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The association of smoking status with SARS-CoV-2 infection, hospitalisation and mortality from COVID-19: A living rapid evidence review with Bayesian meta-analyses (version 9)

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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 MEDLINE and medRxiv.

Setting: Community or hospital. No restrictions on location.

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

Measurements: Outcomes were SARS-CoV-2 infection, hospitalisation, disease severity and mortality stratified by smoking status. Study quality was assessed (i.e. 'good', 'fair' and 'poor').

Findings: Version 9 (searches up to 27 October 2020) included 279 studies with 42 'good' and 'fair' quality studies included in unadjusted meta-analyses. Seventy-nine studies (28%) reported current, former and never smoking status with the remainder using broader categories. Recorded smoking prevalence among people with COVID-19 was generally lower than national prevalence. Current compared with never smokers were at reduced risk of SARS-CoV-2 infection (RR = 0.69, 95% Credible Interval (CrI) = 0.57-0.83, τ = 0.38). Data for former smokers were inconclusive (RR = 1.02, 95% CrI = 0.93-1.12, τ = 0.18) but favoured there being no important association (5% probability of RR ≥1.1). Former compared with never smokers were at somewhat increased risk of hospitalisation (RR = 1.17, CrI = 1.04-1.36, τ = 0.17), greater disease severity (RR = 1.52, CrI = 1.12-2.06, τ = 0.29) and mortality (RR = 1.39, 95% CrI = 1.16-1.69, τ = 0.23). Data for current smokers on hospitalisation, disease severity and mortality were inconclusive (RR = 1.06, CrI =

0.89-1.27, τ = 0.23; RR = 1.26, CrI = 0.86-1.94, τ = 0.34; RR = 1.05, 95% CrI = 0.71-1.49, τ = 0.45, respectively) but favoured there being no important associations with hospitalisation and mortality (32% and 39% probability of RR ≥1.1, respectively) and a small but important association with disease severity (80% probability of RR ≥1.1).

Conclusions: Compared with never smokers, current smokers appear to be at reduced risk of SARS-CoV-2 infection while former smokers appear to be at increased risk of hospitalisation, greater disease severity and mortality from COVID-19. However, it is uncertain whether these associations are causal.

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Introduction

COVID-19 is a respiratory disease caused by the 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], which could put 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 (and all future) version(s) of this living review is available here (https://www.qeios.com/read/latest-UJR2AW). Version 7 of this living review has been published in a peer-reviewed journal[22]. 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 bodies (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 (i.e. independently checked against pre-prints and published reports) 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) and whether it was biochemically verified; 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; xvi) mortality; xvii) adjustment of smoking specific risk estimates for relevant covariates (e.g. age, sex); and xviii) whether a representative or random sampling method was used.

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[23]. 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 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*[24] 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 review[25], 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, the weighted mean prevalence of current and former smoking was calculated for countries with ≥3 studies and plotted for comparison with national prevalence estimates. It should be noted that prevalence estimates in the included studies were not adjusted for age, sex, socioeconomic position, or geographic region within countries.

Results

In the current review version (v9) with searches up to 27 October 2020, a total of 680 records were identified, with 279 studies included in a narrative synthesis and 42 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 34 countries. Seventy-eight studies were conducted in the US, 57 in China, 31 in the UK, 16 in Spain, 14 in France and Mexico, nine in Italy, eight

across multiple international sites, five in Brazil and Iran, four in Israel, three in Turkey, two in Australia, Bangladesh, Chile, Colombia, Denmark, Finland, Germany, India, Japan, the Netherlands and Qatar and one from 13 further countries (see Supplementary figure S1). The majority of studies used observational designs (see Supplementary table S1). One-hundred-and-seventy-nine studies (64%) were conducted in hospital settings, 77 studies (28%) included a community component in addition to hospitalised patients, 21 studies (8%) were conducted exclusively in the community, with one remaining study conducted in a quarantine centre and one study did not state the study setting. Studies had a median of 432 (interquartile range = 132-1,854) participants. The majority of studies (89%) used reverse transcriptase polymerase chain reaction (RT-PCR) for confirmation of SARS-CoV-2 infection, 5.7% used an antibody test to confirm prior infection and 5.3% of studies relied on a combination of RT-PCR and clinical diagnosis (see Supplementary table S1).

Smoking status

Categorisation of smoking status was heterogeneous (see Table 1). One-hundred-and-seventy studies collected data on smoking status through routine electronic health records (EHRs), 80 studies used a bespoke case report form for COVID-19 and 29 studies did not state the source for information on smoking status. None of the studies verified smoking status biochemically. Notably, only 79 (28%) studies reported current, former and never smoking status (see Supplementary table S2a), with a further 18 studies reporting ever and never smoking status (see Supplementary table S2b). The remaining 182 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). Ninety-four studies explicitly reported the proportion with missing data on smoking status, which ranged from 0% to 96%.

Use of alternative nicotine products

Five studies recorded the use of alternative nicotine products in current and/or former smokers but did not report COVID-19 outcomes stratified by alternative nicotine use[26–30].

Quality appraisal

Two studies were performed in random, representative population samples and were rated as ‘good’ quality, and sixty-one studies were rated as ‘fair’ quality, of which 42 studies reported results stratified by smoking status for the outcomes of interest and could be included in meta-analyses. The remaining 216 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/unknow smokers %
1	Guan, Ni	2020-02-28	China	1,099	Hospital	47 (35-58)	41.9	12.5	1.9	-	84.3	-

60	Guan, Liang	2020-03-26	China	1,590	Hospital	49 (33-64)	42.7	-	-	7.0	93.0	-
61	Lian	2020-03-25	China	788	Hospital	NA	38.5	6.9	-	-	-	-
62	Jin	2020-03-24	China	651	Hospital	46 (32-60)	49.2	6.3	-	-	-	-
63	Chen	2020-03-26	China	548	Hospital	62 (44-70)	37.6	4.4	2.6	-	-	-
64	Zhou, Yu	2020-03-11	China	191	Hospital	56 (46-67)	38.0	5.8	-	-	-	-
65	Mo	2020-03-16	China	155	Hospital	54 (53-66)	44.5	3.9	-	-	-	-
66	Zhang, Dong	2020-02-19	China	140	Hospital	57^ (25-87)	46.3	1.4	5.0	-	-	-
67	Wan	2020-03-21	China	135	Hospital	47 (36-55)	46.7	6.7	-	-	-	-
68	Liu, Tao	2020-02-28	China	78	Hospital	38 (33-57)	50.0	-	-	6.4	-	-
69	Huang, Wang	2020-01-24	China	41	Hospital	49 (41-58)	27.0	7.3	-	-	-	-
70	Zhang, Cai	2020-03-20	China	645	Hospital	NA	49.1	6.4	-	-	-	-
71	Guo	2020-03-27	China	187	Hospital	59 (45-73)	51.3	9.6	-	-	-	-
72	Liu, Ming	2020-03-12	China	41	Hospital	39 (30-48)	58.5	9.8	-	-	-	-
73	Huang, Yang	2020-03-05	China	36	Hospital	69 (60-78)	30.6	-	-	11.1	-	-
74	Xu	2020-03-08	China	53	Hospital	NA	47.2	11.3	-	-	-	-
75	Li	2020-02-12	China	17	Hospital	45 (33-57)	47.1	17.6	-	-	-	-
31	Rentsch	2020-04-14	USA	3,528	Community and Hospital	66 (60-70)	4.6	27.2	30.6	-	36.9	-
76	Hu	2020-03-25	China	323	Hospital	61^ (23-91)	48.6	-	-	11.8	-	-
77	Wang, Pan	2020-03-24	China	125	Hospital	41 (26-66)	43.2	-	-	12.8	-	-
78	Chow (US CDC)	2020-03-31	USA	7,162	Community and Hospital	NA	-	1.3	2.3	-	-	-
79	Dong, Cao	2020-03-20	China	9	Hospital	44 (30-46)	66.7	11.1	-	-	-	-
80	Kim	2020-04-01	South Korea	28	Hospital	43 (30-56)	46.4	17.9	-	-	-	-
81	Shi, Yu	2020-03-18	China	487	Hospital	46 (27-65)	46.8	-	-	8.2	-	-
82	Yang, Yu	2020-02-24	China	52	Hospital	60 (47-73)	37.0	3.8	-	-	-	-
83	Argenziano	2020-05-29	USA	1,000	Hospital	63 (50-75)	40.4	4.9	17.9	-	77.2	-

84	Solis	2020-04-25	Mexico	650	Hospital	46 (NA)	42.1	9.4	-	-	-	-
85	Richardson	2020-04-22	USA	5,700	Hospital	63 (52-75)	39.7	-	-	9.8	52.8	-
86	Fontanet	2020-04-23	France	661	Community and Hospital	37 (16-47)	62.0	10.4	-	-	-	89.6
87	Zheng, Gao	2020-04-19	China	66	Hospital	47^ (NA)	25.8	12.1	-	-	-	-
88	Liao, Feng	2020-04-24	China	1,848	Hospital	55 (48-61)	54.7	-	-	0.4	-	-
89	Gil-Agudo	2020-04-24	Spain	7	Hospital	68 (34-75)	28.6	-	-	42.9	57.1	-
90	Shi, Ren	2020-04-23	China	134	Hospital	46 (34-58)	51.5	-	-	10.4	-	-
91	Hadjadj	2020-04-23	France	50	Hospital	55 (50-63)	22.0	2.0	18.0	-	80.0	-
92	Gold (US CDC)	2020-04-20	USA	305	Hospital	NA	50.5	5.2	-	-	-	-
93	Yu, Cai	2020-04-27	China	95	Hospital	NA	44.2	8.4	-	-	-	-
94	Zheng, Xiong	2020-04-30	China	73	Hospital	43^ (NA)	45.2	-	-	11.0	89.0	-
95	de la Rica	2020-05-11	Spain	48	Hospital	66^ (33-88)	33.0	-	-	20.8	-	-
96	Yin, Yang	2020-05-10	China	106	Hospital	73 (61-85)	39.6	-	-	17.0	-	-
97	Shi, Zuo	2020-05-17	USA	172	Hospital	63^ (44-82)	44.0	-	-	26.2	-	-
98	Cho	2020-05-11	UK	322,341	Community and Hospital	NA	49.2	14.2	21.4	-	64.4	-
99	Allenbach	2020-05-08	France	152	Hospital	77 (60-83)	31.1	-	-	6.6	-	-
100	Robilotti	2020-05-08	USA	423	Hospital	NA	50.0	2.1	37.6	-	58.6	-
101	The Opensafely Collaborative	2020-07-01	UK	17,278,392	Community and Hospital	NA	50.1	17.0	32.9	-	45.9	-
102	Borobia	2020-05-06	Spain	2,226	Hospital	61 (46-78)	52.0	7.1	-	-	-	-
103	Giacomelli	2020-05-06	Italy	233	Hospital	61 (50-72)	31.9	-	-	30.0	70.0	-
104	Shah	2020-05-06	USA	316	Hospital	63 (43-72)	48.1	16.5	17.7	-	42.1	-
105	Kolin	2020-05-05	UK	502,536	Community and Hospital	56.5 (48-64)	54.4	10.5	34.4	-	54.4	-
106	Lubetzky	2020-05-	USA	54	Hospital	57	62.0	-	-	22.2	-	-

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107	Goyal	2020-04-17	USA	393	Hospital	62.2 (49-74)	39.3	5.1	-	-	-	-
108	Feng	2020-04-10	China	476	Hospital	53 (40-64)	43.1	9.2	-	-	-	-
109	Yao	2020-04-24	China	108	Hospital	52 (37-58)	60.2	3.7	-	-	-	-
110	Sami	2020-05-19	Iran	490	Hospital	56.6 (41-71)	39.0	14.1	-	-	-	85.9
111	Almazeedi	2020-05-15	Kuwait	1,096	Hospital	41 (25-57)	19.0	4.0	-	-	-	96.0
112	Carillo-Vega	2020-05-14	Mexico	10,544	Community and Hospital	46.5^ (30-62)	42.3	8.9	-	-	-	-
113	Yanover	2020-05-13	Israel	4,353	Community and Hospital	35 (22-54)	44.5	11.8	3.0	-	85.2	-
114	Hamer	2020-05-13	UK	387,109	Hospital	56.2 (48-64)	55.1	9.7	34.8	-	55.5	-
115	Regina	2020-05-14	Switzerland	200	Hospital	70 (55-81)	40.0	4.5	-	-	-	-
116	de Lusignan	2020-05-15	UK	3,802	Community and Hospital	58 (34-73)	57.6	10.9	46.1	-	29.6	-
117	Targher	2020-05-13	China	339	Hospital	48.4^ (NA)	52.8	8.3	-	-	-	-
118	Valenti	2020-05-18	Italy	789	Community	40.7^ (NA)	35.0	25.9	-	-	-	-
119	Feuth	2020-05-18	Finland	28	Hospital	56 (47-72)	46.0	10.7	28.6	-	60.7	-
120	Ge	2020-05-18	China	51	Hospital	70 (58-79)	27.5	13.7	-	-	-	-
121	Parrotta	2020-05-18	USA	76	Community and Hospital	44.9 (13-71)	61.8	2.6	26.3	-	68.4	-
122	Shekhar	2020-05-18	USA	50	Hospital	55.5 (20-85)	54.0	48.0	-	-	-	-
123	Mejia-Vilet	2020-05-16	Mexico	329	Hospital	49 (41-60)	36.0	-	-	7.0	-	-
124	Chen, Jiang	2020-05-16	China	135	Hospital	NA	42.2	-	-	9.6	-	-
125	Li, Chen	2020-05-16	China	1,008	Hospital	55 (44-65)	43.6	5.7	-	-	-	-
27	Rimland	2020-05-19	USA	11	Hospital	59 (48-65)	18.2	9.1	-	-	-	-
126	Palaiodimos	2020-05-15	USA	200	Hospital	64 (50-73.5)	51.0	-	-	32.5	67.5	-
127	Ip	2020-05-25	USA	2,512	Hospital	64 (52-76)	37.6	3.1	17.8	-	64.5	-

