS-CoV-2 infection is reduced in current compared with never smokers. Conversely, former compared with never smokers were at increased risk of greater disease severity in those hospitalised for COVID-19. Both current and former smokers had increased risk of in-hospital mortality from COVID-19 compared with never smokers.

Infection by smoking status

In 12 'fair' quality studies, evidence suggests that current smokers in the community are less likely to test positive for SARS-CoV-2 compared with never smokers. It should be noted that criteria for accessing testing will vary during the course of the epidemic. It is possible that current and former smokers are more likely to receive a test due to increased prevalence of cough or altered sense of smell or taste[172], which are used as screening criteria. Infection positivity rates estimated among random samples will be more informative than currently available data. Smoking status is being collected in at least two large representative infection and antibody surveys in the UK[173,174].

Hospitalisation and disease severity by smoking status

As reported elsewhere[175], smoking prevalence among multiple hospital and community cohorts was consistently lower than national estimates. In a single study conducted in Korea and 15 studies of varying quality conducted in the UK, however, current and former smoking rates were more similar to expected national estimates.

In seven 'fair' quality studies across four countries, there was no evidence that current or former smokers are at lower risk of hospitalisation for COVID-19 compared with never smokers among those testing positive in the community. There was some evidence from six 'fair' quality studies that former (but insufficient evidence that current) smokers are at increased risk of greater disease severity compared with never smokers.

Mortality by smoking status

In five 'fair' quality studies, there was some evidence that current and former smokers are at increased risk of in-hospital mortality from COVID-19 compared with never

smokers. It should, however, be noted that given lack of knowledge of the disease progression and long-term outcomes of COVID-19 disease, it is unclear whether studies conducted thus far in the pandemic have monitored patients for a sufficient time period to report complete survival outcomes or whether they are subject to early censoring.

Issues complicating interpretation

Interpretation of results from studies conducted during the first phase of the SARS-CoV-2 pandemic is complicated by several factors (see Figure 11). First, exposure to SARS-CoV-2 is heterogeneous with different subgroups 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. Second, as mentioned above, current and former 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[172]. Third, testing for acute infection requires swabbing of the mucosal epithelium, which may be disrupted in current smokers, potentially altering the sensitivity of assays[88].

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[176]. Known failings of EHRs include implausible longitudinal changes, such as former smokers being recorded as never smokers at subsequent hospital visits[176]. Misreporting on the part of the patient (perhaps due to perceived stigmatisation) has also been observed, with biochemical measures showing higher rates of smoking compared with self-report in hospitalised patients in the US[177]. It is hence possible that under-reporting of current and former smoking status in hospitals occurred across the included studies. Fifth, individuals with severe COVID-19 symptoms may have stopped smoking immediately before admission to hospital 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 bias) and thus not be recorded. 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 and former 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 pandemic. For example, early 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 former smoking and greater disease severity may be explained by collider bias[178], where conditioning on a collider (e.g. testing or hospitalisation) by design or analysis may introduce a spurious association between current or former smoking (a potential cause of testing or hospitalisation) and SARS-CoV-2 infection/adverse outcomes from COVID-19 (potentially exacerbated by smoking)[179].

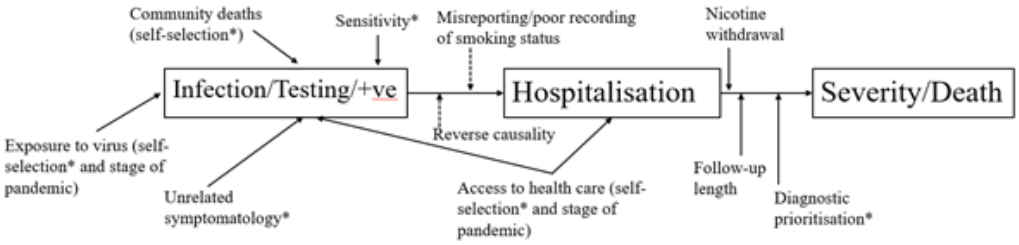

Figure 11. A schematic of some of the interpretation issues for the association of smoking and SARS-CoV-2/COVID-19. * Indicates potential confounding with smoking status.

Limitations

This living rapid evidence 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 three large population surveys due to their reliance on self-reported suspected SARS-CoV-2 infection (which means they do not meet our eligibility criteria)[172,180,181]. 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. . The comparisons of current and former smoking prevalence in the included studies with national prevalence estimates did not adjust observed prevalence for the demographic profile of those tested/admitted to hospital. Other reviews focused on this comparison have applied adjustment for sex, and continue to find lower than expected prevalence – notwithstanding the issues complicating interpretation described above[16]. Future versions of the review will take a Bayesian approach to the comparisons to mitigate the issue of repeating multiple meta-analyses across different versions of this living review.

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 how the SARS-CoV-2 virus causes disease in humans. 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. ingested) since this can affect pharmacokinetics[182] and 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 products 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[183]. GPs and other healthcare providers can play a crucial role – brief, high-quality and free online training is available at National Centre for Smoking Cessation and Training.

Conclusion

Across 148 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 some evidence that current smoking compared with never is associated with reduced risk of testing positive in the community but greater in-hospital mortality from COVID-19. There is some evidence that former compared with never smoking is associated with increased risk of greater disease severity and in-hospital mortality from COVID-19.

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Data availability

Extracted data from included studies is available from a maintained Google Sheet document here: link
The code to reproduce the analysis and generate the plots and figures is available here: link

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