The association of smoking status with SARS-CoV-2 infection, hospitalisation and mortality from COVID-19: A living rapid evidence review (version 6)

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Abstract

Aims: 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.

Design: Living rapid review of observational and experimental studies with random-effects hierarchical Bayesian meta-analyses. Published articles and pre-prints were identified via Ovid MEDLINE and medRxiv.

Setting: Community or hospital with no restrictions on location.

Participants: Adults who had received a test for SARS-CoV-2 infection or a diagnosis of COVID-19.

Measurements: Outcomes were SARS-CoV-2 infection, hospitalisation, disease severity and mortality stratified by smoking status. Study quality was assessed.

Findings: Version 6 with searches up to 17 July 2020 included 174 studies with 26 included in meta-analyses. Thirty-nine studies reported current, former and never smoking status. Notwithstanding recording uncertainties, compared with adult national prevalence estimates, recorded current smoking rates were generally lower than expected. Current compared with never smokers were at reduced risk of SARS-

CoV-2 infection (RR = 0.74, 95% Credible Interval (CrI) = 0.56-0.97, τ = 0.46). Former compared with never smokers were at somewhat increased risk of infection but data were inconclusive (RR = 1.06, 95% CrI = 0.94-1.20, τ = 0.19). Current (RR = 1.05, CrI = 0.82-1.34, τ = 0.29) and former (RR = 1.20, CrI = 1.03-1.44, τ = 0.19) compared with never smokers were both at somewhat increased risk of hospitalisation with COVID-19, but data for current smokers were inconclusive. Current (RR = 1.15, CrI = 0.80-1.66, τ = 0.29) and former (RR = 1.51, CrI = 1.06-2.15, τ = 0.36) compared with never smokers were at increased risk of greater disease severity, but data for current smokers were inconclusive. Current (RR = 1.89, 95% CrI = 0.77-3.41, τ = 0.51) and former (RR = 1.93, 95% CrI = 1.33-2.66, τ = 0.19) compared with never smokers had increased risk of in-hospital death, but data for current smokers were inconclusive.

Conclusions: There is uncertainty about the associations of smoking with COVID-19 outcomes. Recorded smoking prevalence among people with COVID-19 was generally lower than national prevalence. Current smokers were at reduced risk of infection. Former smokers were at increased risk of hospitalisation, disease severity and mortality, while data for current smokers favoured no important associations but were inconclusive.

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 angiotensin-converting enzyme 2 (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 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[11,13–18]. 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[19]. We adopted recommended best practice for rapid evidence reviews, which involved limiting the search to main databases and having one reviewer extract the data and another verify[20]. This study was not pre-registered but evolved from a report written for a UK medical society[21]. The most recent pre-print version is available here (version 6). A completed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist is included in Supplementary file 1.

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) or current vaping and nicotine replacement therapy (NRT) use;

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 (2019-search date) 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 (no time limitations):

1. covid (this term captures both covid and SARS-CoV-2) AND smoking
2. covid AND nicotine
3. covid AND vaping

Additional articles/reports of interest were identified through mailing lists, Twitter, the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) 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 another 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) use of alternative nicotine products; xi) SARS-CoV-2 testing; xii) SARS-CoV-2 infection; xiii) diagnosis of COVID-19; xiv) hospitalisation with COVID-19; xv) disease severity in those hospitalised with COVID-19; and xvi) mortality.

Quality appraisal

The quality of included studies was assessed to determine suitability for inclusion in meta-analyses. Studies were judged as 'good' quality if they: i) had <20% missing data on smoking status 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. Data from 'good' and 'fair' quality studies were pooled in R v.3.6.3[22]. In a living review where new data are regularly added to the analyses, it may be more appropriate to use a Bayesian (as opposed to frequentist) approach where prior knowledge is used in combination with new data to estimate a posterior risk distribution. A Bayesian approach mitigates against the issue of performing multiple statistical tests, which can inflate family-wise error. A series of random-effects hierarchical Bayesian meta-analyses were performed with the *brms*[23] package to estimate the relative risk for each comparison with accompanying 95% credible intervals (CrIs). We first defined prior distributions for the true pooled effect size (μ) and the between-study heterogeneity (τ), with μ specified as a normal distribution with a mean equal to the derived point estimate from each comparison of interest in the immediately preceding version of this living review24, and τ specified as a half-Cauchy distribution with a mean of 0 and standard deviation of 1. The half-Cauchy distribution was selected to reflect prior knowledge that high levels of between-study heterogeneity are more likely than lower levels. Markov Chain Monte Carlo methods (20,000 burn-ins followed by 80,000 iterations) were then used to generate a risk distribution for each study, in addition to a pooled effect for the posterior risk distribution. We report forest plots with the pooled effect for the posterior risk distribution displayed as the median relative risk with an accompanying 95% CrIs. We used the empirical cumulative distribution function (ECDF) to estimate the probability of there being a 10% reduction or 10% increase in relative risk (RR) (i.e. RR ≥1.1 or RR ≤0.9). Due to a lack of indication as to what constitutes a clinically or epidemiologically meaningful effect (e.g. with regards to onward disease transmission or requirements for intensive care beds), we deemed a 10% change in risk as small but important. Where data were inconclusive (as indicated by CrIs crossing RR = 1.0), to disambiguate whether data favoured no effect or there being a small but important association, we estimated whether there was ≥75% probability of RR ≥1.1 or RR ≤0.9.

Two sensitivity analyses were performed. First, a minimally informative prior for μ was specified as a normal distribution with a mean of 0 and standard deviation of 1 and τ as described above. Second, an informative prior as described above for μ was used with τ specified as a half-Cauchy distribution with a mean of 0.3 and standard deviation of 1 to reflect greater between-study heterogeneity.

To aid in the visualisation of smoking prevalence in the included studies, 95% bootstrap percentile confidence intervals were calculated for each study. We performed 1,000 bootstrap replications, with the 2.5th and 97.5th percentiles of the empirical distribution forming the 95% bootstrap percentile confidence intervals25 (CIs). 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 (v6) with searches up to 17 July 2020, a total of 762 new records were identified, with 174 studies included in a narrative synthesis and 26 studies included in meta-analyses (see Figure 1).

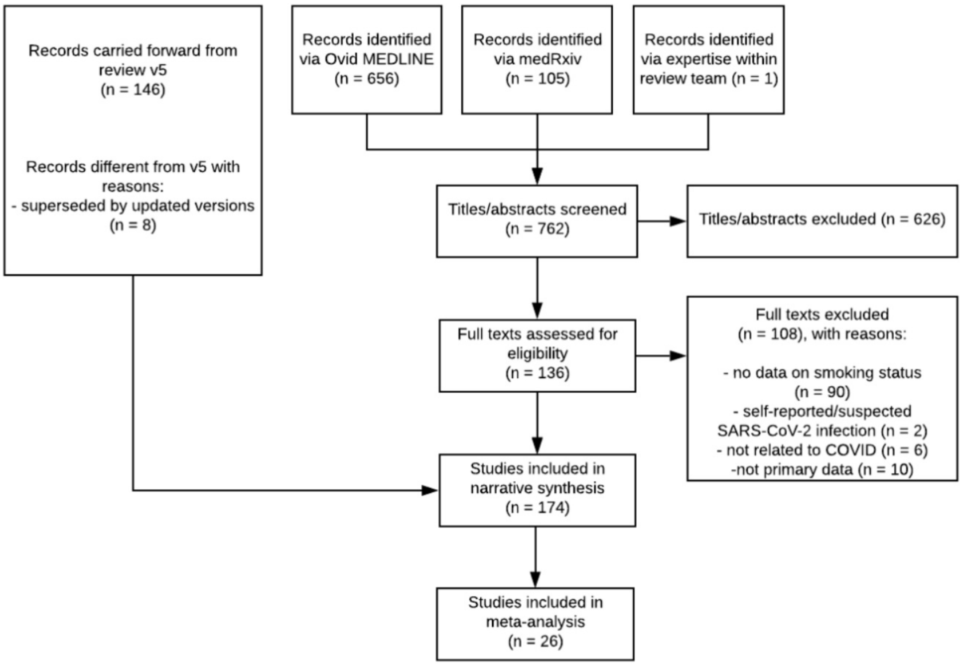

Figure 1. PRISMA flow diagram of included studies.

Study characteristics

Characteristics of included studies are presented in Table 1. Studies were conducted across 27 countries. Forty-five studies were conducted in China, 44 in the US, 18 in the UK, 11 in Mexico, nine in Spain, eight in France, six in Italy, six across multiple international sites, three in Brazil and Israel, two in Finland, Iran and Turkey and one from 15 further countries (see Figure 2). The majority of studies used observational designs (See Supplementary table S1). One-hundred-and-nineteen studies were conducted in hospital settings. Forty-six 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 396 (interquartile range = 124-1,573) participants. The majority of studies (165) used reverse transcriptase polymerase chain reaction (RT-PCR) for confirmation of SARS-CoV-2 infection, with nine further studies relying on either RT-PCR or clinical diagnosis (See Supplementary table S1).