128	Heili-Frades	2020-05-25	Spain	4,712	Hospital	62 (47-77)	50.5	4.9	17.4	-	-	66.5
129	Vaquero-Roncero	2020-05-24	Spain	146	Hospital	66^ (59-72)	32.2	-	-	6.8	-	-
130	Kim, Garg	2020-05-22	USA	2,491	Hospital	62 (50-75)	46.8	6.0	25.8	-	-	68.1
131	Wu	2020-05-21	Italy	174	Hospital	61.2^ (50-71)	30.5	-	-	33.3	-	-
132	Shi, Zhao	2020-05-20	China	101	Hospital	71 (59-80)	40.6	-	-	5.0	-	-
133	Al-Hindawi	2020-05-20	UK	31	Hospital	61 (NA)	12.9	3.2	71.0	-	25.8	-
134	Basse	2020-05-19	France	141	Hospital	62 (52-72)	72.0	17.7	-	-	-	-
135	Freites	2020-05-19	Spain	123	Hospital	59.88^ (44-74)	69.9	3.3	-	-	-	-
136	Alshami	2020-05-19	Saudi Arabia	128	Quarantine Centre	39.6^ (24-55)	53.9	15.6	2.3	-	-	-
137	Berumen	2020-05-26	Mexico	102,875	Hospital	NA	49.1	-	-	9.6	-	90.4
138	Gianfrancesco	2020-05-29	Multiple	600	Community and Hospital	56 (45-67)	71.0	-	-	21.5	64.8	-
139	Li, Long	2020-05-28	China	145	Not Stated	49^ (13-80)	61.0	-	-	5.5	-	-
140	Batty	2020-06-17	UK	908	Hospital	57.27^ (48-66)	44.3	11.2	-	-	-	-
141	Israel	2020-06-01	Israel	24,906	Community and Hospital	40 (27-59)	48.7	16.8	12.7	-	70.5	-
142	del Valle	2020-05-30	USA	1,484	Hospital	62 (52-72)	40.6	5.5	23.3	-	-	-
143	Chaudhry	2020-05-29	USA	40	Community and Hospital	52 (45.5-61)	60.0	-	-	15.0	-	-
144	Louis	2020-05-28	USA	22	Hospital	66.5^ (55-77)	36.4	-	-	45.5	-	-
145	Soto-Mota	2020-06-05	Mexico	400	Hospital	NA	30.0	-	-	12.0	-	-
146	Garibaldi	2020-05-26	USA	832	Hospital	63 (49-75)	47.0	5.5	22.6	-	-	-
147	Docherty	2020-05-22	Multiple	20,133	Hospital	72.9 (58-82)	40.0	4.2	21.7	-	44.5	-
148	Boulware	2020-06-03	Multiple	821	Community	40 (33-50)	51.6	3.3	-	-	-	-
149	Kuderer	2020-05-28	Multiple	928	Community and Hospital	66 (57-76)	50.0	4.6	35.1	-	50.5	-
150	Romao	2020-06-08	Portugal	34	Community	41^ (26-66)	67.7	-	-	26.5	-	-

151	Giannouchos	2020-06-07	Mexico	236,439	Community and Hospital	42.5^ (25-59)	49.1	9.1	-	-	-	90.9
152	Ramlall	2020-06-06	USA	11,116	Community and Hospital	52 (34.7-69.5)	55.2	-	-	26.8	73.2	-
153	Wang, Oekelen	2020-06-05	USA	58	Community and Hospital	67 (NA)	48.0	-	-	36.2	-	-
154	Perrone	2020-06-05	Italy	1,189	Hospital	NA	21.2	-	-	21.9	-	-
155	Sharma	2020-06-05	India	501	Hospital	35.1^ (18-51)	36.0	-	-	4.2	-	-
156	Eugen-Olsen	2020-06-02	Denmark	407	Hospital	64 (47-77)	57.7	20.6	36.9	-	39.6	-
157	Martinez-Portilla	2020-06-02	Mexico	224	Community and Hospital	29 (26-33)	100.0	-	-	3.1	-	-
158	Raisi-Estabragh	2020-06-02	UK	4,510	Hospital	NA	48.8	-	-	51.8	-	-
159	Luo	2020-06-02	China	625	Hospital	46 (NA)	47.7	3.0	-	-	-	-
160	Houlihan	2020-06-09	UK	200	Community	34 (29-44)	61.0	11.0	16.5	-	66.5	-
161	Cen	2020-06-08	China	1,007	Hospital	61 (49-68)	51.0	-	-	8.7	-	-
162	Klang	2020-05-23	USA	3,406	Hospital	NA	61.8	-	-	23.3	-	-
163	Maraschini	2020-06-12	Italy	146	Hospital	32.5^ (27-38)	100.0	-	9.6	-	80.8	-
164	Wang, Zhong	2020-06-12	USA	7,592	Community and Hospital	NA	45.1	3.6	17.1	-	51.9	-
165	McQueenie	2020-06-12	UK	428,199	Community and Hospital	NA	54.9	-	-	44.4	55.0	-
26	Miyara	2020-06-12	France	479	Community and Hospital	NA	44.7	6.7	31.6	-	59.5	-
166	Apea	2020-06-12	UK	1,737	Hospital	63.4^ (NA)	30.4	-	-	10.0	-	-
167	Woolford	2020-06-11	UK	4,510	Community and Hospital	70.5 (NA)	51.2	13.0	38.1	-	48.1	-
168	Hultcrantz	2020-06-11	USA	127	Community and Hospital	68 (41-91)	46.0	-	-	26.8	72.4	-
169	Rajter	2020-06-10	USA	280	Hospital	59.6^ (41-77)	45.5	5.7	10.7	-	74.6	-
170	Lan	2020-06-09	USA	104	Community	49^ (34-63)	47.1	-	-	24.0	-	-
171	Zeng	2020-06-16	China	1,031	Hospital	60.3^ (46-74)	47.8	-	-	10.2	-	-

		16				(40-74)						
172	Suleyman	2020-06-16	USA	463	Hospital	57.5^ (40-74)	55.9	-	-	34.6	-	-
173	Chen, Yu	2020-06-16	China	1,859	Hospital	59 (45-68)	50.0	2.4	3.6	-	94.0	-
174	Garassino	2020-06-12	Multiple	200	Community and Hospital	68 (61.8-75)	30.0	24.0	55.5	-	18.5	-
175	Hernandez-Garduno	2020-06-11	Mexico	32,583	Community and Hospital	45 (34-56)	48.7	-	-	11.0	-	88.8
176	Govind	2020-06-20	UK	6,309	Community and Hospital	46.5^ (31-61)	38.3	66.3	26.8	-	5.5	-
177	Siso-Almirall	2020-06-20	Spain	322	Community and Hospital	56.7^ (38-74)	50.0	-	-	25.2	-	-
178	Gu	2020-06-18	USA	5,698	Community and Hospital	47^ (26-67)	62.0	7.0	24.7	-	50.8	-
179	Kibler	2020-06-16	France	702	Community and Hospital	82^ (75-88)	56.0	3.7	-	-	-	-
180	Ikitimur	2020-06-03	Turkey	81	Hospital	55^ (38-72)	44.0	-	-	28.4	-	-
181	Sierpinski	2020-06-03	Poland	1,942	Community	50 (NA)	60.0	6.3	-	-	-	49.7
182	Zhou, He	2020-06-10	China	238	Hospital	55.5 (35-67)	57.0	2.9	-	-	-	-
183	Crovetto	2020-06-19	Spain	874	Community and Hospital	33.7^ (28-38)	100.0	1.1	-	-	-	13.2
184	Veras	2020-06-09	Brazil	32	Hospital	58.9^ (40-77)	47.0	-	-	25.0	-	-
185	Sterlin	2020-06-11	France	135	Hospital	61 (50-72)	41.0	3.7	38.5	-	57.8	-
186	Rossi	2020-06-09	France	246	Hospital	68^ (53-83)	39.0	-	-	25.2	-	-
187	Duan	2020-06-22	China	616	Hospital	64 (53-70)	57.5	3.7	-	-	-	-
188	Martin-Jimenez	2020-06-09	Spain	339	Hospital	81.6 (72-87)	39.5	-	-	30.7	-	-
189	Elezkurtaj	2020-06-17	Germany	26	Hospital	70 (61.8-78.3)	34.6	-	-	19.2	-	-
190	Lenka	2020-06-22	USA	32	Hospital	62.2^ (51-73)	37.5	-	-	50.0	-	-
191	Olivares	2020-06-16	Chile	21	Hospital	61^ (26-85)	76.2	-	-	9.5	-	-
192	Salton	2020-06-20	Italy	173	Hospital	64.4^ (NA)	34.9	-	-	29.5	-	-
193	Wei	2020-06-	USA	147	Hospital	52^	41.0	14.3	-	-	-	-

	Wei	18	USA	147	Hospital	(34-70)	41.0	14.3	-	-	-	-
194	Zuo, Estes	2020-06-17	China	172	Hospital	61^ (25-95)	44.0	-	-	26.2	-	-
195	Killerby	2020-06-17	USA	531	Community and Hospital	51.6 (38-62)	57.1	-	-	17.1	71.4	-
196	Petrilli	2020-05-22	USA	5,279	Community and Hospital	54 (38-66)	51.5	5.5	17.1	-	61.9	-
197	Magagnoli	2020-06-05	USA	807	Hospital	70 (60-75)	4.3	-	-	15.9	-	-
33	Niedzwiedz	2020-05-29	UK	392,116	Community and Hospital	NA	54.9	9.8	34.8	-	55.4	-
198	Bello-Chavolla	2020-05-31	Mexico	177,133	Community and Hospital	42.6 (26-59)	48.9	-	-	9.3	-	-
199	Zuo, Yalavarthi	2020-04-24	USA	50	Hospital	61 (46-76)	34.0	-	-	36.0	-	-
200	Sigel	2020-06-28	USA	493	Hospital	60 (55-67)	24.1	-	-	28.6	-	-
201	Nguyen	2020-06-29	USA	689	Community and Hospital	55 (40-68)	57.0	-	-	24.8	-	-
202	de Melo	2020-06-29	Brazil	181	Hospital	55.3^ (34-76)	60.8	9.9	12.2	-	38.1	-
203	Auvinen	2020-06-29	Finland	61	Hospital	53 (41-67)	36.0	18.0	27.9	-	54.1	-
204	Souza	2020-06-28	Brazil	8,443	Hospital	NA	53.0	-	-	1.7	-	96.3
205	Mendy	2020-06-27	USA	689	Community and Hospital	49.5 (35.2-67.5)	47.0	-	-	24.7	-	-
206	Pongpirul	2020-06-26	Thailand	193	Hospital	37 (29-53)	41.5	-	-	15.0	66.3	-
207	Jin, Gu	2020-06-25	China	6	Hospital	60.5^ (51-75)	33.3	33.3	-	-	-	-
208	Fisman	2020-06-23	Canada	21,922	Community and Hospital	NA	57.0	-	-	2.3	-	-
209	Madariaga	2020-06-23	USA	103	Community and Hospital	41.8^ (27-55)	48.5	-	-	25.2	74.8	-
210	Senkal	2020-07-07	Turkey	611	Hospital	57^ (18-98)	40.6	11.3	-	-	-	-
211	Mohamud	2020-07-02	USA	6	Hospital	65.8^ (55-78)	16.7	-	-	16.7	-	-
212	Magleby	2020-06-30	USA	678	Hospital	68 (50-81)	38.9	-	-	28.6	-	-
213	Kimmig	2020-07-06	USA	111	Hospital	63^ (48-78)	44.1	7.2	36.0	-	56.8	-
214	Bello-Chavolla,	2020-07-	Mexico	60,121	Community and	45.5^	47.0	-	-	10.5	-	-

	Antonio-Villa	04			Hospital	(29-61)						
215	Zacharioudakis	2020-07-04	USA	314	Hospital	64 (54-72)	34.7	-	-	22.8	-	-
216	Antonio-Villa	2020-07-04	Mexico	34,263	Community and Hospital	40^ (29-50)	62.9	9.7	-	-	-	-
217	Patel	2020-07-03	USA	129	Hospital	60.8^ (47-74)	45.0	37.2	-	-	-	55.8
218	Merzon	2020-07-03	Israel	7,807	Community and Hospital	46.2^ (NA)	58.6	-	-	16.2	-	-
34	Trubiano	2020-07-02	Australia	2,935	Community and Hospital	39 (29-53)	63.5	-	-	8.8	-	-
219	Fan	2020-07-11	UK	1,425	Community and Hospital	NA	46.7	12.2	40.1	-	46.9	-
220	Shi, Resurreccion	2020-07-11	UK	1,521	Community and Hospital	61.5^ (57-66.8)	45.9	-	-	54.9	-	-
221	Maucourant	2020-07-10	Sweden	27	Hospital	57 (18-78)	22.2	11.1	25.9	-	40.7	-
222	Elmunzer	2020-07-09	Multiple	1,992	Hospital	60^ (43-76)	43.0	6.3	28.6	-	59.0	-
223	Alizadehsani	2020-07-09	Iran	319	Hospital	45.48^ (26-63)	55.5	-	-	0.3	-	-
224	Xie	2020-07-07	China	619	Hospital	NA	52.0	-	-	8.2	-	-
42	Merkely	2020-07-17	Hungary	10,474	Community	48.7^ (30-66)	53.6	28.0	20.5	-	51.4	-
225	Fox	2020-07-17	UK	55	Community and Hospital	63 (23-88)	31.0	1.8	10.9	-	56.4	-
66	Zhang, Cao	2020-07-14	China	289	Hospital	57 (22-88)	46.6	3.5	6.2	-	-	-
226	Martinez--Resendez	2020-07-20	Mexico	8	Hospital	57 (48-69)	25.0	-	-	12.5	-	-
227	Hoertel	2020-07-20	France	12,612	Hospital	58.7^ (39-77)	49.6	-	-	9.3	-	-
228	Mcgrail	2020-07-19	USA	209	Hospital	62.5 (NA)	38.8	-	-	18.7	-	-
229	Pandolfi	2020-07-17	Italy	33	Hospital	62 (52-65)	21.1	3.0	24.2	-	72.7	-
28	Girardeau	2020-07-17	France	10	Community	30 (29-33)	50.0	40.0	10.0	-	-	-
230	Kurashima	2020-07-17	Japan	53	Hospital	62.9^ (49-76)	35.8	-	-	50.9	-	-
231	Zhan	2020-07-16	China	75	Hospital	57 (25-75)	48.0	-	-	12.0	-	-
		2020-07-			Community	39						