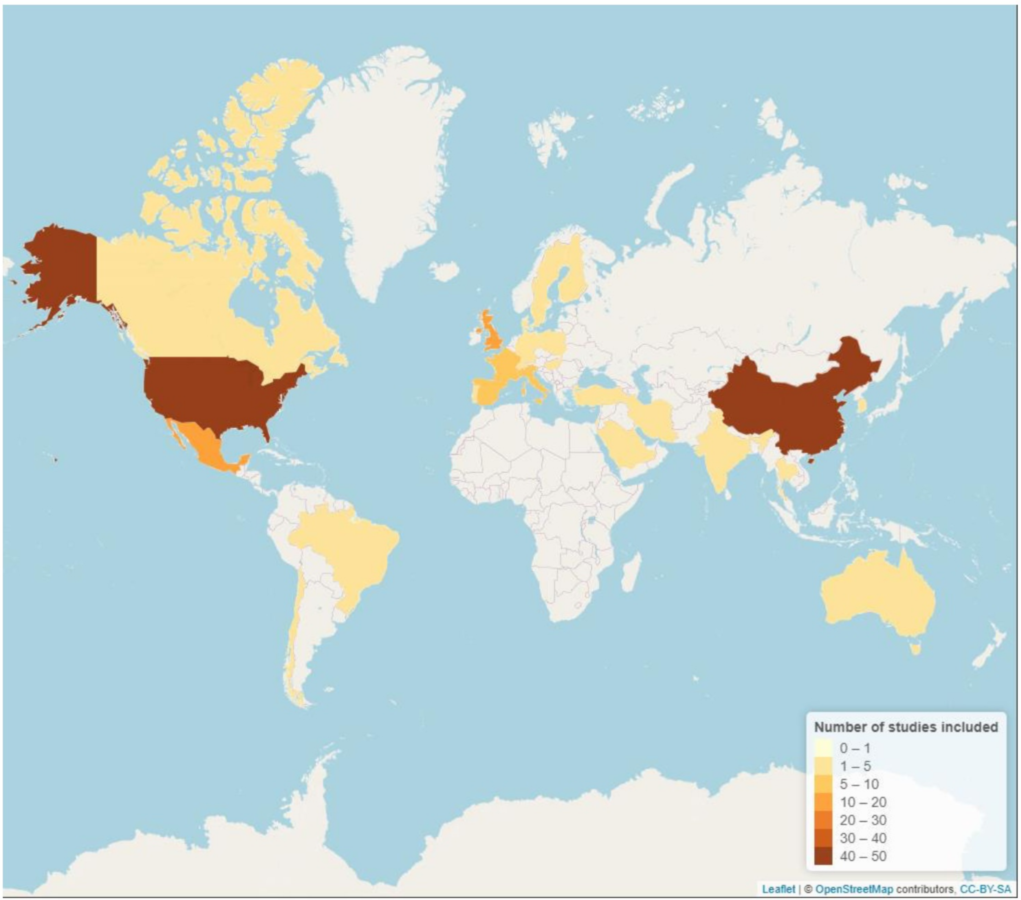

Figure 2. Map of countries where included studies were conducted. Six studies were performed in multiple countries and are hence not included here.

Smoking status

Categorisation of smoking status was heterogeneous (see Table 1). One-hundred and four studies collected data on smoking status through routine electronic health records (EHRs), 45 studies used a bespoke case report form for COVID-19 and 25 studies did not state the source for information on smoking status. None of the studies verified smoking status biochemically. Notably, only 39 (23.2%) studies reported current, former and never smoking status (see Supplementary table S2a), with a further 13 studies reporting ever and never smoking status (see Supplementary table S2b). The remaining 116 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 (see Supplementary table S2c). Fifty-five 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[26,27].

Quality appraisal

One study was performed in a random, representative population sample and was rated as 'good' quality. Thirty-three studies were rated as 'fair' quality. The remaining 140 studies were rated as 'poor' quality (see Table 1).

Table 1: Characteristics of included studies

Ref.	Lead author	Date published	Country	Sample size	Study setting	Median (IQR)	Female %	Current smoker %	Former smokers %	Current/former smokers %	Never smokers %	Never/unknown smokers %	Missing %	Study quality
1	Guan, Ni	2020-02-28	China	1,099	Hospital	47 (35-58)	41.9	12.5	1.9	-	84.3	-	1.27	fair
46	Guan, Liang	2020-03-26	China	1,590	Hospital	49 (33-64)	42.7	-	-	7.0	93.0	-	0.00	poor
47	Lian	2020-03-25	China	788	Hospital	NA	38.5	6.9	-	-	-	-	93.15	poor
48	Jin	2020-03-24	China	651	Hospital	46 (32-60)	49.2	6.3	-	-	-	-	93.70	poor
49	Chen	2020-03-26	China	548	Hospital	62 (44-70)	37.6	4.4	2.6	-	-	-	93.07	poor
50	Zhou, Yu	2020-03-11	China	191	Hospital	56 (46-67)	38.0	5.8	-	-	-	-	94.24	poor
51	Mo	2020-03-16	China	155	Hospital	54 (53-66)	44.5	3.9	-	-	-	-	96.13	poor
52	Zhang, Dong	2020-02-19	China	140	Hospital	57^ (25-87)	46.3	1.4	5.0	-	-	-	93.57	poor
53	Wan	2020-03-21	China	135	Hospital	47 (36-55)	46.7	6.7	-	-	-	-	93.33	poor
54	Liu, Tao	2020-02-28	China	78	Hospital	38 (33-57)	50.0	-	-	6.4	-	-	93.59	poor
55	Huang, Wang	2020-01-24	China	41	Hospital	49 (41-58)	27.0	7.3	-	-	-	-	92.68	poor
56	Zhang, Cai	2020-03-20	China	645	Hospital	NA	49.1	6.4	-	-	-	-	93.64	poor
57	Guo	2020-03-27	China	187	Hospital	59 (45-73)	51.3	9.6	-	-	-	-	90.37	poor
58	Liu, Ming	2020-03-12	China	41	Hospital	39 (30-48)	58.5	9.8	-	-	-	-	90.24	poor
59	Huang, Yang	2020-03-05	China	36	Hospital	69 (60-78)	30.6	-	-	11.1	-	-	88.89	poor
60	Xu	2020-03-08	China	53	Hospital	NA	47.2	11.3	-	-	-	-	88.68	poor
61	Li	2020-02-12	China	17	Hospital	45 (33-57)	47.1	17.6	-	-	-	-	82.35	poor

[28] Rentsch	2020-04-14	USA	3,528	Community and Hospital	66 (60-70)	4.6	27.2	30.6	-	36.9	-	5.30	fair
[62] Hu	2020-03-25	China	323	Hospital	61^ (23-91)	48.6	-	-	11.8	-	-	88.24	poor
[63] Wang, Pan	2020-03-24	China	125	Hospital	41 (26-66)	43.2	-	-	12.8	-	-	87.20	poor
[64] Chow (US CDC)	2020-03-31	USA	7,162	Community and Hospital	NA	-	1.3	2.3	-	-	-	96.36	poor
[65] Dong, Cao	2020-03-20	China	9	Hospital	44 (30-46)	66.7	11.1	-	-	-	-	88.89	poor
[66] Kim	2020-04-01	South Korea	28	Hospital	43 (30-56)	46.4	17.9	-	-	-	-	82.14	poor
[67] Shi, Yu	2020-03-18	China	487	Hospital	46 (27-65)	46.8	-	-	8.2	-	-	91.79	poor
[68] Yang, Yu	2020-02-24	China	52	Hospital	60 (47-73)	37.0	3.8	-	-	-	-	96.15	poor
[69] Argenziano	2020-05-29	USA	1,000	Hospital	63 (50-75)	40.4	4.9	17.9	-	77.2	-	0.00	fair
[70] Solis	2020-04-25	Mexico	650	Hospital	46 (NA)	42.1	9.4	-	-	-	-	90.62	poor
[71] Richardson	2020-04-22	USA	5,700	Hospital	63 (52-75)	39.7	-	-	9.8	52.8	-	37.42	poor
[72] Fontanet	2020-04-23	France	661	Community and Hospital	37 (16-47)	62.0	10.4	-	-	-	89.6	0.00	poor
[73] Zheng, Gao	2020-04-19	China	66	Hospital	47^ (NA)	25.8	12.1	-	-	-	-	87.88	poor
[74] Liao, Feng	2020-04-24	China	1,848	Hospital	55 (48-61)	54.7	-	-	0.4	-	-	99.57	poor
[75] Gil-Agudo	2020-04-24	Spain	7	Hospital	68 (34-75)	28.6	-	-	42.9	57.1	-	0.00	poor
[76] Shi, Ren	2020-04-23	China	134	Hospital	46 (34-58)	51.5	-	-	10.4	-	-	89.55	poor
[77] Hadjadj	2020-04-23	France	50	Hospital	55 (50-63)	22.0	2.0	18.0	-	80.0	-	0.00	fair
[78] Gold (US CDC)	2020-04-20	USA	305	Hospital	NA	50.5	5.2	-	-	-	-	94.75	poor
[79] Yu, Cai	2020-04-27	China	95	Hospital	NA	44.2	8.4	-	-	-	-	91.58	poor
[80] Zheng, Xiong	2020-04-30	China	73	Hospital	43^ (NA)	45.2	-	-	11.0	89.0	-	0.00	poor
[81] de la Rica	2020-05-11	Spain	48	Hospital	66^ (33-88)	33.0	-	-	20.8	-	-	79.17	poor
[82] Yin, Yang	2020-05-10	China	106	Hospital	73 (61-85)	39.6	-	-	17.0	-	-	83.02	poor
[83] Shi, Zuo	2020-05-17	USA	172	Hospital	63^ (44-82)	44.0	-	-	26.2	-	-	73.84	poor
[84] Cho	2020-05-11	UK	322,341	Community and Hospital	NA	49.2	14.2	21.4	-	64.4	-	0.00	fair
[85] Allenbach	2020-05-08	France	152	Hospital	77 (60-83)	31.1	-	-	6.6	-	-	93.42	poor
[86] Robilotti	2020-05-08	USA	423	Hospital	NA	50.0	2.1	37.6	-	58.6	-	1.65	fair
[87] The Opensafely Collaborative	2020-07-01	UK	17,278,392	Community and Hospital	NA	50.1	17.0	32.9	-	45.9	-	4.17	fair
[88] Borobia	2020-05-06	Spain	2,226	Hospital	61 (46-78)	52.0	7.1	-	-	-	-	92.95	poor
[89] Giacomelli	2020-05-06	Italy	233	Hospital	61 (50-72)	31.9	-	-	30.0	70.0	-	0.00	poor
[90] Shah	2020-05-06	USA	316	Hospital	63 (43-72)	48.1	16.5	17.7	-	42.1	-	23.73	poor
[91] Kolin	2020-05-05	UK	502,536	Community and Hospital	56.5 (48-64)	54.4	10.5	34.4	-	54.4	-	0.59	fair
[92] Lubetzky	2020-05-08	USA	54	Hospital	57 (29-83)	62.0	-	-	22.2	-	-	77.78	poor
[93] Goyal	2020-04-17	USA	393	Hospital	62.2 (49-74)	39.3	5.1	-	-	-	-	94.91	poor
[94] Feng	2020-04-10	China	476	Hospital	53 (40-64)	43.1	9.2	-	-	-	-	90.76	poor
[95] Yao	2020-04-24	China	108	Hospital	52 (37-58)	60.2	3.7	-	-	-	-	96.30	poor
[96] Sami	2020-05-19	Iran	490	Hospital	56.6 (41-71)	39.0	14.1	-	-	-	85.9	0.00	poor