232	Omrani	2020-07-16	Qatar	1,409	and Hospital	(30-50)	17.2	-	-	9.2	-	-
233	Gupta	2020-07-16	USA	496	Hospital	70 (60-78)	46.0	-	-	7.3	-	31.7
97	Shi, Zuo	2020-07-15	USA	172	Hospital	61.48^ (25-96)	44.0	-	-	26.2	-	-
234	Hussein	2020-07-15	USA	502	Hospital	60.9^ (45-76)	52.0	9.0	22.1	-	-	68.9
235	Bian	2020-07-15	China	28	Hospital	56^ (42-67)	42.9	7.1	-	-	-	-
236	Eiros	2020-07-14	Spain	139	Community and Hospital	52 (41-57)	72.0	4.3	50.4	-	-	-
237	Marcos	2020-07-14	Spain	918	Hospital	72.8^ (58-87)	42.2	6.1	-	15.3	-	-
238	Hoertel, Sanchez-Rico	2020-07-14	France	7,345	Hospital	NA	49.3	8.5	-	-	-	-
239	Soares	2020-07-16	Brazil	10,713	Community and Hospital	NA	55.0	2.0	-	-	-	98.0
240	Zobairy	2020-07-28	Iran	203	Community and Hospital	49.2^ (32-65)	44.8	5.9	-	-	-	94.1
241	Altamimi	2020-07-27	Qatar	68	Hospital	49^ (40-58)	2.0	16.4	-	-	-	83.6
242	Thompson	2020-07-27	UK	470	Hospital	71 (57-82)	46.0	14.0	27.2	-	58.7	-
243	Reiter	2020-07-26	Austria	235	Community	44.2^ (32-55)	70.0	22.6	22.6	-	54.7	-
244	Motta	2020-07-26	USA	374	Hospital	64.7^ (46-82)	41.4	-	-	33.2	66.8	-
245	Santos	2020-07-25	USA	43	Community and Hospital	50 (34-73)	63.0	-	-	4.7	-	-
246	Schneeweiss	2020-07-22	USA	24,313	Community and Hospital	67^ (53-80)	53.0	-	-	2.9	-	-
247	Concha-Mejia	2020-07-24	Colombia	72	Community and Hospital	46 (28-64)	47.0	8.3	11.1	-	-	-
248	Izquierdo	2020-07-24	Spain	71,192	Community and Hospital	42^ (18-66)	59.0	10.0	-	-	-	90.0
249	Bernaola	2020-07-21	Spain	1,645	Hospital	NA	38.5	2.5	10.9	-	86.6	-
30	Islam	2020-08-18	Bangladesh	1,016	Community and Hospital	37 (28-49)	35.9	18.2	-	-	-	-
250	Qi	2020-03-03	China	267	Hospital	48 (35-65)	45.2	19.9	-	-	-	80.1
251	Peters	2020-08-15	Netherlands	1,893	Hospital	66.8^ (52-81)	39.4	4.9	-	-	-	-

252	Ouyang	2020-08-14	China	217	Hospital	46.5^ (30-62)	53.5	16.6	-	-	-	-
57	Ward	2020-08-21	UK	99,908	Community	NA	56.1	10.6	-	-	-	88.4
253	Valenzuela	2020-08-14	Chile	29	Hospital	56.9^ (43-70)	6.9	17.2	-	-	-	82.8
254	Monteiro	2020-08-14	USA	112	Hospital	61 (45-74)	34.0	6.2	17.9	-	68.8	-
255	Philipose	2020-08-14	UK	466	Hospital	67 (6-97)	41.8	6.0	73.2	-	16.5	-
256	Weerahandi	2020-08-14	USA	394	Community	63 (55-70)	37.0	5.3	25.9	-	55.8	-
29	Ebinger	2020-08-04	USA	6,062	Community	41.5^ (29-53)	67.8	1.7	-	-	-	-
257	Altibi	2020-08-11	USA	706	Hospital	66.7^ (51-81)	43.0	4.0	37.3	-	58.8	-
258	Izzi-Engbeaya	2020-08-11	UK	889	Hospital	65.8^ (48-83)	40.0	-	-	21.3	33.2	-
259	Rizzo	2020-08-11	USA	76,819	Hospital	54 (38-67)	55.2	6.7	20.8	-	50.4	-
260	Dashti	2020-08-04	USA	4,140	Community and Hospital	52 (36-65)	55.0	-	-	28.4	51.6	-
261	Morshed	2020-08-02	Bangladesh	103	Community	37 (31-53)	28.2	31.1	-	-	-	68.9
262	Jun	2020-08-01	USA	3,086	Hospital	66 (56-77)	40.9	3.7	21.3	-	52.8	-
263	Higuchi	2020-07-30	Japan	57	Hospital	52 (35-70)	43.9	12.3	29.8	-	57.9	-
264	Zhou, Sun	2020-07-29	China	144	Hospital	47 (38-56)	46.5	9.0	-	-	-	91.0
265	Salerno	2020-08-22	USA	15,920	Hospital	49 (30-65)	57.0	-	-	36.8	55.9	-
266	Kumar	2020-07-29	India	91	Hospital	47^ (41-52)	21.0	44.0	-	-	-	-
267	Hao	2020-06-01	China	788	Hospital	46 (35-56)	48.4	6.9	-	-	-	-
268	Iversen	2020-08-03	Denmark	28,792	Community and Hospital	44.4^ (31-57)	78.9	16.0	6.5	-	76.8	-
269	Hippisley-Cox	2020-07-13	UK	8,275,949	Community and Hospital	48.5^ (30-66)	50.3	17.2	21.4	-	57.3	-
270	Fillmore	2020-08-24	USA	22,914	Community and Hospital	NA	-	37.5	40.7	-	15.5	-
271	Rashid	2020-08-22	UK	517	Hospital	72.8^ (59-86)	31.9	9.9	29.0	-	29.4	-
272	Pan	2020-08-22	USA	12,084	Community and Hospital	45.5^ (27-63)	54.3	-	-	17.5	-	-
					Community							

273	Alkurt	2020-08-20	Turkey	932	and Hospital	34.8^ (25-44)	64.4	24.5	-	-	-	-
274	Zhao, Chen	2020-07-30	USA	641	Hospital	60 (NA)	40.1	21.7	-	-	-	-
275	Holman	2020-08-13	UK	10,989	Community and Hospital	NA	38.8	5.5	42.6	-	49.0	-
276	Qu	2020-07-29	China	246	Hospital	53.6^ (38-68)	53.3	42.3	-	-	-	-
277	Chand	2020-08-19	USA	300	Hospital	58.2^ (45-70)	39.3	22.3	-	-	-	-
278	Oliveira	2020-08-31	USA	131	Hospital	61 (49.5-71.5)	64.9	-	-	17.6	26.7	-
279	Hussein, Galal	2020-09-01	Egypt	444	Community	33.1^ (21-45)	56.8	13.1	9.0	-	77.9	-
280	Vilar-Garcia	2020-09-01	Spain	7,699,568	Community and Hospital	43 (24-59)	50.9	17.1	-	-	-	-
281	Ibarra, Nava	2020-09-01	Mexico	416,546	Community and Hospital	NA	46.9	7.4	-	-	-	-
282	Ibrahim	2020-08-27	USA	38	Hospital	63^ (51-75)	47.0	10.5	-	-	-	-
283	Rubio-Rivas	2020-09-01	Spain	186	Hospital	64.3^ (51-77)	30.6	4.3	20.4	-	75.3	-
284	Mamtani	2020-09-02	USA	403	Hospital	55^ (41-68)	32.3	9.7	12.7	-	68.5	-
285	Ren	2020-09-02	China	432	Hospital	NA	57.9	10.0	-	-	90.0	-
286	Yoo	2020-08-31	USA	4,840	Hospital	66.4 (54.9-77.8)	43.5	4.4	21.4	-	53.3	-
287	Mutambudzi	2020-09-03	UK	120,075	Community and Hospital	NA	54.2	11.7	26.4	-	61.9	-
288	Yan	2020-09-07	China	578	Hospital	49.2^ (35-63)	49.3	9.2	-	-	-	-
289	Mancilla-Galindo	2020-09-08	Mexico	183,779	Community and Hospital	45^ (28-61)	46.0	7.6	-	-	-	-
290	Ullah	2020-09-08	UK	212	Community and Hospital	66.7 (54.2-80.5)	44.8	11.3	48.1	-	37.7	-
260	Dashti	2020-09-13	USA	12,347	Community and Hospital	47 (32-62)	53.3	4.6	15.9	-	57.1	-
291	Nicholson	2020-09-17	USA	1,042	Hospital	64 (53-75)	43.2	8.3	22.2	-	37.1	-
292	Ariza	2020-09-18	Colombia	351	Community and Hospital	30.5 (NA)	54.0	6.8	-	-	-	93.2
43		2020-09-										

	Carrat	18	France	14,628	Community	NA	60.3	12.0	40.8	-	45.6	-
293	Zhu	2020-09-21	China	432	Community and Hospital	49 (35-60)	47.9	14.4	-	-	-	-
294	Sun	2020-08-16	USA	323	Community and Hospital	NA	57.6	-	-	39.3	-	60.7
295	Kalan	2020-05-01	Iran	193	Hospital	52.6^ (37-67)	36.3	7.3	-	-	85.0	-
296	Burrell	2020-09-16	Australia	204	Hospital	63.5 (53-72)	31.4	-	-	13.2	-	82.8
297	Meini	2020-09-23	Italy	461	Hospital	NA	51.2	10.4	25.8	-	63.8	-
298	Favara	2020-09-20	UK	434	Community	40 (19-66)	82.0	8.5	-	-	-	91.5
299	da Silva Neto	2020-09-23	Brazil	91	Community and Hospital	49^ (29-68)	49.4	-	-	19.8	-	80.2
300	Li, Cai	2020-09-28	China	98	Hospital	68.5 (63-75)	58.2	-	-	11.2	-	88.8
301	Wang	2020-09-29	USA	1,078	Hospital	NA	38.2	3.7	24.9	-	49.0	-
302	Lopez-Medrano	2020-09-30	Spain	261	Hospital	NA	43.7	-	-	37.2	-	62.8
303	Incerti	2020-10-02	USA	13,658	Hospital	62 (49-75)	48.1	6.3	22.6	-	45.4	-
304	Collard	2020-10-01	Netherlands	1,604	Hospital	65.7^ (50-80)	39.5	4.9	-	-	-	-
305	Robinson	2020-10-05	USA	3,248	Hospital	51^ (34-68)	72.0	4.0	17.6	-	61.8	-
306	Erber	2020-10-06	Germany	4,554	Community	38.5^ (NA)	70.4	-	-	18.0	-	82.0
307	Chaudhary	2020-10-06	Nepal	220	Hospital	31.5 (25-37)	17.7	11.4	7.7	-	80.0	-
308	Roederer	2020-10-09	France	818	Community	NA	20.4	36.9	8.8	-	53.9	-
309	Savarraj	2020-10-18	USA	48	Hospital	50^ (33-67)	48.0	10.4	-	-	-	-
310	Israel, Schaffer	2020-10-18	Israel	26,959	Hospital	NA	50.6	6.8	15.2	-	77.0	-
311	El-Solh	2020-10-20	USA	7,816	Hospital	69 (60-74)	5.5	-	-	45.3	-	54.7
312	Chudasama	2020-10-23	UK	1,706	Community and Hospital	68 (48-85)	42.5	13.8	41.0	-	45.3	-
313	Salama	2020-10-23	Multiple	377	Hospital	55.9^ (41-70)	40.8	5.8	17.0	-	77.2	-
314	Makaronidis	2020-10-01	UK	567	Community	39.4^ (27-51)	69.1	9.3	-	-	-	90.7
315	Ramachandran	2020-10-12	USA	188	Hospital	NA	-	18.6	-	-	-	-

316	Hadi	2020-08-05	USA	370	Community and Hospital	48.2^ (34-62)	29.5	-	-	15.1	84.9	-
317	Luo, Rizvi	2020-10-03	USA	102	Hospital	68 (61-75)	52.0	-	-	26.5	-	73.5
318	Ioannou	2020-09-23	USA	88,747	Community and Hospital	NA	9.0	20.6	37.5	-	29.3	-
319	ISARIC	2020-10-04	Multiple	88,463	Hospital	72 (NA)	43.0	-	-	5.2	-	37.6
320	Perico	2020-10-22	Italy	423	Community	44.3^ (34-54)	36.4	21.7	18.0	-	60.3	-
321	Lamure	2020-10-12	France	89	Hospital	67 (19-92)	34.0	5.6	32.6	-	48.3	-
322	Yadaw	2020-10-01	USA	5,051	Community and Hospital	NA	-	3.6	15.9	-	51.4	-

Note. – Age not provided for total sample; ^ Denotes mean (SD). * This study was rated as 'poor' quality as the manuscript only presents data for current (but not former) smokers despite having obtained complete smoking status, thus resulting in >20% missing data on smoking status.