79	Yu, Cai	2020-04-27	China	95	Hospital	NA	44.2	8.4	-	-	-	-	91.58	poor
80	Zheng, Xiong	2020-04-30	China	73	Hospital	43^ (NA)	45.2	-	-	11.0	89.0	-	0.00	poor
81	de la Rica	2020-05-11	Spain	48	Hospital	66^ (33-88)	33.0	-	-	20.8	-	-	79.17	poor
82	Yin, Yang	2020-05-10	China	106	Hospital	73 (61-85)	39.6	-	-	17.0	-	-	83.02	poor
83	Shi, Zuo	2020-05-17	USA	172	Hospital	63^ (44-82)	44.0	-	-	26.2	-	-	73.84	poor
84	Cho	2020-05-11	UK	322,341	Community and Hospital	NA	49.2	14.2	21.4	-	64.4	-	0.00	fair
85	Allenbach	2020-05-08	France	152	Hospital	77 (60-83)	31.1	-	-	6.6	-	-	93.42	poor
86	Robilotti	2020-05-08	USA	423	Hospital	NA	50.0	2.1	37.6	-	58.6	-	1.65	fair
87	The Opensafely Collaborative	2020-07-01	UK	17,278,392	Community and Hospital	NA	50.1	17.0	32.9	-	45.9	-	4.17	fair
88	Borobia	2020-05-06	Spain	2,226	Hospital	61 (46-78)	52.0	7.1	-	-	-	-	92.95	poor
89	Giacomelli	2020-05-06	Italy	233	Hospital	61 (50-72)	31.9	-	-	30.0	70.0	-	0.00	poor
90	Shah	2020-05-06	USA	316	Hospital	63 (43-72)	48.1	16.5	17.7	-	42.1	-	23.73	poor
91	Kolin	2020-05-05	UK	502,536	Community and Hospital	56.5 (48-64)	54.4	10.5	34.4	-	54.4	-	0.59	fair
92	Lubetzky	2020-05-08	USA	54	Hospital	57 (29-83)	62.0	-	-	22.2	-	-	77.78	poor
93	Goyal	2020-04-17	USA	393	Hospital	62.2 (49-74)	39.3	5.1	-	-	-	-	94.91	poor
94	Feng	2020-04-10	China	476	Hospital	53 (40-64)	43.1	9.2	-	-	-	-	90.76	poor
95	Yao	2020-04-24	China	108	Hospital	52 (37-58)	60.2	3.7	-	-	-	-	96.30	poor
96	Sami	2020-05-19	Iran	490	Hospital	56.6 (41-71)	39.0	14.1	-	-	-	85.9	0.00	poor
114	Heili-Frades	2020-05-25	Spain	4,712	Hospital	62 (47-77)	50.5	4.9	17.4	-	-	66.5	11.16	poor
115	Vaquero-Roncero	2020-05-24	Spain	146	Hospital	66^ (59-72)	32.2	-	-	6.8	-	-	93.15	poor
116	Kim, Garg	2020-05-22	USA	2,491	Hospital	62 (50-75)	46.8	6.0	25.8	-	-	68.1	0.08	poor
117	Wu	2020-05-21	Italy	174	Hospital	61.2^ (50-71)	30.5	-	-	33.3	-	-	66.67	poor
118	Shi, Zhao	2020-05-20	China	101	Hospital	71 (59-80)	40.6	-	-	5.0	-	-	95.05	poor
119	Al-Hindawi	2020-05-20	UK	31	Hospital	61 (NA)	12.9	3.2	71.0	-	25.8	-	0.00	fair
120	Basse	2020-05-19	France	141	Hospital	62 (52-72)	72.0	17.7	-	-	-	-	82.27	poor
121	Freites	2020-05-19	Spain	123	Hospital	59.88^ (44-74)	69.9	3.3	-	-	-	-	96.75	poor
122	Alshami	2020-05-19	Saudi Arabia	128	Quarantine Centre	39.6^ (24-55)	53.9	15.6	2.3	-	-	-	82.03	poor
123	Berumen	2020-05-26	Mexico	102,875	Hospital	NA	49.1	-	-	9.6	-	90.4	0.00	poor
124	Gianfrancesco	2020-05-29	Multiple	600	Community and Hospital	56 (45-67)	71.0	-	-	21.5	64.8	-	13.67	poor
125	Li, Long	2020-05-28	China	145	Not Stated	49^ (13-80)	61.0	-	-	5.5	-	-	94.48	poor
126	Batty	2020-06-17	UK	908	Hospital	57.27^ (48-66)	44.3	11.2	-	-	-	-	88.77	poor
127	Israel	2020-06-01	Israel	24,906	Community and Hospital	40 (27-59)	48.7	16.8	12.7	-	70.5	-	0.00	fair
128	del Valle	2020-05-30	USA	1,484	Hospital	62 (52-72)	40.6	5.5	23.3	-	-	-	71.16	poor
129	Chaudhry	2020-05-29	USA	40	Community and Hospital	52 (45.5-61)	60.0	-	-	15.0	-	-	85.00	poor
130	Louis	2020-05-28	USA	22	Hospital	66.5^ (55-77)	36.4	-	-	45.5	-	-	54.55	poor
131	Soto-Mota	2020-06-05	Mexico	400	Hospital	NA	30.0	-	-	12.0	-	-	88.00	poor

132	Garibaldi	2020-05-26	USA	832	Hospital	63 (49-75)	47.0	5.5	22.6	-	-	-	71.88	poor
133	Docherty	2020-05-22	Multiple	20,133	Hospital	72.9 (58-82)	40.0	4.2	21.7	-	44.5	-	29.55	poor
134	Boulware	2020-06-03	Multiple	821	Community	40 (33-50)	51.6	3.3	-	-	-	-	96.71	poor
135	Kuderer	2020-05-28	Multiple	928	Community and Hospital	66 (57-76)	50.0	4.6	35.1	-	50.5	-	9.70	fair
136	Romao	2020-06-08	Portugal	34	Community	41^ (26-66)	67.7	-	-	26.5	-	-	73.53	poor
137	Giannouchos	2020-06-07	Mexico	236,439	Community and Hospital	42.5^ (25-59)	49.1	9.1	-	-	-	90.9	0.00	poor
138	Ramlall	2020-06-06	USA	11,116	Community and Hospital	52 (34.7-69.5)	55.2	-	-	26.8	73.2	-	0.00	poor
139	Wang, Oekelen	2020-06-05	USA	58	Community and Hospital	67 (NA)	48.0	-	-	36.2	-	-	63.79	poor
140	Perrone	2020-06-05	Italy	1,189	Hospital	NA	21.2	-	-	21.9	-	-	78.13	poor
141	Sharma	2020-06-05	India	501	Hospital	35.1^ (18-51)	36.0	-	-	4.2	-	-	95.81	poor
142	Eugen-Olsen	2020-06-02	Denmark	407	Hospital	64 (47-77)	57.7	20.6	36.9	-	39.6	-	2.95	fair
143	Martinez-Portilla	2020-06-02	Mexico	224	Community and Hospital	29 (26-33)	100.0	-	-	3.1	-	-	96.88	poor
144	Raisi-Estabragh	2020-06-02	UK	4,510	Hospital	NA	48.8	-	-	51.8	-	-	48.20	poor
145	Luo	2020-06-02	China	625	Hospital	46 (NA)	47.7	3.0	-	-	-	-	96.96	poor
146	Houlihan	2020-06-09	UK	200	Community	34 (29-44)	61.0	11.0	16.5	-	66.5	-	6.00	fair
147	Cen	2020-06-08	China	1,007	Hospital	61 (49-68)	51.0	-	-	8.7	-	-	91.26	poor
148	Klang	2020-05-23	USA	3,406	Hospital	NA	61.8	-	-	23.3	-	-	76.72	poor
149	Maraschini	2020-06-12	Italy	146	Hospital	32.5^ (27-38)	100.0	-	9.6	-	80.8	-	9.59	poor
150	Wang, Zhong	2020-06-12	USA	7,592	Community and Hospital	NA	45.1	3.6	17.1	-	51.9	-	27.42	poor
151	McQueenie	2020-06-12	UK	428,199	Community and Hospital	NA	54.9	-	-	44.4	55.0	-	0.59	poor
26	Miyara	2020-06-12	France	479	Community and Hospital	NA	44.7	6.7	31.6	-	59.5	-	1.87	fair
152	Apea	2020-06-12	UK	1,737	Hospital	63.4^ (NA)	30.4	-	-	10.0	-	-	90.04	poor
153	Woolford	2020-06-11	UK	4,510	Community and Hospital	70.5 (NA)	51.2	13.0	38.1	-	48.1	-	0.80	fair
154	Hultcrantz	2020-06-11	USA	127	Community and Hospital	68 (41-91)	46.0	-	-	26.8	72.4	-	0.79	poor
155	Rajter	2020-06-10	USA	280	Hospital	59.6^ (41-77)	45.5	5.7	10.7	-	74.6	-	8.93	fair
156	Lan	2020-06-09	USA	104	Community	49^ (34-63)	47.1	-	-	24.0	-	-	75.96	poor
157	Zeng	2020-06-16	China	1,031	Hospital	60.3^ (46-74)	47.8	-	-	10.2	-	-	89.82	poor
158	Suleyman	2020-06-16	USA	463	Hospital	57.5^ (40-74)	55.9	-	-	34.6	-	-	65.44	poor
159	Chen, Yu	2020-06-16	China	1,859	Hospital	59 (45-68)	50.0	2.4	3.6	-	94.0	-	0.00	fair
160	Garassino	2020-06-12	Multiple	200	Community and Hospital	68 (61.8-75)	30.0	24.0	55.5	-	18.5	-	2.00	fair
161	Hernandez-Garduno	2020-06-11	Mexico	32,583	Community and Hospital	45 (34-56)	48.7	-	-	11.0	-	88.8	0.15	poor
162	Govind	2020-06-20	UK	6,309	Community and Hospital	46.5^ (31-61)	38.3	66.3	26.8	-	5.5	-	1.49	fair
163	Siso-Almirall	2020-06-20	Spain	322	Community and Hospital	56.7^ (38-74)	50.0	-	-	25.2	-	-	74.84	poor
164	Gu	2020-06-18	USA	5,698	Community and Hospital	47^ (26-67)	62.0	7.0	24.7	-	50.8	-	17.53	fair
165	Kibler	2020-06-16	France	702	Community and Hospital	82^ (75-88)	56.0	3.7	-	-	-	-	96.30	poor
166	Ikitimur	2020-06-03	Turkey	81	Hospital	55^ (38-72)	44.0	-	-	28.4	-	-	71.60	poor

167	Sierpinski	2020-06-03	Poland	1,942	Community	50 (NA)	60.0	6.3	-	-	-	49.7	44.03	poor
168	Zhou, He	2020-06-10	China	238	Hospital	55.5 (35-67)	57.0	2.9	-	-	-	-	97.06	poor
169	Crovetto	2020-06-19	Spain	874	Community and Hospital	33.7^ (28-38)	100.0	1.1	-	-	-	13.2	85.70	poor
170	Veras	2020-06-09	Brazil	32	Hospital	58.9^ (40-77)	47.0	-	-	25.0	-	-	75.00	poor
171	Sterlin	2020-06-11	France	135	Hospital	61 (50-72)	41.0	3.7	38.5	-	57.8	-	0.00	fair
172	Rossi	2020-06-09	France	246	Hospital	68^ (53-83)	39.0	-	-	25.2	-	-	74.80	poor
173	Duan	2020-06-22	China	616	Hospital	64 (53-70)	57.5	3.7	-	-	-	-	96.27	poor
174	Martin-Jimenez	2020-06-09	Spain	339	Hospital	81.6 (72-87)	39.5	-	-	30.7	-	-	69.32	poor
175	Elezkurtaj	2020-06-17	Germany	26	Hospital	70 (61.8-78.3)	34.6	-	-	19.2	-	-	80.77	poor
176	Lenka	2020-06-22	USA	32	Hospital	62.2^ (51-73)	37.5	-	-	50.0	-	-	50.00	poor
177	Olivares	2020-06-16	Chile	21	Hospital	61^ (26-85)	76.2	-	-	9.5	-	-	90.48	poor
178	Salton	2020-06-20	Italy	173	Hospital	64.4^ (NA)	34.9	-	-	29.5	-	-	70.52	poor
179	Wei	2020-06-18	USA	147	Hospital	52^ (34-70)	41.0	14.3	-	-	-	-	85.71	poor
180	Zuo, Estes	2020-06-17	China	172	Hospital	61^ (25-95)	44.0	-	-	26.2	-	-	73.84	poor
181	Killerby	2020-06-17	USA	531	Community and Hospital	51.6 (38-62)	57.1	-	-	17.1	71.4	-	11.49	poor
182	Petrilli	2020-05-22	USA	5,279	Community and Hospital	54 (38-66)	51.5	5.5	17.1	-	61.9	-	15.55	fair
183	Magagnoli	2020-06-05	USA	807	Hospital	70 (60-75)	4.3	-	-	15.9	-	-	84.14	poor
30	Niedzwiedz	2020-05-29	UK	392,116	Community and Hospital	NA	54.9	9.8	34.8	-	55.4	-	0.00	fair
184	Bello-Chavolla	2020-05-31	Mexico	177,133	Community and Hospital	42.6 (26-59)	48.9	-	-	9.3	-	-	90.72	poor
185	Zuo, Yalavarthi	2020-04-24	USA	50	Hospital	61 (46-76)	34.0	-	-	36.0	-	-	64.00	poor
186	Sigel	2020-06-28	USA	493	Hospital	60 (55-67)	24.1	-	-	28.6	-	-	71.40	poor
187	Nguyen	2020-06-29	USA	689	Community and Hospital	55 (40-68)	57.0	-	-	24.8	-	-	75.18	poor
188	de Melo	2020-06-29	Brazil	181	Hospital	55.3^ (34-76)	60.8	9.9	12.2	-	38.1	-	39.78	poor
189	Auvinen	2020-06-29	Finland	61	Hospital	53 (41-67)	36.0	18.0	27.9	-	54.1	-	0.00	fair
190	Souza	2020-06-28	Brazil	8,443	Hospital	NA	53.0	-	-	1.7	-	96.3	2.01	poor
191	Mendy	2020-06-27	USA	689	Community and Hospital	49.5 (35.2-67.5)	47.0	-	-	24.7	-	-	75.33	poor
192	Pongpirul	2020-06-26	Thailand	193	Hospital	37 (29-53)	41.5	-	-	15.0	66.3	-	18.65	poor
193	Jin, Gu	2020-06-25	China	6	Hospital	60.5^ (51-75)	33.3	33.3	-	-	-	-	66.67	poor
194	Favara	2020-05-23	UK	70	Community and Hospital	41 (23-64)	87.1	10.0	-	-	-	-	90.00	poor
195	Fisman	2020-06-23	Canada	21,922	Community and Hospital	NA	57.0	-	-	2.3	-	-	97.65	poor
196	Madariaga	2020-06-23	USA	103	Community and Hospital	41.8^ (27-55)	48.5	-	-	25.2	74.8	-	0.00	poor
197	Senkal	2020-07-07	Turkey	611	Hospital	57^ (18-98)	40.6	11.3	-	-	-	-	88.71	poor
198	Mohamud	2020-07-02	USA	6	Hospital	65.8^ (55-78)	16.7	-	-	16.7	-	-	83.33	poor
199	Magleby	2020-06-30	USA	678	Hospital	68 (50-81)	38.9	-	-	28.6	-	-	71.39	poor
200	Kimmig	2020-07-06	USA	111	Hospital	63^ (48-78)	44.1	7.2	36.0	-	56.8	-	0.00	fair
201	Bello-Chavolla, Antonio-Villa	2020-07-04	Mexico	60,121	Community and Hospital	45.5^ (29-61)	47.0	-	-	10.5	-	-	89.52	poor

202	Zacharioudakis	2020-07-04	USA	314	Hospital	64 (54-72)	34.7	-	-	22.8	-		-	77.22	poor
203	Antonio-Villa	2020-07-04	Mexico	34,263	Community and Hospital	40^ (29-50)	62.9	9.7	-	-	-		-	90.32	poor
204	Patel	2020-07-03	USA	129	Hospital	60.8^ (47-74)	45.0	37.2	-	-	-		55.8	6.98	poor
205	Merzon	2020-07-03	Israel	7,807	Community and Hospital	46.2^ (NA)	58.6	-	-	16.2	-		-	83.82	poor
31	Trubiano	2020-07-02	Australia	2,935	Community and Hospital	39 (29-53)	63.5	-	-	8.8	-		-	91.18	poor
206	Fan	2020-07-11	UK	1,425	Community and Hospital	NA	46.7	12.2	40.1	-	46.9		-	0.84	fair
207	Shi, Resurreccion	2020-07-11	UK	1,521	Community and Hospital	61.5^ (57-66.8)	45.9	-	-	54.9	-		-	45.10	poor
208	Riley	2020-07-11	UK	120,620	Community and Hospital	NA	54.0	2.2	-	-	-		16.5	81.32	poor
209	Maucourant	2020-07-10	Sweden	27	Hospital	57 (18-78)	22.2	11.1	25.9	-	40.7		-	22.22	poor
210	Elmunzer	2020-07-09	Multiple	1,992	Hospital	60^ (43-76)	43.0	6.3	28.6	-	59.0		-	6.12	fair
211	Alizadehsani	2020-07-09	Iran	319	Hospital	45.48^ (26-63)	55.5	-	-	0.3	-		-	99.69	poor
212	Xie	2020-07-07	China	619	Hospital	NA	52.0	-	-	8.2	-		-	91.76	poor
33	Merkely	2020-07-17	Hungary	10,474	Community	48.7^ (30-66)	53.6	28.0	20.5	-	51.4		-	0.16	good

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 smoking prevalence was generally observed. Former smoking prevalence was more similar to expected prevalence when reported. National smoking prevalence estimates used for comparison are presented in Supplementary table 3.