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 2a and 2b. Lower than expected current smoking prevalence was generally observed, especially in studies with hospitalised samples. Former smoking prevalence was more similar to expected prevalence when reported; however, prevalence was typically higher than national estimates. National smoking prevalence estimates used for comparison are presented in Supplementary table 3.

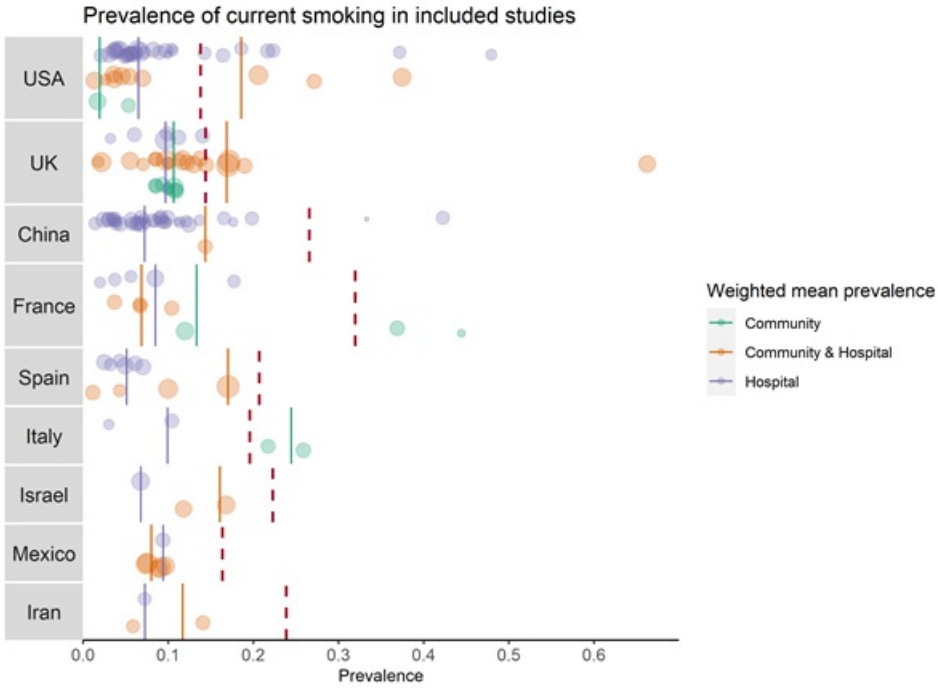

Figure 2a. Weighted mean prevalence of current smoking in included studies, split by country (solid lines). The circles represent individual studies, with colour corresponding to study setting (i.e. community, community and hospital, hospital) and size corresponding to relative study sample size. For comparison, national current smoking prevalence is shown by the dashed red lines. Countries with three or more eligible studies are shown.

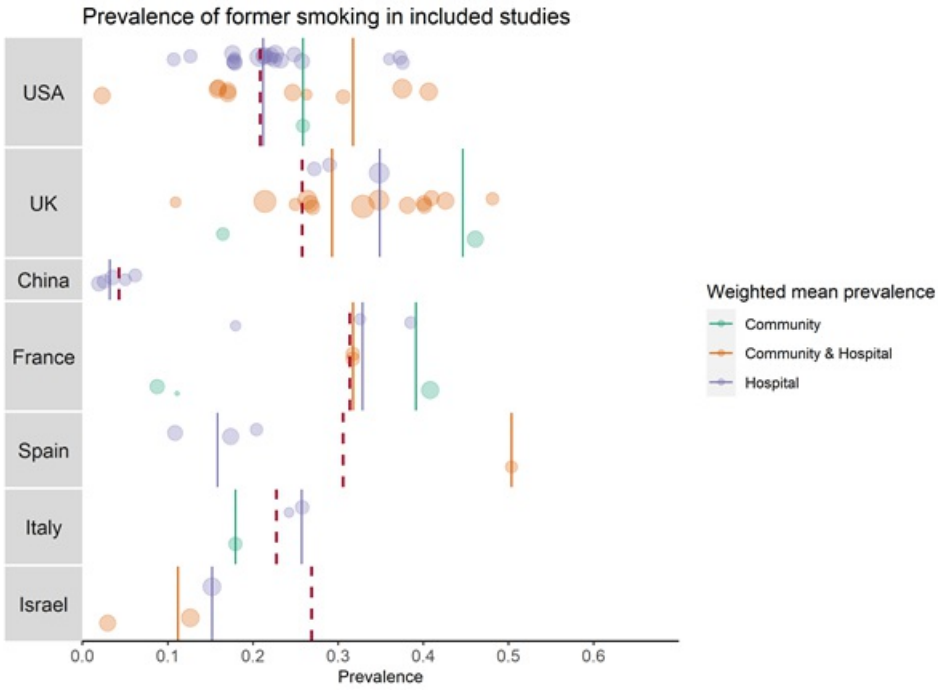

Figure 2b. Prevalence of former smoking in included studies, split by country (solid lines). The circles represent individual studies, with colour corresponding to study setting (i.e. community, community and hospital, hospital) and size corresponding to relative study sample size. For comparison, national former smoking prevalence is shown by dashed red lines. Countries with three or more eligible

studies are shown.

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 54-75[31], 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 2010-2015[32]. In the UK Biobank cohort[33], a multivariable analysis showed 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 to be more likely to receive a test. In an Australian rapid assessment screening clinic for COVID-19[34], 9.4% (397/4,226) of the self-referred sample (subsequently assessed by a healthcare professional to decide on testing) were current smokers. Of these self-referrals, healthcare professionals decided that 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

Fifty-five 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 two 'good' and 19 'fair' quality studies (see Figure 3 and 4). Current smokers were at reduced risk of testing positive for SARS-CoV-2 compared with never smokers (RR = 0.69, 95% CrI = 0.57-0.83, $\tau = 0.38$, 95% CI = 0.25-0.56). The probability of current smokers being at reduced risk of infection compared with never smokers (RR ≤0.9) was 99.6%. Former compared with never smokers were at increased risk of testing positive, but data were inconclusive (RR = 1.02, 95% CrI = 0.93-1.12, $\tau = 0.18$, 95% CI = 0.12-0.26) and favoured there being no important association. The probability of former smokers being at increased risk of infection (RR ≥1.1) compared with never smokers was 5%. Results were materially unchanged in the two sensitivity analyses (see Supplementary figure S2).

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 (%)
Rentsch	3528	2974 (84.30%)	1444 (48.55%)	704 (23.67%)	-	826 (27.77%)	-	554 (15.70%)	159 (28.70%)	179 (32.31%)	-
Fontanet	661	490 (74.13%)	64 (13.06%)	-	-	426 (86.94%)	-	171 (25.87%)	5 (2.92%)	-	-
Cho	1331	793 (59.58%)	142 (17.91%)	214 (26.99%)	-	437 (55.11%)	-	538 (40.42%)	111 (20.63%)	145 (26.95%)	-
Shah	243	212 (87.24%)	52 (24.53%)	47 (22.17%)	-	113 (53.30%)	-	29 (11.93%)	0 (0.00%)	9 (31.03%)	-
		805	141	307		354		669	72	285	

Kolin	1474	(54.61%)	(17.52%)	(38.14%)	-	(43.98%)	3 (0.37%)	(45.39%)	(10.76%)	(42.60%)	-
de Lusignan	3291	2740 (83.26%)	366 (13.36%)	1450 (52.92%)	-	924 (33.72%)	-	551 (16.74%)	47 (8.53%)	303 (54.99%)	-
Valenti	789	689 (87.33%)	197 (28.59%)	-	-	-	492 (71.41%)	40 (5.07%)	7 (17.50%)	-	-
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%)	-
Berumen	102875	71353 (69.36%)	-	-	7173 (10.05%)	64180 (89.95%)	-	31522 (30.64%)	-	-	2748 (8.72%)
Israel	24906	20755 (83.33%)	3783 (18.23%)	2671 (12.87%)	-	14301 (68.90%)	-	41151 (165.23%)	406 (0.99%)	483 (1.17%)	-
del Valle	1108	143 (12.91%)	27 (18.88%)	53 (37.06%)	-	-	63 (44.06%)	965 (87.09%)	55 (5.70%)	293 (30.36%)	-
Romao	34	20 (58.82%)	-	-	5 (25.00%)	-	15 (75.00%)	14 (41.18%)	-	-	4 (28.57%)
Ramlall	11116	4723 (42.49%)	-	-	-	-	-	6393 (57.51%)	-	-	1643.001 (25.70%)
Sharma	501	267 (53.29%)	-	-	1 (0.37%)	-	266 (99.63%)	234 (46.71%)	-	-	20 (8.55%)
Eugen-Olsen	407	290 (71.25%)	76 (26.21%)	104 (35.86%)	-	102 (35.17%)	-	117 (28.75%)	8 (6.84%)	46 (39.32%)	-
Raisi-Estabragh	4510	3184 (70.60%)	-	-	1653 (51.92%)	-	1531 (48.08%)	1326 (29.40%)	-	-	683 (51.51%)
Houlihan	177	97 (54.80%)	14 (14.43%)	14 (14.43%)	-	69 (71.13%)	-	80 (45.20%)	7 (8.75%)	19 (23.75%)	-
McQueenie	428199	424355 (99.10%)	-	-	189299 (44.61%)	235056 (55.39%)	-	1311 (0.31%)	-	-	669 (51.03%)
Woolford	4474	3161 (70.65%)	441 (13.95%)	1194 (37.77%)	-	1526 (48.28%)	-	1313 (29.35%)	145 (11.04%)	525 (39.98%)	-
Lan	104	83 (79.81%)	-	-	24 (28.92%)	-	59 (71.08%)	21 (20.19%)	-	-	1 (4.76%)
Hernandez-Garduno	32583	20279 (62.24%)	-	-	2399 (11.83%)	17861 (88.08%)	-	12304 (37.76%)	-	-	1191 (9.68%)
Govind	6215	6207 (99.87%)	4104 (66.12%)	1669 (26.89%)	-	342 (5.51%)	-	102 (1.64%)	78 (76.47%)	20 (19.61%)	-
Gu	4699	3815 (81.19%)	360 (9.44%)	1142 (29.93%)	-	2313 (60.63%)	-	884 (18.81%)	40 (4.52%)	264 (29.86%)	-
Kibler	702	680 (96.87%)	25 (3.68%)	-	-	-	655 (96.32%)	22 (3.13%)	1 (4.55%)	-	-
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%)	-
Bello-Chavolla	150200	98567 (65.62%)	-	-	9624 (9.76%)	-	88943 (90.24%)	51633 (34.38%)	-	-	4366 (8.46%)
Auvinen	61	33 (54.10%)	10 (30.30%)	8 (24.24%)	-	15 (45.45%)	-	28 (45.90%)	1 (3.57%)	9 (32.14%)	-
Favara	70	55 (78.57%)	5 (9.09%)	-	-	-	50 (90.91%)	15 (21.43%)	2 (13.33%)	-	-
Antonio-Villa	34263	23338 (68.11%)	2293 (9.83%)	-	-	-	21045 (90.17%)	10925 (31.89%)	1023 (9.36%)	-	-
Merzon	7807	7025	-	-	1136 (16.17%)	-	5889	782	-	-	127 (16.24%)

		(89.98%)					(83.83%)	(10.02%)			
Trubiano	2676	2827 (105.64%)	-	-	256 (9.06%)	-	2586 (91.48%)	108 (4.04%)	-	-	3 (2.78%)
Shi, Resurreccion	1521	1265 (83.17%)	-	-	681 (53.83%)	-	584 (46.17%)	256 (16.83%)	-	-	154 (60.16%)
Riley	120620	120461 (99.87%)	2594 (2.15%)	-	-	19914 (16.53%)	97953 (81.32%)	159 (0.13%)	3 (1.89%)	-	-
Alizadehsani	319	196 (61.44%)	-	-	-	-	196 (100.00%)	123 (38.56%)	-	-	1 (0.81%)
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%)	-
Mcgrail	209	118 (56.46%)	-	-	31 (26.27%)	-	87 (73.73%)	91 (43.54%)	-	-	8 (8.79%)
Izquierdo	71192	NA (NA%)	-	-	-	-	-	1006 (1.41%)	111 (11.03%)	-	-
Ward	99908	94416 (94.50%)	10202 (10.81%)	-	-	-	84214 (89.19%)	5492 (5.50%)	433 (7.88%)	-	-
Ebinger	6062	5850 (96.50%)	99 (1.69%)	-	-	-	5668 (96.89%)	212 (3.50%)	3 (1.42%)	-	-
Salerno	15920	14753 (92.67%)	-	-	5517 (37.40%)	8278 (56.11%)	958 (6.49%)	1167 (7.33%)	-	-	339 (29.05%)
Iversen	28792	27629 (95.96%)	4430 (16.03%)	1799 (6.51%)	-	21217 (76.79%)	246 (0.89%)	1163 (4.04%)	177 (15.22%)	78 (6.71%)	-
Hippisley-Cox	8275949	NA (NA%)	-	-	-	-	-	19486 (0.24%)	1354 (6.95%)	5715 (29.33%)	-
Fillmore	22914	21120 (92.17%)	8137 (38.53%)	8416 (39.85%)	-	3227 (15.28%)	1340 (6.34%)	1794 (7.83%)	452 (25.20%)	899 (50.11%)	-
Alkurt	119	NA (NA%)	-	-	-	-	-	119 (100.00%)	14 (11.76%)	-	-
Ariza	351	322 (91.74%)	21 (6.52%)	-	-	-	301 (93.48%)	29 (8.26%)	3 (10.34%)	-	-
Carrat	14393	13426 (93.28%)	1652 (12.30%)	5620 (41.86%)	-	6154 (45.84%)	-	967 (6.72%)	98 (10.13%)	353 (36.50%)	-
Meini	461	243 (52.71%)	39 (16.05%)	66 (27.16%)	-	138 (56.79%)	-	218 (47.29%)	9 (4.13%)	53 (24.31%)	-
Favara	434	354 (81.57%)	28 (7.91%)	-	-	-	326 (92.09%)	80 (18.43%)	9 (11.25%)	-	-
Erber	4554	4446 (97.63%)	-	-	806 (18.13%)	-	3640 (81.87%)	108 (2.37%)	-	-	11 (10.19%)
Roederer	815	390 (47.85%)	175 (44.87%)	32 (8.21%)	-	183 (46.92%)	-	425 (52.15%)	127 (29.88%)	40 (9.41%)	-
Makaronidis	567	127 (22.40%)	16 (12.60%)	-	-	-	111 (87.40%)	440 (77.60%)	37 (8.41%)	-	-
Ioannou	88747	78616 (88.58%)	17138 (21.80%)	29245 (37.20%)	-	22327 (28.40%)	9906 (12.60%)	10131 (11.42%)	1135 (11.20%)	4073 (40.20%)	-
Perico	423	260 (61.47%)	69 (26.54%)	35 (13.46%)	-	156 (60.00%)	-	163 (38.53%)	23 (14.11%)	41 (25.15%)	-

Note. Niedzwiedz et al. reported on SARS-CoV-2 infection by smoking status in multivariable analyses but did not present

raw data.