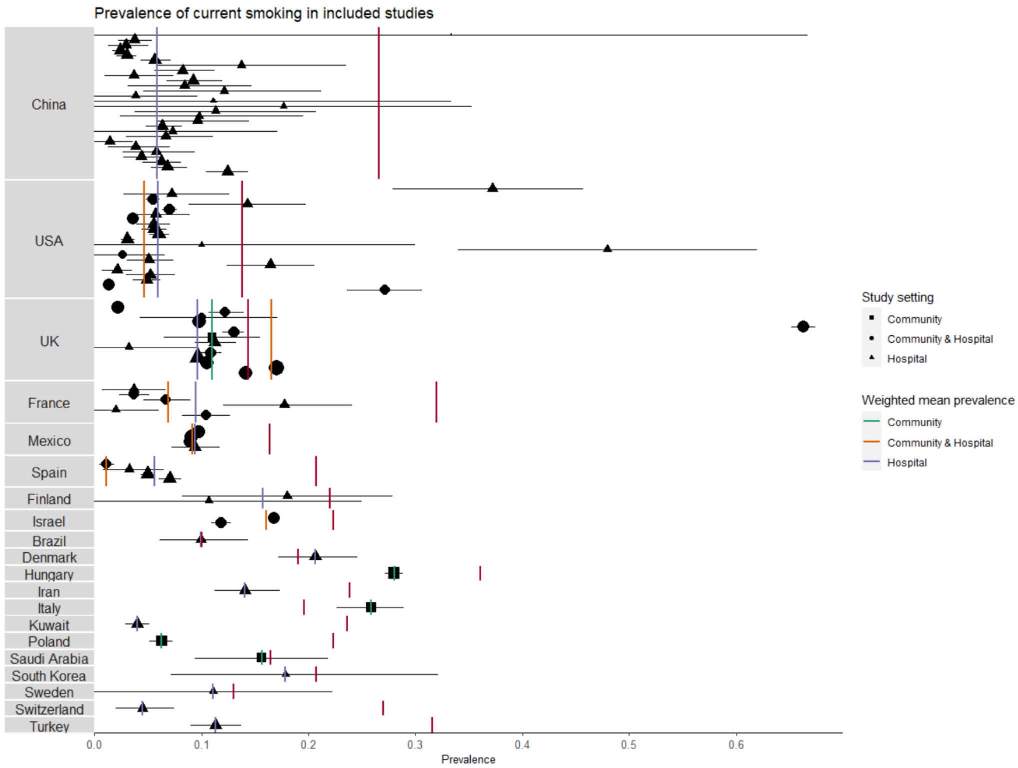

Figure 3a. Weighted mean prevalence of current smoking in included studies with 95% bootstrap confidence intervals compared with national current smoking prevalence (solid red lines), split by country. Shape corresponds to study setting (community, community and hospital, hospital) and shape size corresponds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

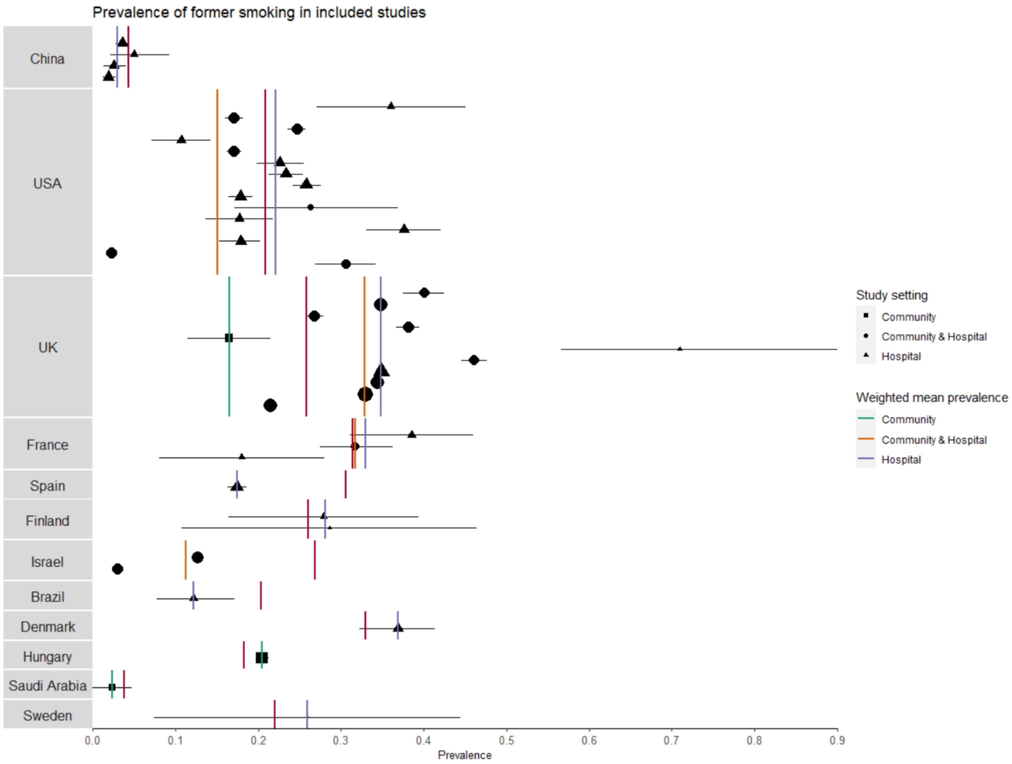

Figure 3b. Weighted mean prevalence of former smoking in included studies (where this was reported) with 95% bootstrap confidence intervals compared with national former smoking prevalence (solid red lines), split by country. Shape corresponds to study setting (community, community and hospital, hospital)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

SARS-CoV-2 testing by smoking status

Three studies provided data on access to SARS-CoV-2 diagnostic testing for those meeting local testing criteria by smoking status. In a cohort study of US military veterans aged 54-7528, current smokers were more likely to receive a test: 42.3% (1,603/3,789) of the sample were current smokers compared with 23.8% of all veterans aged 50+ years using any tobacco product between 2010-201529. In the UK Biobank cohort30, former (RR = 1.29, 95% CI = 1.14-1.45, p < .001) and current (RR = 1.44, 95% CI = 1.20-1.71, p < .001) compared with never smokers were more likely to receive a test in a multivariable analysis. In an Australian rapid assessment screening clinic for COVID-1931, 9.4% (397/4,226) of the self-referred sample (subsequently assessed by a healthcare professional to decide on testing) were current smokers. Current compared with former or never smokers were less likely to require a test (RR = 0.93, 95% CI = 0.86-1.0, p = 0.045).

SARS-CoV-2 infection by smoking status

Thirty-six studies provided data on SARS-CoV-2 infection for people meeting local testing criteria by smoking status (see Table 2). Meta-analyses were performed for one 'good' and 14 '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 = 0.74, 95% CrI = 0.56-0.97, τ = 0.46, 95% CI = 0.27-0.77). The probability of current smokers being at reduced risk of infection compared with never smokers (RR $\leq$0.9) was 93%. Former compared with never smokers were at increased risk of testing positive, but data were inconclusive (RR = 1.06, 95% CrI = 0.94-1.20, τ = 0.19, 95% CI = 0.12-0.32) and favoured there being no important association. The probability of former smokers being at increased risk of infection (RR $\geq$1.1) compared with never smokers was 25%. Results were materially unchanged in the two sensitivity analyses (see Supplementary figure S1).

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%)	-
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	24906	20755 (83.33%)	3783 (18.23%)	2671 (12.87%)	-	14301 (68.90%)	-	41151 (165.23%)	406 (0.99%)	483 (1.17%)	-	3262 (7.93%)	-
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%)
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%)
Petrilli	10620	5341 (50.29%)	3454 (64.67%)	816 (15.28%)	-	541 (10.13%)	530 (9.92%)	5279 (49.71%)	3268 (61.91%)	902 (17.09%)	-	288 (5.46%)	821 (15.55%)
Bello-Chavolla	150200	98567 (65.62%)	-	-	9624 (9.76%)	-	88943 (90.24%)	51633 (34.38%)	-	-	4366 (8.46%)	-	47267 (91.54%)
Auvinen	61	33 (54.10%)	10 (30.30%)	8 (24.24%)	-	15 (45.45%)	-	28 (45.90%)	1 (3.57%)	9 (32.14%)	-	18 (64.29%)	-
Favara	70	55 (78.57%)	5 (9.09%)	-	-	-	50 (90.91%)	15 (21.43%)	2 (13.33%)	-	-	-	13 (86.67%)
Antonio-Villa	34263	23338 (68.11%)	2293 (9.83%)	-	-	-	21045 (90.17%)	10925 (31.89%)	1023 (9.36%)	-	-	-	9902 (90.64%)
Merzon	7807	7025 (89.98%)	-	-	1136 (16.17%)	-	5889 (83.83%)	782 (10.02%)	-	-	127 (16.24%)	-	655 (83.76%)
Trubiano	2676	2827 (105.64%)	-	-	256 (9.06%)	-	2586 (91.48%)	108 (4.04%)	-	-	3 (2.78%)	-	105 (97.22%)
Shi, Resurreccion	1521	1265 (83.17%)	-	-	681 (53.83%)	-	584 (46.17%)	256 (16.83%)	-	-	154 (60.16%)	-	102 (39.84%)
Riley	120620	120461 (99.87%)	2594 (2.15%)	-	-	19914 (16.53%)	97953 (81.32%)	159 (0.13%)	3 (1.89%)	-	-	17 (10.69%)	139 (87.42%)
Alizadehsani	319	196 (61.44%)	-	-	-	-	196 (100.00%)	123 (38.56%)	-	-	1 (0.81%)	-	122 (99.19%)
Merkely	10474	10336 (98.68%)	2904 (28.10%)	2107 (20.39%)	-	5310 (51.37%)	15 (0.15%)	70 (0.67%)	16 (22.86%)	15 (21.43%)	-	38 (54.29%)	1 (1.43%)

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.