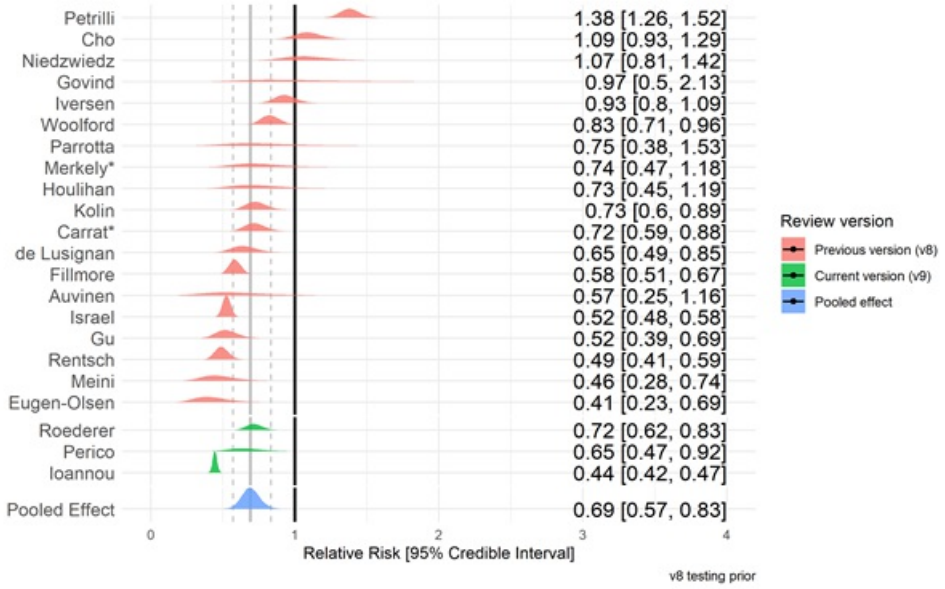

Figure 3. Forest plot for risk of testing positive for SARS-CoV-2 in current vs. never smokers. * Indicates 'good' quality studies. The prior from the previous review version (v8) was RR = 0.72.

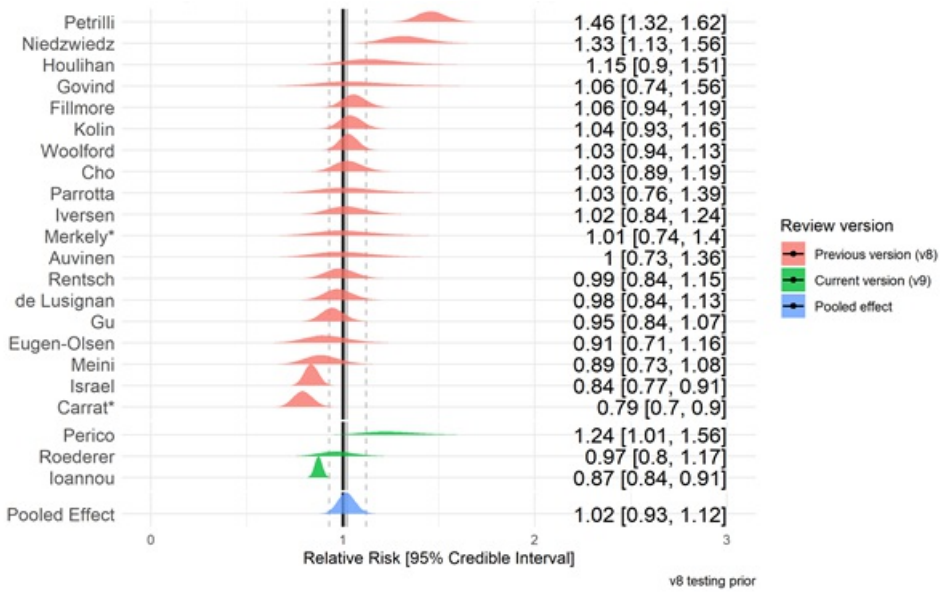

Figure 4. Forest plot for risk of testing positive for SARS-CoV-2 in former vs. never smokers. * Indicates 'good' quality studies. The prior from the previous review version (v8) was RR = 1.02.

Hospitalisation for COVID-19 by smoking status

Thirty-five studies examined hospitalisation for COVID-19 disease, stratified by smoking status (see Table 3). Meta-analyses were performed for ten 'fair' quality studies (see Figure 5 and 6). Current (RR = 1.06, CrI = 0.89-1.27, τ = 0.23, 95% CI = 0.09-0.43) and former (RR = 1.17, CrI = 1.04-1.36, τ = 0.17, 95% CI = 0.08-0.32) compared with never smokers were at increased risk of hospitalisation with COVID-19. However, 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 (RR ≥1.1) compared with never smokers was 32% and 87%, respectively. Results were materially unchanged in two sensitivity analyses (see Supplementary figure S3).

Table 3. Hospitalisation with 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 (%)	Cur smo
Rentsch	554	269 (48%)	69 (25.65%)	90 (33.46%)	-	110 (40.89%)	-	-	285 (51%)	90 (31.58%)	89 (31.23%)	-
Chow (US CDC)	6637	5143 (77%)	61 (1.19%)	80 (1.56%)	-	-	-	5002 (97.26%)	1494 (22%)	27 (1.81%)	78 (5.22%)	-
Argenziano	1000	151 (15%)	14 (9.27%)	18 (11.92%)	-	119 (78.81%)	-	-	849 (84%)	35 (4.12%)	161 (18.96%)	-
Lubetzky	54	15 (27%)	-	-	4 (26.67%)	-	-	11 (73.33%)	39 (72%)	-	-	8 (2
Carillo-Vega	9946	3922 (39%)	408 (10.40%)	-	-	-	-	3514 (89.60%)	6024 (60%)	486 (8.07%)	-	-
Yanover	4353	4180 (96%)	484 (11.58%)	118 (2.82%)	-	3578 (85.60%)	-	-	173 (3%)	30 (17.34%)	11 (6.36%)	-
Hamer	387109	386349 (99%)	37333 (9.66%)	134542 (34.82%)	-	214474 (55.51%)	-	-	760 (0%)	93 (12.24%)	313 (41.18%)	-
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%)	-
Freites	123	69 (56%)	1 (1.45%)	-	-	-	-	68 (98.55%)	54 (43%)	3 (5.56%)	-	-
Berumen	102875	18832 (18%)	-	-	1546 (8.21%)	-	17286 (91.79%)	-	12690 (12%)	-	-	120
Gianfrancesco	600	323 (53%)	-	-	61 (18.89%)	-	-	262 (81.11%)	277 (46%)	-	-	68 (
Chaudhry	40	19 (47%)	-	-	0 (0.00%)	-	-	19 (100.00%)	21 (52%)	-	-	6 (2
Giannouchos	89756	58485 (65%)	4679 (8.00%)	-	-	-	53806 (92.00%)	-	31271 (34%)	2721 (8.70%)	-	-
Wang, Oekelen	57	22 (38%)	-	-	6 (27.27%)	-	-	16 (72.73%)	36 (63%)	-	-	15 (
Miyara	470	132 (28%)	14 (10.61%)	41 (31.06%)	-	77 (58.33%)	-	-	338 (71%)	18 (5.33%)	111 (32.84%)	-
Suleyman	463	108 (23%)	-	-	23 (21.30%)	-	-	85 (78.70%)	355 (76%)	-	-	137
Garassino	196	48 (24%)	10 (20.83%)	27 (56.25%)	-	11 (22.92%)	-	-	152 (77%)	38 (25.00%)	84 (55.26%)	-
Siso-Almirall	260	119 (45%)	-	-	31 (26.05%)	-	-	88 (73.95%)	141 (54%)	-	-	50 (
Gu	884	511 (57%)	30 (5.87%)	126 (24.66%)	-	355 (69.47%)	-	-	373 (42%)	10 (2.68%)	138 (37.00%)	-
Killerby	531	311	-	-	37 (11.90%)	222	-	52	220	-	-	54 (

		(58%)				(71.38%)		(16.72%)	(41%)			
Petrilli	5279	2538 (48%)	147 (5.79%)	337 (13.28%)	-	1678 (66.12%)	-	376 (14.81%)	2741 (51%)	141 (5.14%)	565 (20.61%)	-
Nguyen	689	333 (48%)	-	-	57 (17.12%)	-	-	276 (82.88%)	356 (51%)	-	-	114
Mendy	689	473 (68%)	-	-	84 (17.76%)	-	-	389 (82.24%)	216 (31%)	-	-	86 (
Soares	10713	9561 (89%)	132 (1.38%)	-	-	-	9429 (98.62%)	-	1152 (10%)	77 (6.68%)	-	-
Zobairy	203	65 (32%)	1 (1.54%)	-	-	-	64 (98.46%)	-	138 (67%)	11 (7.97%)	-	-
Izquierdo	1006	743 (73%)	52 (7.00%)	-	-	-	691 (93.00%)	-	263 (26%)	16 (6.08%)	-	-
Rizzo	76819	60039 (78%)	3931 (6.55%)	11379 (18.95%)	-	30042 (50.04%)	-	14687 (24.46%)	16780 (21%)	1254 (7.47%)	4585 (27.32%)	-
Dashti	4140	2759 (66%)	-	-	600 (21.75%)	1541 (55.85%)	-	618 (22.40%)	1381 (33%)	-	-	577
Pan	12084	8548 (70%)	-	-	1263 (14.78%)	-	-	7285 (85.22%)	3536 (29%)	-	-	874
Vilar-Garcia	328892	291254 (88%)	64792 (22.25%)	-	-	-	-	226462 (77.75%)	37638 (11%)	9526 (25.31%)	-	-
Ibarra-Nava	416546	302693 (72%)	26773 (8.84%)	-	-	-	-	275920 (91.16%)	113853 (27%)	8875 (7.80%)	-	-
Dashti	12347	8946 (72%)	353 (3.95%)	1099 (12.28%)	-	5133 (57.38%)	-	2361 (26.39%)	3401 (27%)	210 (6.17%)	860 (25.29%)	-
Da Silva Neto	91	44 (48%)	-	-	4 (9.09%)	-	40 (90.91%)	-	47 (51%)	-	-	14 (
Israel, Schaffer	26676	13706 (51%)	944 (6.89%)	2166 (15.80%)	-	10596 (77.31%)	-	-	12970 (48%)	880 (6.78%)	1936 (14.93%)	-
Ioannou	10131	6624 (65%)	716 (10.81%)	2484 (37.50%)	-	2542 (38.38%)	-	882 (13.32%)	3507 (34%)	419 (11.95%)	1593 (45.42%)	-

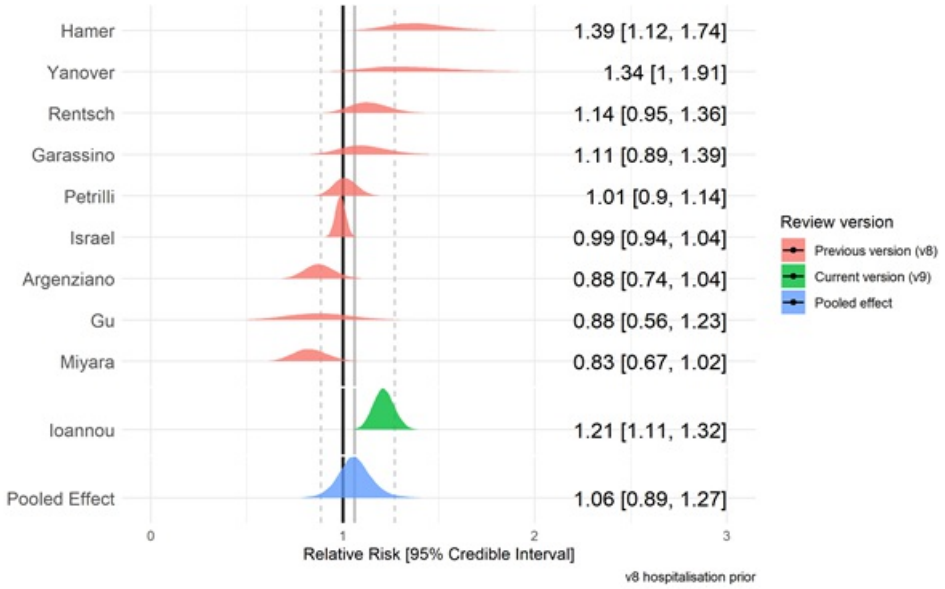

Figure 5. Forest plot for risk of hospitalisation in current vs. never smokers. The prior from the previous review version (v8) was RR = 1.06.