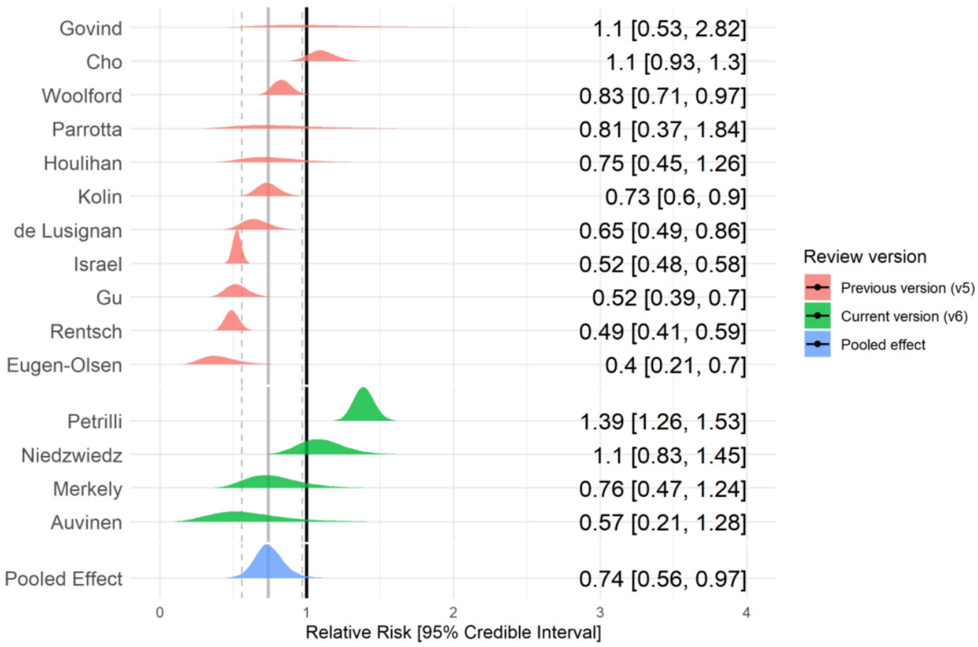

Figure 4. Forest plot for risk of testing positive for SARS-CoV-2 in current vs. never smokers.

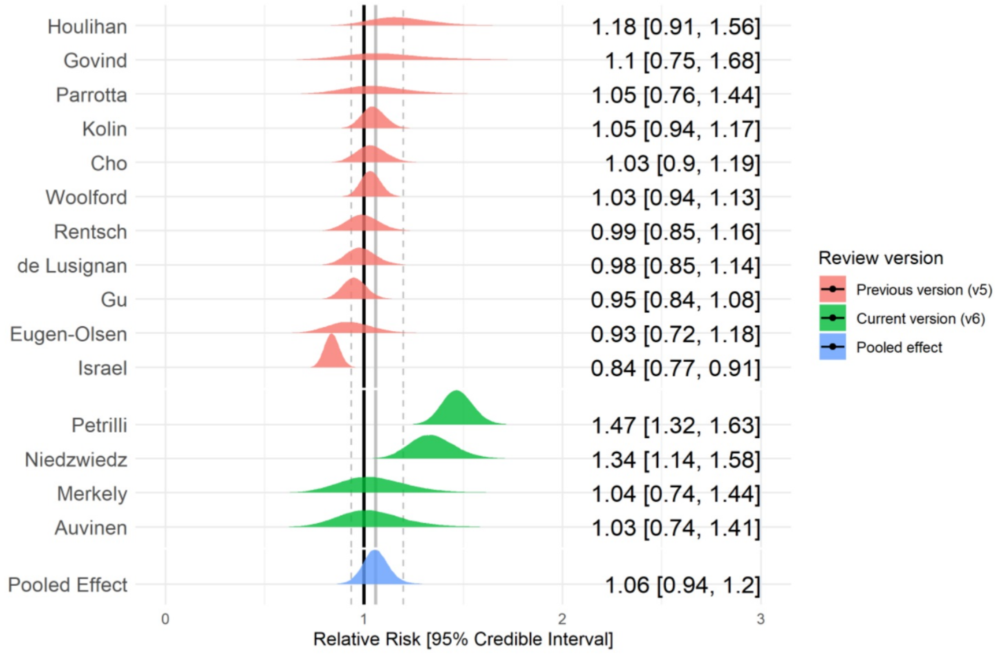

Figure 5. Forest plot for risk of testing positive for SARS-CoV-2 in former vs. never smokers.

Hospitalisation for COVID-19 by smoking status

Twenty-three studies examined hospitalisation for COVID-19 disease stratified by smoking status (see Table 3). Meta-analyses were performed for eight 'fair' quality studies (see Figure 6 and 7). Current (RR = 1.05, CrI = 0.82-1.34, τ = 0.29, 95% CI = 0.11-0.61) and former (RR = 1.20, CrI = 1.03-1.44, τ = 0.19, 95% CI = 0.08-0.42) compared with never smokers were at increased risk of hospitalisation with COVID-19, but data for current smokers were inconclusive and favoured there being no important association. The probability of current and former smokers being at increased risk of hospitalisation compared with never smokers was 34% and 89%, respectively. Results were materially unchanged in two sensitivity analyses (see Supplementary figure S2).

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%)	-	-
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%)	-	-
Lubetzky	54	15 (27%)	-	-	4 (26.67%)	-	-	11 (73.33%)	39 (72%)	-	-	8 (20.51%)	-	-	31 (79.49%)
Carillo-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%)	-
Wang, Oekelen	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%)
Petrilli	5279	2538 (48%)	147 (5.79%)	337 (13.28%)	-	1678 (66.12%)	-	376 (14.81%)	2741 (51%)	141 (5.14%)	565 (20.61%)	-	1590 (58.01%)	-	445 (16.23%)
Nguyen	689	333 (48%)	-	-	57 (17.12%)	-	-	276 (82.88%)	356 (51%)	-	-	114 (32.02%)	-	-	242 (67.98%)
Mendy	689	473 (68%)	-	-	84 (17.76%)	-	-	389 (82.24%)	216 (31%)	-	-	86 (39.81%)	-	-	130 (60.19%)

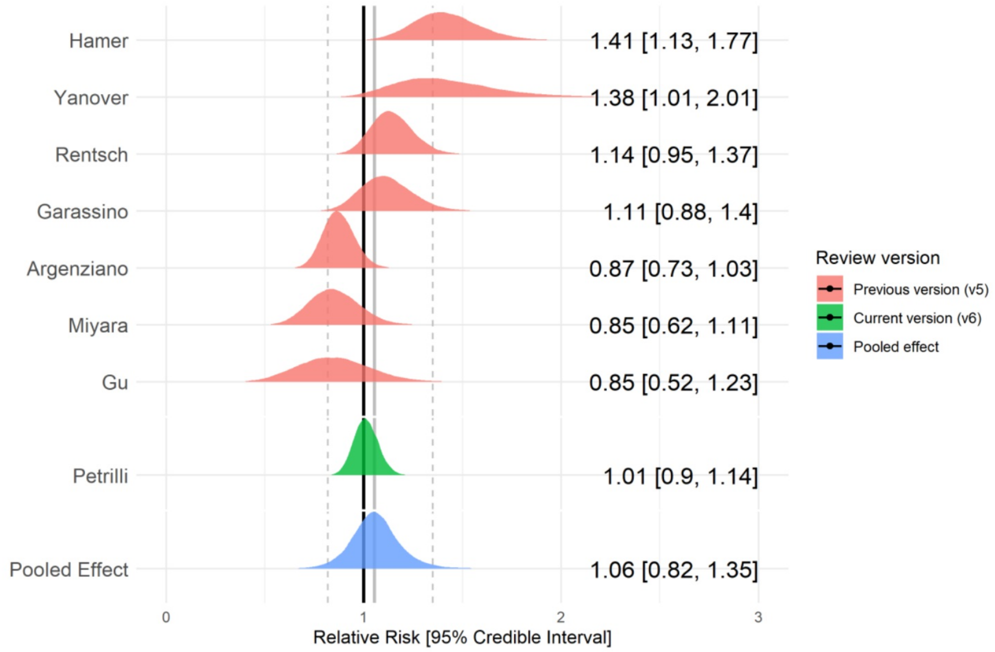

Figure 6. Forest plot for risk of hospitalisation in current vs. never smokers.

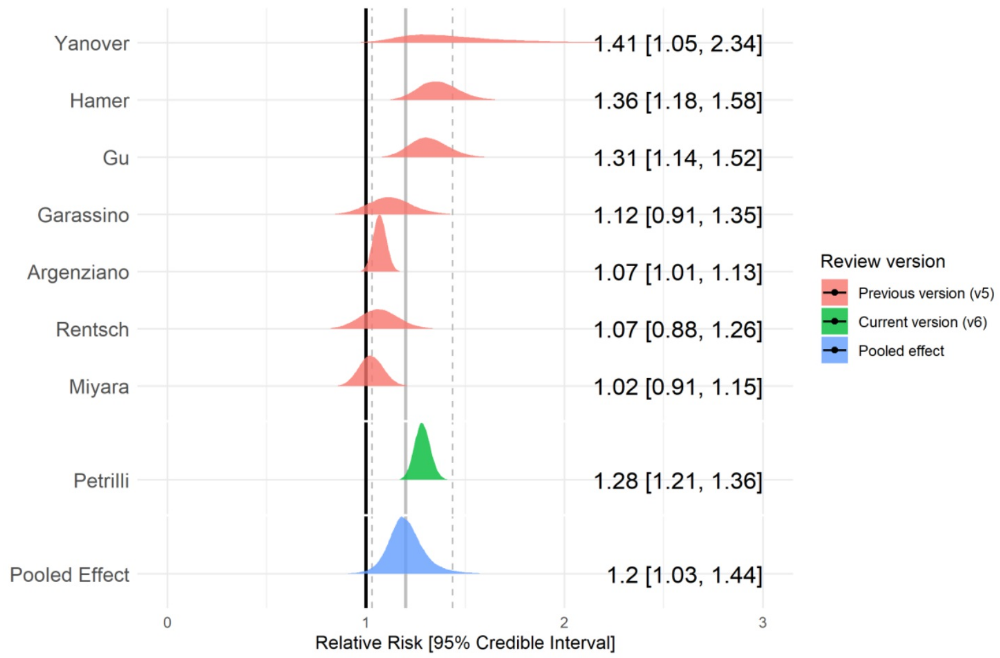

Figure 7. Forest plot for risk of hospitalisation in former vs. never smokers.

Disease severity by smoking status

Forty-four 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 seven 'fair' quality studies (see Figure 8 and 9). Current (RR = 1.15, CrI = 0.8-1.66, τ = 0.29, 95% CI = 0.02-0.87) and former (RR = 1.51, CrI = 1.06-2.15, τ = 0.36, 95% CI = 0.09-0.83) compared with never smokers were at increased risk of greater disease severity, but data for current smokers were inconclusive and favoured there being no important association. The probability of current and former smokers having increased risk of greater disease severity compared with never smokers was 63% and 97%, respectively. Results were materially unchanged in two sensitivity analyses (see Supplementary figure S3).

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%)	-
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%)	-
Chaudhry	40	34 (85%)	-	-	5 (14.71%)	-	-	29 (85.29%)	6 (15%)	-	-	1 (16.67%)	-	-	5 (83.33%)
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%)	-	-

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%)	-	-
Petrilli	2729	1739 (63%)	97 (5.58%)	325 (18.69%)	-	1067 (61.36%)	-	250 (14.38%)	990 (36%)	44 (4.44%)	236 (23.84%)	-	517 (52.22%)	-	193 (19.49%)
Mendy	689	598 (86%)	-	-	133 (22.24%)	-	-	465 (77.76%)	91 (13%)	-	-	37 (40.66%)	-	-	54 (59.34%)
Pongpirul	193	161 (83%)	-	-	25 (15.53%)	106 (65.84%)	-	30 (18.63%)	32 (16%)	-	-	4 (12.50%)	21 (65.62%)	-	7 (21.88%)
Jin, Gu	6	2 (33%)	-	-	0 (0.00%)	-	-	4 (200.00%)	4 (66%)	-	-	2 (50.00%)	-	-	2 (50.00%)
Senkal	611	446 (73%)	48 (10.76%)	-	-	-	-	398 (89.24%)	165 (27%)	21 (12.73%)	-	-	-	-	144 (87.27%)
Patel	129	89 (68%)	26 (29.21%)	-	-	-	58 (65.17%)	5 (5.62%)	40 (31%)	22 (55.00%)	-	-	-	14 (35.00%)	4 (10.00%)
Maucourant	27	10 (37%)	1 (10.00%)	2 (20.00%)	-	2 (20.00%)	-	5 (50.00%)	17 (62%)	2 (11.76%)	5 (29.41%)	-	9 (52.94%)	-	1 (5.88%)
Xie	619	469 (75%)	-	-	32 (6.82%)	-	-	437 (93.18%)	150 (24%)	-	-	19 (12.67%)	-	-	131 (87.33%)

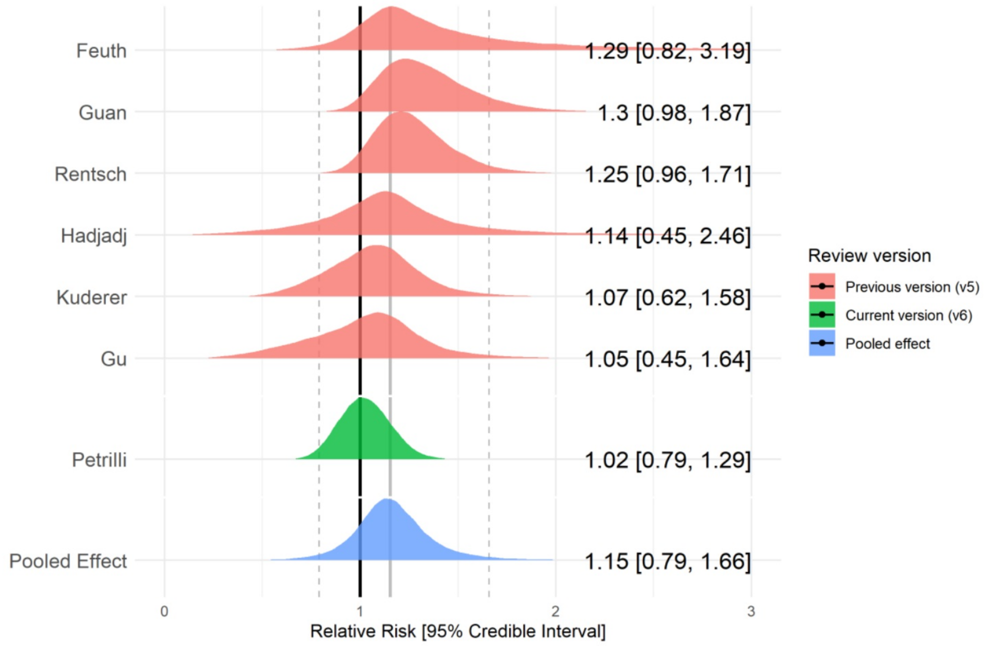

Figure 8. Forest plot for the risk of severe disease in current vs. never smokers.

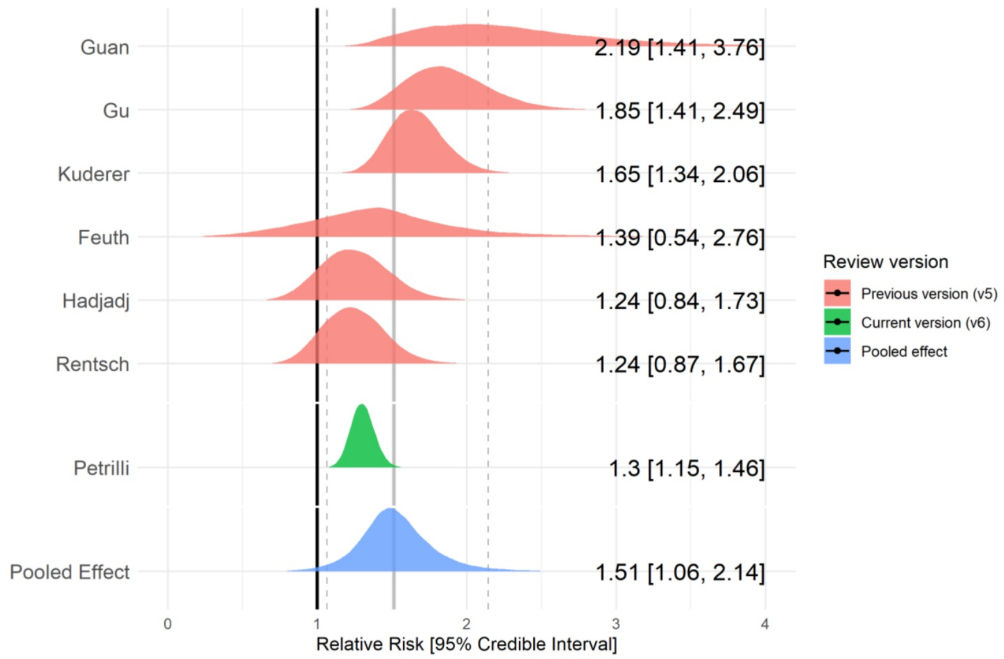

Figure 9. Forest plot for the risk of severe disease in former vs. never smokers.

Mortality by smoking status

Thirty-five 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 = 1.89, 95% CrI = 0.77-3.41, τ = 0.51, 95% CI = 0.02-1.58) and former (RR = 1.93, 95% CrI = 1.33-2.66, τ = 0.19, 95% CI = 0.01-0.68) compared with never smokers were at increased risk of in-hospital mortality from COVID-19. Data for current smokers were inconclusive but favoured there being a small but important association. The probability of current and former smokers being at greater risk of in-hospital mortality compared with never smokers was 91% and >99%, respectively. Results were materially unchanged in two sensitivity analyses(see Supplementary figure S4).

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	NA (NA%)	-	-	-	-	-	-	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%)	-	-
Rajter	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%)	-	-
Sigel	88	70 (79%)	-	-	37 (52.86%)	-	-	33 (47.14%)	18 (20%)	-	-	11 (61.11%)	-	-	7 (38.89%)
Nguyen	356	308 (86%)	-	-	91 (29.55%)	-	-	217 (70.45%)	45 (12%)	-	-	23 (51.11%)	-	-	22 (48.89%)
de Souza	8443	7826 (92%)	-	-	95 (1.21%)	-	7571 (96.74%)	160 (2.04%)	617 (7%)	-	-	47 (7.62%)	-	560 (90.76%)	10 (1.62%)
Mendy	532	663 (124%)	-	-	160 (24.13%)	-	-	502 (75.72%)	26 (4%)	-	-	10 (38.46%)	-	-	16 (61.54%)
Shi, Resurreccion	256	210 (82%)	-	-	128 (60.95%)	-	-	82 (39.05%)	46 (17%)	-	-	26 (56.52%)	-	-	20 (43.48%)
Xie	619	591 (95%)	-	-	43 (7.28%)	-	-	548 (92.72%)	28 (4%)	-	-	8 (28.57%)	-	-	20 (71.43%)

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.