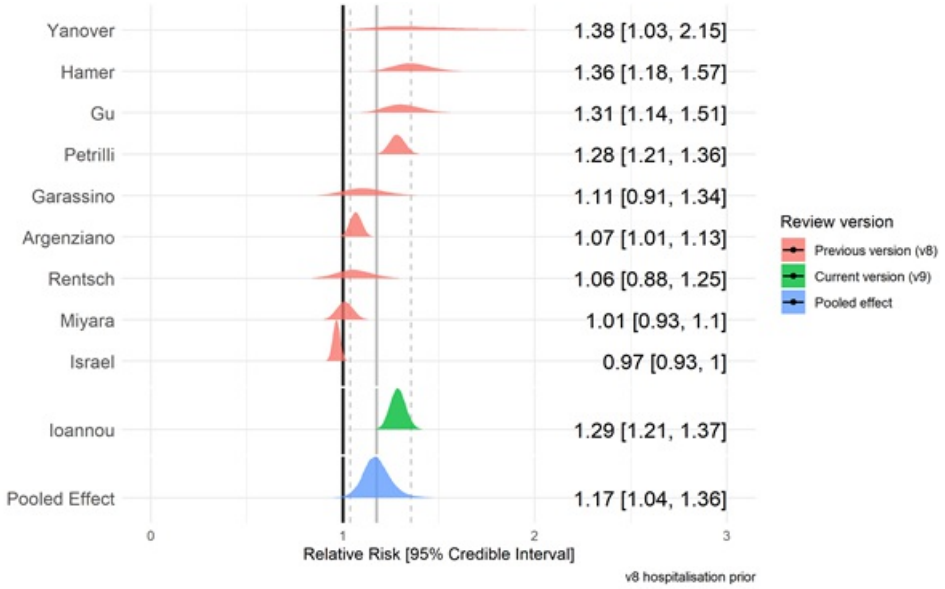

Figure 6. Forest plot for risk of hospitalisation in former vs. never smokers. The prior from the previous version (v8) was RR = 1.19.

Disease severity by smoking status

Sixty-five 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 intensive treatment unit (ITU) admission, requiring oxygen as a hospital inpatient or in-hospital death. Meta-analyses were performed for eight 'fair' quality studies (see Figure 7 and 8). Current (RR = 1.26, CrI = 0.86-1.94, τ = 0.34, 95% CI = 0.01-0.86) and former (RR = 1.52, CrI = 1.12-2.06, τ = 0.29, 95% CI = 0.05-0.65) compared with never smokers were at increased risk of greater disease severity; data for current smokers were inconclusive but favoured there being a small but important association. The probability of current and former smokers having increased risk of greater disease severity (RR ≥1.1) compared with never smokers was 80% and

98%, respectively. Results were materially unchanged in two sensitivity analyses (see Supplementary figure S4).

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 (%)	C sr
Guan, Ni	1085	913 (84%)	108 (11.83%)	12 (1.31%)	-	793 (86.86%)	-	-	172 (15%)	29 (16.86%)	9 (5.23%)	-
Zhang, Dong	9	3 (33%)	0 (0.00%)	3 (100.00%)	-	0 (0.00%)	-	-	6 (66%)	2 (33.33%)	4 (66.67%)	-
Wan	9	8 (88%)	8 (100.00%)	0 (0.00%)	-	0 (0.00%)	-	-	1 (11%)	1 (100.00%)	0 (0.00%)	-
Huang, Wang	3	3 (100%)	3 (100.00%)	0 (0.00%)	-	0 (0.00%)	-	-	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%)	-
Hu	323	151 (46%)	-	-	12 (7.95%)	-	139 (92.05%)	-	172 (53%)	-	-	26
Wang, Pan	125	100 (80%)	-	-	9 (9.00%)	-	91 (91.00%)	-	25 (20%)	-	-	7
Kim	27	21 (77%)	3 (14.29%)	-	-	-	18 (85.71%)	-	6 (22%)	2 (33.33%)	0 (0.00%)	-
Shi, Yu	474	425 (89%)	-	-	34 (8.00%)	-	391 (92.00%)	-	49 (10%)	-	-	6
Liao, Feng	148	92 (62%)	-	-	5 (5.43%)	-	-	87 (94.57%)	56 (37%)	3 (5.36%)	-	-
Shi, Ren	134	88 (65%)	-	-	8 (9.09%)	-	-	80 (90.91%)	46 (34%)	-	-	6
Hadjadj	50	15 (30%)	1 (6.67%)	2 (13.33%)	-	12 (80.00%)	-	-	35 (70%)	0 (0.00%)	7 (20.00%)	-
Zheng, Xiong	73	43 (58%)	-	-	6 (13.95%)	37 (86.05%)	-	-	30 (41%)	-	-	2
de la Rica	48	26 (54%)	-	-	6 (23.08%)	-	-	20 (76.92%)	20 (41%)	-	-	4
Yin, Yang	106	47 (44%)	-	-	6 (12.77%)	-	-	41 (87.23%)	59 (55%)	-	-	12
Allenbach	147	100 (68%)	-	-	9 (9.00%)	-	-	91 (91.00%)	47 (31%)	-	-	0
Goyal	393	263 (66%)	14 (5.32%)	-	-	-	-	249 (94.68%)	130 (33%)	6 (4.62%)	-	-
Feng	454	333 (73%)	27 (8.11%)	-	-	-	-	306 (91.89%)	121 (26%)	17 (14.05%)	-	-
Yao	108	83 (76%)	1 (1.20%)	-	-	-	-	82 (98.80%)	25 (23%)	3 (12.00%)	-	-
Sami	490	400 (81%)	53 (13.25%)	-	-	-	-	347 (86.75%)	90 (18%)	16 (17.78%)	-	-
Regina	200	163 (81%)	9 (5.52%)	-	-	-	-	154 (94.48%)	37 (18%)	0 (0.00%)	-	-

Feuth	28	21 (75%)	1 (4.76%)	7 (33.33%)	-	13 (61.90%)	-	-	7 (25%)	2 (28.57%)	1 (14.29%)	-
Mejia-Vilet	329	214 (65%)	-	-	13 (6.07%)	-	-	201 (93.93%)	115 (34%)	-	-	10
Chen, Jiang	135	54 (40%)	-	-	4 (7.41%)	-	-	50 (92.59%)	81 (60%)	-	-	9
Vaquero-Roncero	146	75 (51%)	-	-	4 (5.33%)	-	-	71 (94.67%)	71 (48%)	-	-	6
Kim, Garg	2490	1692 (67%)	112 (6.62%)	395 (23.35%)	-	-	1185 (70.04%)	-	798 (32%)	38 (4.76%)	247 (30.95%)	-
Wu	174	92 (52%)	-	-	47 (51.09%)	-	45 (48.91%)	-	82 (47%)	11 (13.41%)	-	-
Chaudhry	40	34 (85%)	-	-	5 (14.71%)	-	-	29 (85.29%)	6 (15%)	-	-	1
Garibaldi	832	532 (63%)	25 (4.70%)	107 (20.11%)	-	-	-	400 (75.19%)	300 (36%)	21 (7.00%)	81 (27.00%)	-
Kuderer	928	686 (73%)	35 (5.10%)	210 (30.61%)	-	370 (53.94%)	-	29 (4.23%)	242 (26%)	8 (3.31%)	116 (47.93%)	-
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%)	-	-
Cen	1007	720 (71%)	-	-	70 (9.72%)	-	-	650 (90.28%)	287 (28%)	-	-	18
Maraschini	132	89 (67%)	-	11 (12.36%)	-	78 (87.64%)	-	-	43 (32%)	-	3 (6.98%)	-
Siso-Almirall	260	212 (81%)	-	-	60 (28.30%)	-	-	152 (71.70%)	48 (18%)	-	-	21
Gu	884	511 (57%)	30 (5.87%)	126 (24.66%)	-	355 (69.47%)	-	-	134 (15%)	3 (2.24%)	61 (45.52%)	-
Petrilli	2729	1739 (63%)	97 (5.58%)	325 (18.69%)	-	1067 (61.36%)	-	250 (14.38%)	990 (36%)	44 (4.44%)	236 (23.84%)	-
Mendy	689	598 (86%)	-	-	133 (22.24%)	-	-	465 (77.76%)	91 (13%)	-	-	37
Pongpirul	193	161 (83%)	-	-	25 (15.53%)	106 (65.84%)	-	30 (18.63%)	32 (16%)	-	-	4
Jin, Gu	6	2 (33%)	-	-	0 (0.00%)	-	-	4 (200.00%)	4 (66%)	-	-	2
Senkal	611	446 (73%)	48 (10.76%)	-	-	-	-	398 (89.24%)	165 (27%)	21 (12.73%)	-	-
Patel	129	89 (68%)	26 (29.21%)	-	-	-	58 (65.17%)	5 (5.62%)	40 (31%)	22 (55.00%)	-	-
Maucourant	27	10 (37%)	1 (10.00%)	2 (20.00%)	-	2 (20.00%)	-	5 (50.00%)	17 (62%)	2 (11.76%)	5 (29.41%)	-
Xie	619	469 (75%)	-	-	32 (6.82%)	-	-	437 (93.18%)	150 (24%)	-	-	19
Fox	55	30 (54%)	1 (3.33%)	4 (13.33%)	-	17 (56.67%)	-	8 (26.67%)	25 (45%)	0 (0.00%)	2 (8.00%)	-
Zhang, Cao	240	162 (67%)	2 (1.23%)	6 (3.70%)	-	-	-	154 (95.06%)	78 (32%)	4 (5.13%)	4 (5.13%)	-

Kurashima	53	10 (18%)	-	-	3 (30.00%)	-	-	7 (70.00%)	43 (81%)	-	-	24
Zhan	75	NA (NA%)	-	-	-	-	-	-	75 (100%)	-	-	9
Omrani	858	806 (93%)	-	-	121 (15.01%)	-	-	685 (84.99%)	52 (6%)	-	-	9
Marcos	918	555 (60%)	38 (6.85%)	-	69 (12.43%)	-	-	448 (80.72%)	363 (39%)	18 (4.96%)	-	71
Hoertel, Sanchez-Rico	7345	6014 (81%)	433 (7.20%)	-	-	-	-	5581 (92.80%)	1331 (18%)	190 (14.27%)	-	-
Qi	267	217 (81%)	22 (10.14%)	-	-	-	195 (89.86%)	-	50 (18%)	31 (62.00%)	-	-
Monteiro	112	84 (75%)	3 (3.57%)	14 (16.67%)	-	63 (75.00%)	-	4 (4.76%)	28 (25%)	4 (14.29%)	6 (21.43%)	-
Dashti	1381	619 (44%)	-	-	239 (38.61%)	292 (47.17%)	-	88 (14.22%)	762 (55%)	-	-	33
Morshed	103	87 (84%)	28 (32.18%)	-	-	-	59 (67.82%)	-	16 (15%)	4 (25.00%)	-	-
Zhou, Sun	144	108 (75%)	11 (10.19%)	-	-	-	-	97 (89.81%)	36 (25%)	2 (5.56%)	-	-
Hippisley-Cox	-	NA	-	-	-	-	-	-	1286	56 (4.35%)	427 (33.20%)	-
Zhao, Chen	641	398 (62%)	87 (21.86%)	-	-	-	-	311 (78.14%)	195 (30%)	52 (26.67%)	-	-
Qu	246	226 (91%)	90 (39.82%)	-	-	-	-	136 (60.18%)	20 (8%)	14 (70.00%)	-	-
Ren	432	314 (72%)	26 (8.28%)	-	-	288 (91.72%)	-	-	118 (27%)	17 (14.41%)	-	-
Yan	578	450 (77%)	31 (6.89%)	-	-	-	-	419 (93.11%)	128 (22%)	20 (15.62%)	-	-
Nicholson	1042	550 (52%)	37 (6.73%)	106 (19.27%)	-	211 (38.36%)	-	196 (35.64%)	401 (38%)	41 (10.22%)	92 (22.94%)	-
Zhu	432	285 (65%)	46 (16.14%)	-	-	-	-	239 (83.86%)	147 (34%)	16 (10.88%)	-	-
Kalan	193	122 (63%)	9 (7.38%)	-	-	102 (83.61%)	-	11 (9.02%)	71 (36%)	5 (7.04%)	-	-
Burrell	204	85 (41%)	-	-	7 (8.24%)	-	75 (88.24%)	3 (3.53%)	119 (58%)	-	-	20
Chudasama	1706	NA (NA%)	-	-	-	-	-	-	1706 (100%)	235 (13.77%)	699 (40.97%)	-
Lamure	89	NA (NA%)	-	-	-	-	-	-	25 (28%)	1 (4.00%)	5 (20.00%)	-

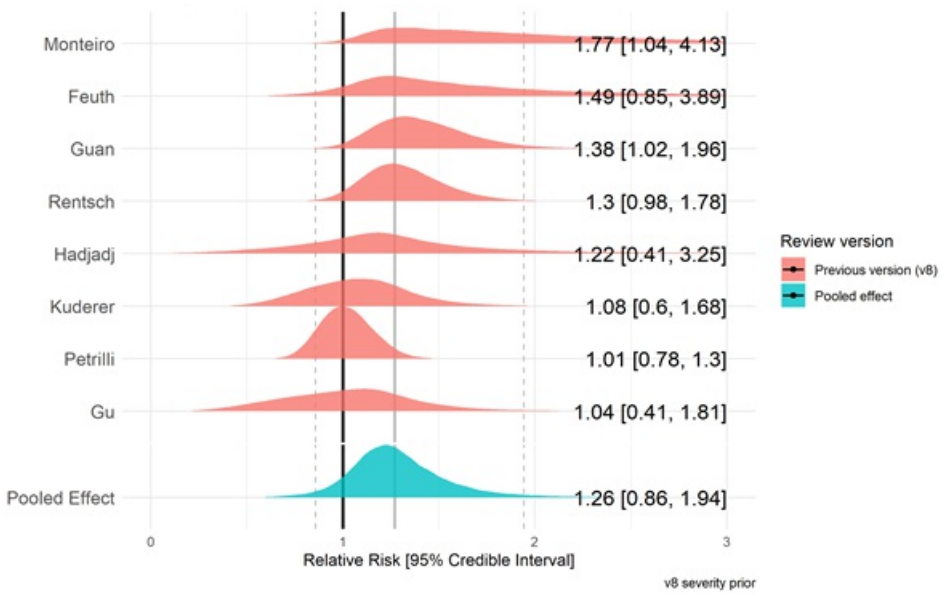

Figure 7. Forest plot for the risk of severe disease in current vs. never smokers. The prior from the previous review version (v8) was RR = 1.25.