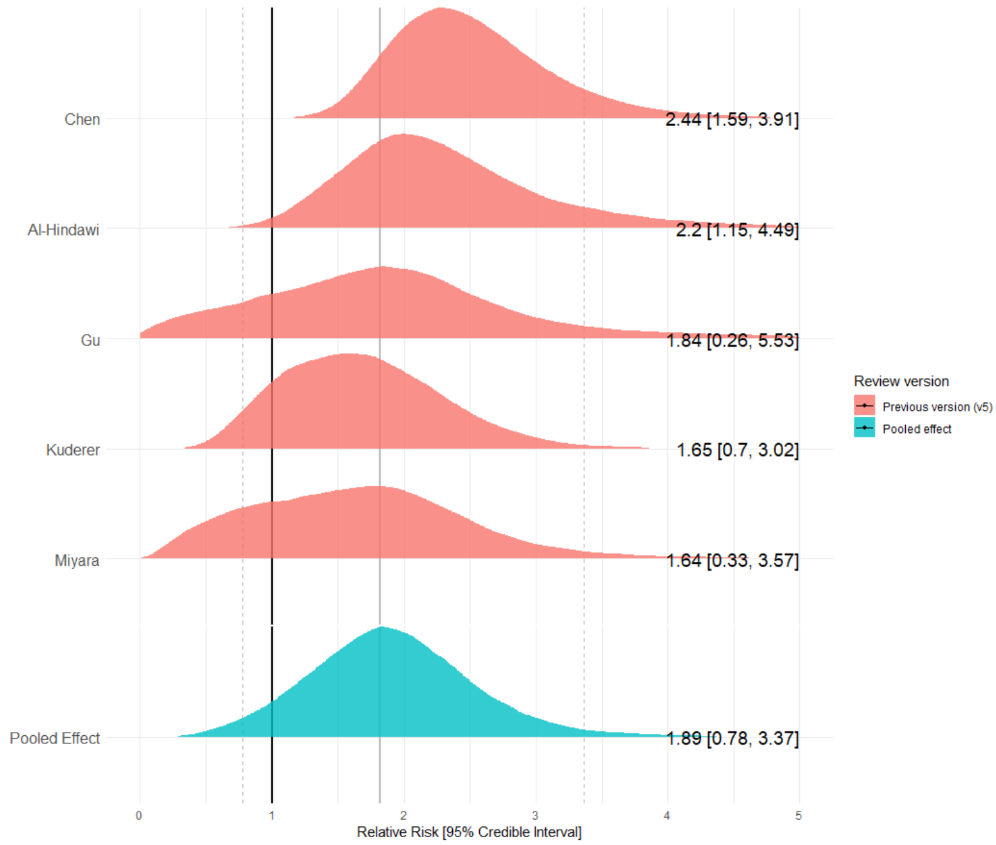

Figure 10. Forest plot for the risk of mortality in current vs. never smokers.

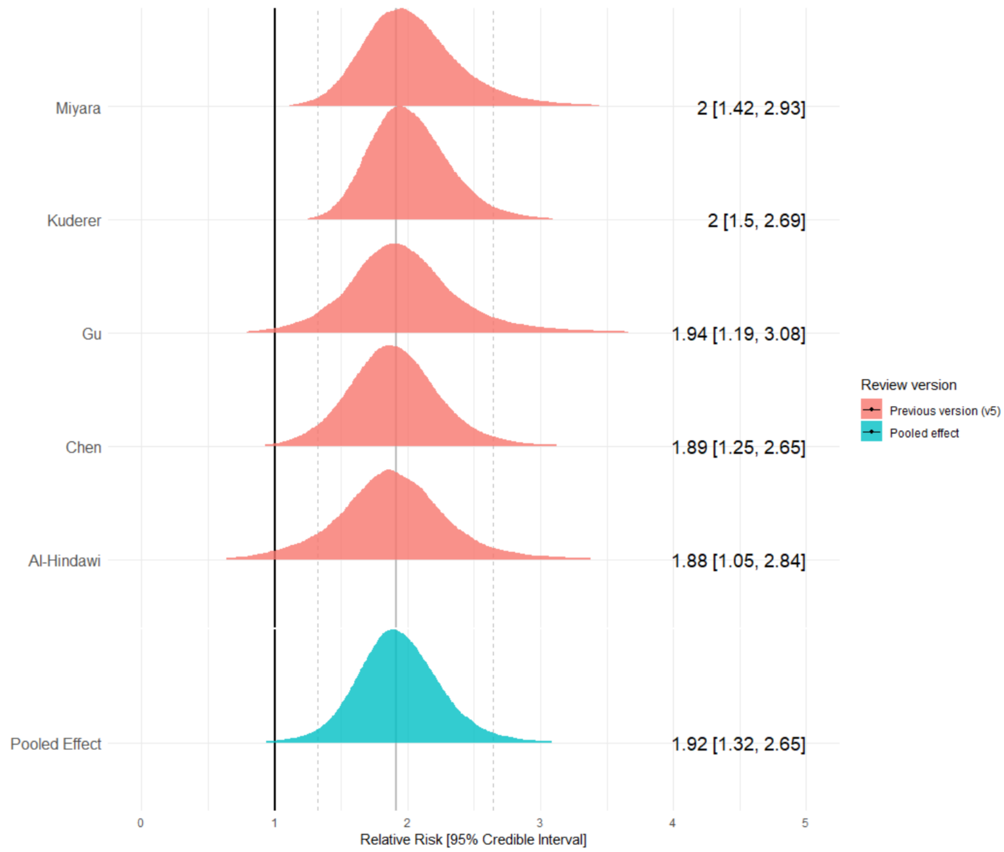

Figure 11. Forest plot for the risk of mortality in former vs. never smokers.

Discussion

This living rapid review of 174 studies found substantial uncertainty arising from the recording of smoking status. Notwithstanding these uncertainties, compared with overall adult national prevalence estimates, recorded current smoking rates in most countries were lower than expected. Current smokers had a reduced risk of testing positive for SARS-CoV-2 but appeared more likely to present for testing and/or receive a test. Current smokers were at increased risk of hospitalisation, disease severity and mortality but data were inconclusive. Former smokers were at increased risk of hospitalisation, disease severity and mortality compared with never smokers.

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 12):

1) 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.

2) 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[32]. Evidence from a small number of studies indicates that current smokers may be more likely to present for testing, hence increasing the denominator in comparisons with never smokers and potentially inflating the rate of negative tests in current smokers. Infection positivity rates estimated among random samples will be more informative than currently available data. We identified one population study conducted in Hungary reporting on seroprevalence and smoking status[33]; however, the response rate was fairly low at 58.8% and the current smoking rate was 10 percentage points below national prevalence estimates, thus questioning the representativeness of the final sample. Smoking status is being collected in at least two large representative infection and antibody surveys in the UK[34,35].

3) Testing for acute infection requires swabbing of the mucosal epithelium, which may be disrupted in current smokers, potentially altering the sensitivity of assays[36].

4) Diagnostic criteria for SARS-CoV-2 infection and COVID-19 have changed during the course of the pandemic[37]. It was not possible to extract details on the specific RT-PCR technique or platforms used across the included studies due to reporting gaps. Different platforms have varying sensitivity and specificity to detect SARS-CoV-2 infection.

5) Most included studies relied on EHRs as the source of information on smoking status. Research shows large discrepancies between EHRs and actual behaviour[38]. Known failings of EHRs include implausible longitudinal changes, such as former smokers being recorded as never smokers at subsequent hospital visits[38]. 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[39]. It is hence possible that under-reporting of current and former smoking status in hospitals occurred across the included studies.

6) 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).

7) 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.

8) If there is a protective effect of nicotine on COVID-19 disease outcomes, abrupt nicotine withdrawal upon hospitalisation may lead to worse outcomes[12].

9) 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.

10) Given lack of knowledge of the disease progression and long-term outcomes of COVID-19, 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.

11) Reasons for hospitalisation vary 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 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[40], 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)[41].

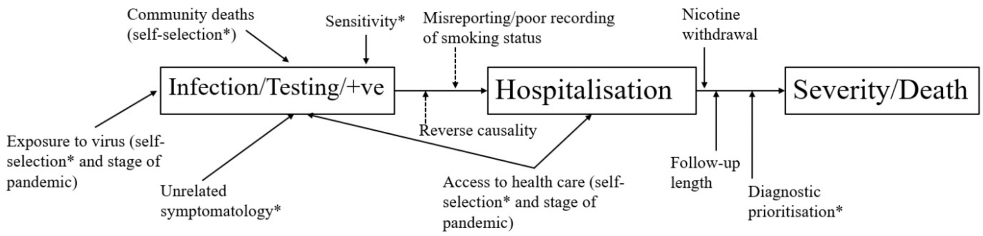

Figure 12. A schematic of some of the interpretation issues for the association of smoking and SARS-CoV-2/COVID-19. * Indicates potential confounding with smoking status

Limitations

This living rapid evidence review was limited by having a single reviewer extracting data with a second independently reviewing the data extracted to minimise data extraction errors, restricting 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)[32,42,43]. 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 adjustments for sex and age, and continue to find lower than expected prevalence – notwithstanding the issues complicating interpretation described above[17].

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[44] 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[45]. 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 174 studies, recorded smoking prevalence was generally lower than national prevalence estimates. Current smokers were at reduced risk of testing positive for SARS-CoV-2 and former smokers were at increased risk of hospitalisation, disease severity and mortality compared with never smokers.

Declaration of conflicts of interest

DS and OP have no conflicts of interest to declare. LS has received a research grant and honoraria for a talk and travel expenses from manufacturers of smoking cessation medications (Pfizer and Johnson & Johnson). JB has received unrestricted research funding to study smoking cessation from companies who manufacture smoking cessation medications. All authors declare no financial links with tobacco companies or e-cigarette manufacturers or their representatives.

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Previous versions

Version 1

Version 2

Version 3

Version 4

Version 5

Data and code

Data is available here

Code is available here

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