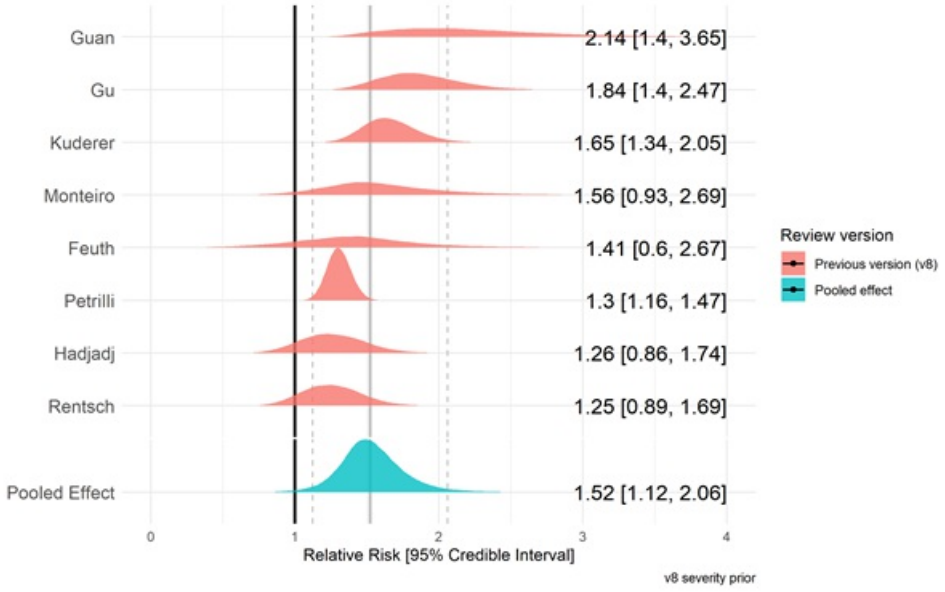

Figure 8. Forest plot for the risk of severe disease in former vs. never smokers. The prior from the previous review version (v8) was RR = 1.52.

Mortality by smoking status

Sixty-two studies reported mortality from COVID-19 by smoking status (see Table 5), with 13 'fair' quality studies included in meta-analyses (see Figure 9 and 10). Current (RR = 1.05, 95% CrI = 0.71-1.49, τ = 0.45, 95% CI = 0.17-0.85) and former (RR = 1.39, 95% CrI = 1.16-1.69, τ = 0.23, 95% CI = 0.05-0.44) compared with never smokers were at increased risk of in-hospital mortality from COVID-19. However, data for current smokers were inconclusive and favoured there being no important association. The probability of current and former smokers being at greater risk of in-hospital mortality (RR ≥1.1) compared with never smokers was 39% and 99%, respectively. Results were materially unchanged in two sensitivity analyses (see Supplementary figure S5).

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 (%)	Curre smok
Chen	274	161 (58%)	5 (3.11%)	5 (3.11%)	-	-	-	151 (93.79%)	113 (41%)	7 (6.19%)	2 (1.77%)	-
Zhou, Yu	191	137 (71%)	6 (4.38%)	-	-	-	-	131 (95.62%)	54 (28%)	5 (9.26%)	-	-
Yang, Yu	52	20 (38%)	2 (10.00%)	-	-	-	18 (90.00%)	-	32 (61%)	-	-	-
Borobia	2226	1766 (79%)	113 (6.40%)	-	-	-	-	1653 (93.60%)	460 (20%)	44 (9.57%)	-	-
Giacomelli	233	185 (79%)	-	-	53 (28.65%)	132 (71.35%)	-	-	48 (20%)	-	-	17 (35
Yao	108	96 (88%)	1 (1.04%)	-	-	-	-	95 (98.96%)	12 (11%)	3 (25.00%)	-	-
Carillo-Vega	9946	8983 (90%)	795 (8.85%)	-	-	-	-	8188 (91.15%)	963 (9%)	99 (10.28%)	-	-
Heng	51	39 (76%)	6 (15.38%)	-	-	-	-	33 (84.62%)	12 (23%)	1 (8.33%)	-	-
Chen, Jiang	135	NA (NA%)	-	-	-	-	-	-	31 (22%)	-	-	4 (12.9
Heili-Frades	4712	4086 (86%)	210 (5.14%)	659 (16.13%)	-	-	3217 (78.73%)	-	626 (13%)	23 (3.67%)	161 (25.72%)	-
Kim, Garg	2490	2070 (83%)	128 (6.18%)	481 (23.24%)	-	-	1461 (70.58%)	-	420 (16%)	22 (5.24%)	161 (38.33%)	-
Al-Hindawi	31	15 (48%)	0 (0.00%)	10 (66.67%)	-	5 (33.33%)	-	-	16 (51%)	1 (6.25%)	12 (75.00%)	-
Louis	22	16 (72%)	-	-	7 (43.75%)	-	-	9 (56.25%)	6 (27%)	-	-	3 (50.0
Soto-Mota	400	200 (50%)	-	-	23 (11.50%)	-	-	177 (88.50%)	200 (50%)	-	-	25 (12
Garibaldi	747	634 (84%)	36 (5.68%)	129 (20.35%)	-	-	-	469 (73.97%)	113 (15%)	6 (5.31%)	36 (31.86%)	-
Docherty	13364	8199 (61%)	370 (4.51%)	1832 (22.34%)	-	4179 (50.97%)	-	1818 (22.17%)	5165 (38%)	214 (4.14%)	1350 (26.14%)	-
Kuderer	928	807 (86%)	38 (4.71%)	262 (32.47%)	-	425 (52.66%)	-	31 (3.84%)	121 (13%)	5 (4.13%)	64 (52.89%)	-
Ramlall	11116	10498 (94%)	-	-	2771 (26.40%)	7727 (73.60%)	-	-	618 (5%)	-	-	208 (3
Wang, Oekelen	57	43 (75%)	-	-	14 (32.56%)	-	-	29 (67.44%)	14 (24%)	-	-	7 (50.0
Martinez-Portilla	224	217 (96%)	-	-	7 (3.23%)	-	-	210 (96.77%)	7 (3%)	-	-	0 (0.0
Cen	1007	964 (95%)	-	-	87 (9.02%)	-	-	877 (90.98%)	43 (4%)	-	-	1 (2.3
Klang	3406	2270	-	-	492 (21.67%)	-	-	1778	1136	-	-	301 (2

		(66%)						(78.33%)	(33%)			
Wang, Zhong	5510	4874 (88%)	247 (5.07%)	1083 (22.22%)	-	3544 (72.71%)	-	-	636 (11%)	28 (4.40%)	214 (33.65%)	-
Miyara	338	211 (62%)	13 (6.16%)	58 (27.49%)	-	141 (66.82%)	-	-	46 (13%)	1 (2.17%)	23 (50.00%)	-
Rajter	255	209 (81%)	-	-	28 (13.40%)	181 (86.60%)	-	-	53 (20%)	-	-	18 (33
Zeng	1031	866 (84%)	-	-	69 (7.97%)	-	-	797 (92.03%)	165 (16%)	-	-	36 (21
Chen, Yu	1859	1651 (88%)	32 (1.94%)	54 (3.27%)	-	1565 (94.79%)	-	-	208 (11%)	13 (6.25%)	12 (5.77%)	-
Garassino	190	124 (65%)	-	-	92 (74.19%)	32 (25.81%)	-	-	66 (34%)	-	61 (92.42%)	-
Gu	884	864 (97%)	40 (4.63%)	250 (28.94%)	-	219 (25.35%)	-	-	20 (2%)	0 (0.00%)	14 (70.00%)	-
Sigel	88	70 (79%)	-	-	37 (52.86%)	-	-	33 (47.14%)	18 (20%)	-	-	11 (61
Nguyen	356	308 (86%)	-	-	91 (29.55%)	-	-	217 (70.45%)	45 (12%)	-	-	23 (51
de Souza	8443	7826 (92%)	-	-	95 (1.21%)	-	7571 (96.74%)	160 (2.04%)	617 (7%)	-	-	47 (7.6
Mendy	532	663 (124%)	-	-	160 (24.13%)	-	-	502 (75.72%)	26 (4%)	-	-	10 (38
Shi, Resurreccion	256	210 (82%)	-	-	128 (60.95%)	-	-	82 (39.05%)	46 (17%)	-	-	26 (56
Xie	619	591 (95%)	-	-	43 (7.28%)	-	-	548 (92.72%)	28 (4%)	-	-	8 (28.5
Fox	54	35 (64%)	1 (2.86%)	4 (11.43%)	-	18 (51.43%)	-	12 (34.29%)	19 (35%)	0 (0.00%)	2 (10.53%)	-
Zhang, Cao	289	240 (83%)	10 (4.17%)	6 (2.50%)	-	-	-	224 (93.33%)	49 (16%)	4 (8.16%)	8 (16.33%)	-
Gupta	496	255 (51%)	-	-	15 (5.88%)	-	80 (31.37%)	160 (62.75%)	241 (48%)	-	-	21 (8.7
Soares	1075	696 (64%)	38 (5.46%)	-	-	-	658 (94.54%)	-	456 (42%)	39 (8.55%)	-	-
Thompson	470	301 (64%)	39 (12.96%)	79 (26.25%)	-	183 (60.80%)	-	-	169 (35%)	27 (15.98%)	49 (28.99%)	-
Bernaola	1645	1382 (84%)	35 (2.53%)	146 (10.56%)	-	1201 (86.90%)	-	-	263 (15%)	6 (2.28%)	33 (12.55%)	-
Islam	654	631 (96%)	103 (16.32%)	-	-	-	-	507 (80.35%)	23 (3%)	3 (13.04%)	-	-
Philipose	466	267 (57%)	19 (7.12%)	204 (76.40%)	-	44 (16.48%)	-	-	199 (42%)	9 (4.52%)	137 (68.84%)	-
Dashti	4140	3953 (95%)	-	-	1068 (27.02%)	2078 (52.57%)	-	804 (20.34%)	187 (4%)	-	-	109 (5
Fillmore	1794	1566 (87%)	408 (26.05%)	758 (48.40%)	-	279 (17.82%)	-	98 (6.26%)	228 (12%)	44 (19.30%)	141 (61.84%)	-
Pan	3536	3302 (93%)	-	-	862 (26.11%)	-	-	2440 (73.89%)	234 (6%)	-	-	82 (35
Zhao, Chen	474	398 (83%)	87 (21.86%)	-	-	-	-	311 (78.14%)	82 (17%)	36 (43.90%)	-	-

Holman	10989	NA (NA%)	-	-	-	-	-	-	10989 (100%)	609 (5.54%)	4684 (42.62%)	-
Chand	300	143 (47%)	23 (16.08%)	-	-	-	-	120 (83.92%)	157 (52%)	44 (28.03%)	-	-
Oliveira	131	105 (80%)	-	-	16 (15.24%)	-	83 (79.05%)	6 (5.71%)	26 (19%)	-	-	7 (26.9
Vilar-Garcia	328892	316605 (96%)	71215 (22.49%)	-	-	-	-	245390 (77.51%)	12287 (3%)	3103 (25.25%)	-	-
Ibarra-Nava	416546	370038 (88%)	27001 (7.30%)	-	-	-	-	343037 (92.70%)	46508 (11%)	3817 (8.21%)	-	-
Rubio-Rivas	186	147 (79%)	7 (4.76%)	32 (21.77%)	-	108 (73.47%)	-	-	39 (20%)	1 (2.56%)	6 (15.38%)	-
Ren	432	289 (66%)	25 (8.65%)	-	-	264 (91.35%)	-	-	143 (33%)	18 (12.59%)	-	125 (8
Ullah	212	158 (74%)	22 (13.92%)	67 (42.41%)	-	63 (39.87%)	-	6 (3.80%)	54 (25%)	2 (3.70%)	35 (64.81%)	-
Dashti	3401	2892 (85%)	190 (6.57%)	689 (23.82%)	-	1756 (60.72%)	-	257 (8.89%)	509 (14%)	20 (3.93%)	171 (33.60%)	-
Nicholson	1040	829 (79%)	70 (8.44%)	163 (19.66%)	-	320 (38.60%)	-	276 (33.29%)	211 (20%)	16 (7.58%)	68 (32.23%)	-
Kalan	193	188 (97%)	14 (7.45%)	-	-	162 (86.17%)	-	12 (6.38%)	5 (2%)	0 (0.00%)	-	-
Incerti	13658	11495 (84%)	785 (6.83%)	2450 (21.31%)	-	5450 (47.41%)	2810 (24.45%)	-	2163 (15%)	81 (3.74%)	642 (29.68%)	-
Ioannou	10131	9033 (89%)	1054 (11.67%)	3549 (39.29%)	-	3339 (36.96%)	-	1091 (12.08%)	1098 (10%)	81 (7.38%)	528 (48.09%)	-
Lamure	89	59 (66%)	4 (6.78%)	16 (27.12%)	-	31 (52.54%)	-	8 (13.56%)	30 (33%)	1 (3.33%)	13 (43.33%)	-
Yadaw	5051	4635 (91%)	162 (3.50%)	709 (15.30%)	-	2394 (51.65%)	-	1370 (29.56%)	416 (8%)	17 (4.09%)	105 (25.24%)	-

Note. Solis et al. and the OpenSAFELY Collaborative reported on mortality by smoking status in a multivariable analysis but did not present raw data for both the exposure and outcome variables.

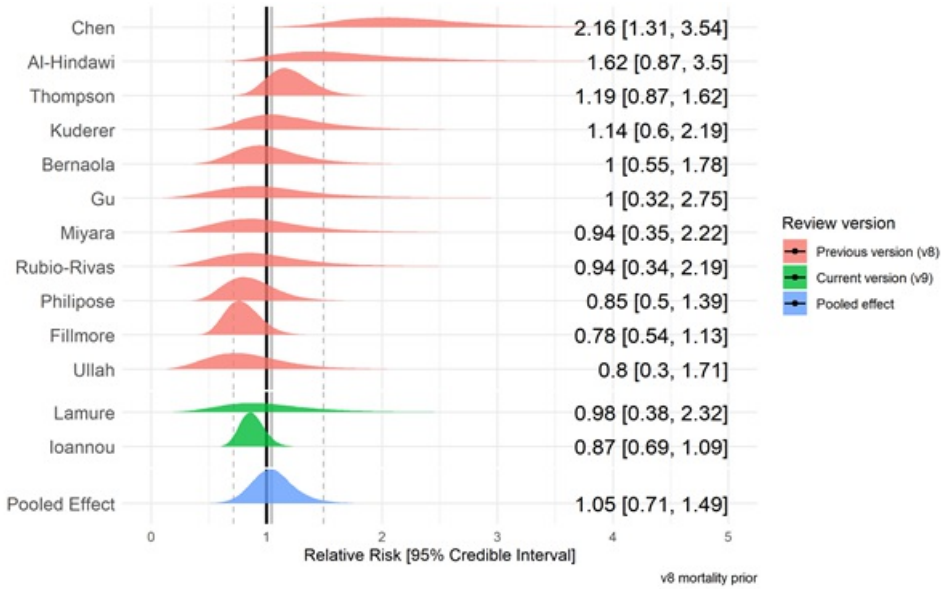

Figure 9. Forest plot for the risk of mortality in current vs. never smokers. The prior from the previous review version (v8) was RR = 1.1.

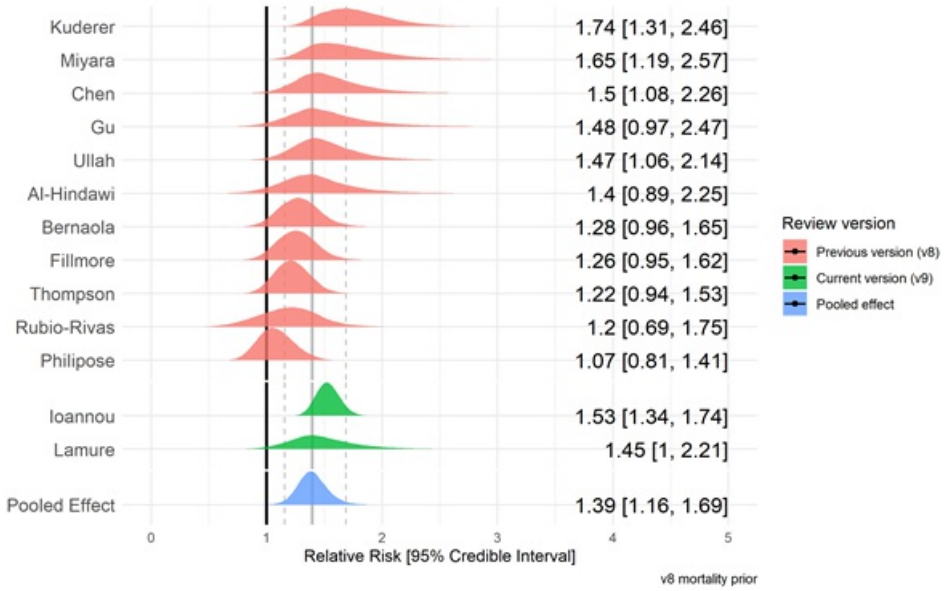

Figure 10. Forest plot for the risk of mortality in former smokers vs. never smokers. The prior from the previous version (v8) was RR = 1.35.

Discussion

This living rapid review found uncertainty in the majority of 279 studies arising from the recording of smoking status. Notwithstanding these uncertainties, compared with overall adult national prevalence estimates, recorded current smoking rates in most studies were lower than expected. In a subset of better-quality studies (n = 21), current but not former smokers had a reduced risk of testing positive for SARS-CoV-2 but current smokers appeared somewhat more likely to present for testing and/or receive a test. Data for current smokers on the risk of hospitalisation, disease severity and mortality were inconclusive, and favoured there being no important associations with hospitalisation and mortality and a small but

important increase in the risk of severe disease. 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 11):

1) Exposure to SARS-CoV-2

i. Exposure to the SARS-CoV-2 virus is heterogeneous with different subgroups at heightened risk of infection at different stages of the pandemic, at least partly due to differential contact matrices by age, sex and socioeconomic position[35], which are associated with smoking status.

ii. The probability of viral exposure depends largely on local prevalence, which varies over time. This likely introduces bias in studies assessing the rate of infection by smoking status conducted in the early phase of the pandemic.

2) Infection with SARS-CoV-2

i. Infection following viral exposure depends on individual differences in, for example, genetic susceptibility or immunocompetence, which are poorly understood at present. For example, the household secondary attack rate for COVID-19 is estimated at 17%[36].

ii. Heated and humidified air may act to disrupt the ability of the virus to persist in the airway mucosa of smokers. There is some evidence that transient localised hyperthermia can inhibit replication of rhinoviruses, a non-enveloped virus that causes the common cold[37]. However, as SARS-CoV-2 is an enveloped virus[38], it is unclear whether a similar protective effect against viral replication or invasion by heated and humidified air may occur.

3) Symptomatic COVID-19

i. An estimated 20% (95% CI = 17-25%) of COVID-19 cases are asymptomatic[39], with some evidence suggesting younger people are more likely to be asymptomatic[40]. Testing is hence likely limited in some subgroups, with the potential for these groups to include an overrepresentation of current smokers.

ii. 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[41]. 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 are more informative. We identified one population study conducted in Hungary reporting on seroprevalence and smoking status[42]; however, the response rate was only 58.8% and the current smoking rate was 10 percentage points below national prevalence estimates, which raises some doubt about representativeness of the final sample. Similarly, a second representative population survey with results from three regions in France[43] reported a current smoking rate of more than 10 percentage points below national

prevalence (12% vs. 25% daily smoking prevalence)[44].

4) Testing positive for SARS-CoV-2

i. 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[48].

ii. Diagnostic criteria for SARS-CoV-2 infection and COVID-19 have changed during the course of the pandemic[49]. It was not possible to extract details on the specific RT-PCR or antibody-based techniques or platforms used across the included studies due to reporting gaps. Different platforms have varying sensitivity and specificity to detect SARS-CoV-2 infection. In addition, testing for acute infection requires swabbing of the mucosal epithelium, which may be disrupted in current smokers, potentially altering the sensitivity of assays[47].

5) Hospitalisation with COVID-19

i. 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[52], 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)[53].

ii. The majority of included studies relied on EHRs as the source of information on smoking status. Research shows large discrepancies between EHRs and actual behaviour[50]. Known failings of EHRs include implausible longitudinal changes, such as former smokers being recorded as never smokers at subsequent hospital visits[50]. Misreporting on the part of the patient (perhaps due to perceived stigma) has also been observed, with biochemical measures showing higher rates of smoking compared with self-report in hospitalised patients in the US[51]. It is hence possible that under-reporting of current and former smoking status in hospitals occurred across the included studies.

iii. The majority of included studies were conducted in hospital settings. It is plausible that a non-trivial proportion of patients were infected with SARS-CoV-2 while being an inpatient for a different medical reason. If so, this may have biased the hospitalised populations towards older and more frail groups, who are less likely to be smokers[54].

iv. 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).

6) COVID-19 disease severity and death

i. 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. Adding to this, COVID-19 related mortality has been differentially defined across countries and epidemic phases. For example, in some UK reporting, death within 28 days of a COVID-19 diagnosis is required for attributing the cause of death to the virus. However, according to the UK Office for National

Statistics, COVID-19 deaths are recorded only if this was stated on the death certificate.

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

iii. 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.

iv. COVID-19 outcomes are currently limited to in-hospital death or survival to discharge. This binary outcome does not capture potential long-term morbidity attributed to COVID-19, such as stroke, amputation or acute cardiac events, which may be moderated by smoking status.

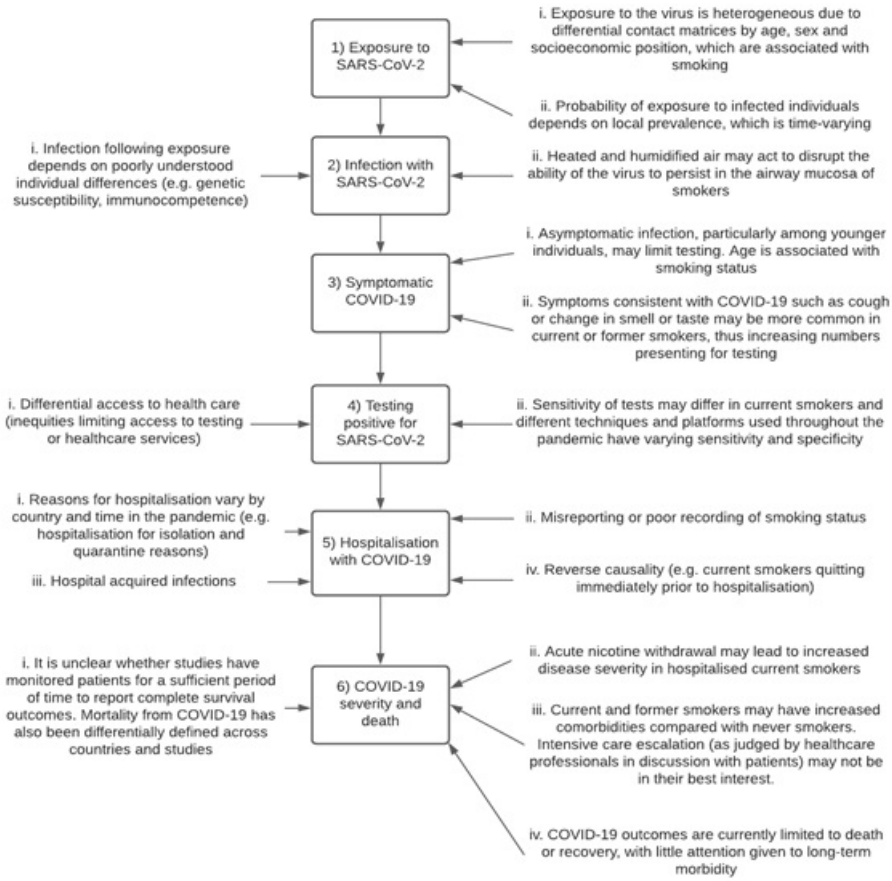

Figure 11. A schematic of some of the interpretation issues for the association of smoking status and COVID-19 infection, hospitalisation, disease severity and mortality. Numbers refer to the issues listed in the above section. Issues on the right-hand side relate explicitly to smoking status.

Limitations

This living rapid evidence review was limited by having a single reviewer extracting data with a second independently verifying the data extracted to minimise 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 or confirmed SARS-CoV-2 infection (which means they do not meet our eligibility criteria)[41,55,56]. We also did not include a large, UK-based, representative seroprevalence study[57] in our meta-analyses as the odds of testing positive in former smokers was not reported. However, the odds of infection for current smokers (OR = 0.64, 95% CI = 0.58-0.71) was in concordance with the pooled estimate in our meta-analysis. Population surveys – particularly with linked data on confirmed infection or antibodies – 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[58] 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[59]. 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 279 studies, recorded current but not past 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.

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Future review versions

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Previous review versions

Version 1: https://doi.org/10.32388/UJR2AW

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Version 4: https://doi.org/10.32388/UJR2AW.5

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Version 6: https://doi.org/10.32388/UJR2AW.7

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Data availability

All data contributing to the current and future review versions are available here: https://doi.org/10.6084/m9.figshare.12756020

All code required to reproduce the current and future analyses are available here: https://doi.org/10.5281/zenodo.4002046

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