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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 11)

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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: v11 (searches up to 2021-02-16) included 405 studies with 62 'good' and 'fair' quality studies included in unadjusted meta-analyses. 121 studies (29.9%) 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 = 0.71, 95% Credible Interval (CrI) = 0.61-0.82, τ = 0.34). Data for former smokers were inconclusive (RR = 1.03, 95% CrI = 0.95-1.11, τ = 0.17) but favoured there being no important association (4% probability of RR ≥1.1). Former compared with never smokers were at increased risk of hospitalisation (RR = 1.19, CrI = 1.1-1.29, τ = 0.13), greater disease severity (RR = 1.8, CrI = 1.27-2.55, τ = 0.46) and mortality (RR = 1.56, CrI = 1.23-2, τ = 0.43). Data for current smokers on hospitalisation, disease severity and mortality were inconclusive (RR = 1.1, 95% CrI = 0.99-1.21, τ = 0.15; RR 1.26,

95% CrI = 0.92-1.73, τ = 0.32; RR = 1.12, 95% CrI = 0.84-1.47, τ = 0.42, respectively) but favoured there being no important associations with hospitalisation and mortality (49% and 56% probability of RR ≥1.1, respectively) and a small but important association with disease severity (83% 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.

v7 of this living review article has been published in *Addiction*

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 (Guan, Ni, et al., 2020); however, these differences are currently unexplained. SARS-CoV-2 enters epithelial cells through the angiotensin-converting enzyme 2 (ACE-2) receptor (Hoffmann et al., 2020). Some evidence suggests that gene expression and subsequent receptor levels are elevated in the airway and oral epithelium of current smokers (Brake et al., 2020; Cai, 2020), which could put smokers at higher risk of contracting SARS-CoV-2. Other studies, however, suggest that nicotine downregulates the ACE-2 receptor (Oakes et al., 2018). These uncertainties notwithstanding, both former and current smoking is known to increase the risk of respiratory viral (Abadom et al., 2016; Denholm et al., 2010) and bacterial (Almirall et al., 1999; Feldman and Anderson, 2013) 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 (Dye and Adler, 1994). 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 (Vardavas and Nikitara, 2020). 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 (Farsalinos, Niaura, et al., 2020).

There are several reviews that fall within the scope of smoking and COVID-19 (Alqahtani et al., 2020; Berlin et al., 2020; Emami et al., 2020; Farsalinos, Barbouni, et al., 2020; Grundy et al., 2020; Patanavanich and Glantz, 2020; Vardavas and Nikitara, 2020). 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 (Elliott et al., 2014). 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 (Tricco et al., 2015). This study was not pre-registered but evolved from a report written for a UK medical society (Simons, Brown, et al., 2020). The most recent version of this living review is available here. Version 7 of this living review has been published in a peer-reviewed journal (Simons, Shahab, et al., 2020). 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; 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;
4. Were available in English;
5. 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 (R Team, 2013). 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 (Bürkner, 2018) 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, 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 (v11) with searches up to 2021-02-16, a total of 1133 records were identified, with 405 studies included in a narrative synthesis and 62 studies included in meta-analyses (see Figure 1).

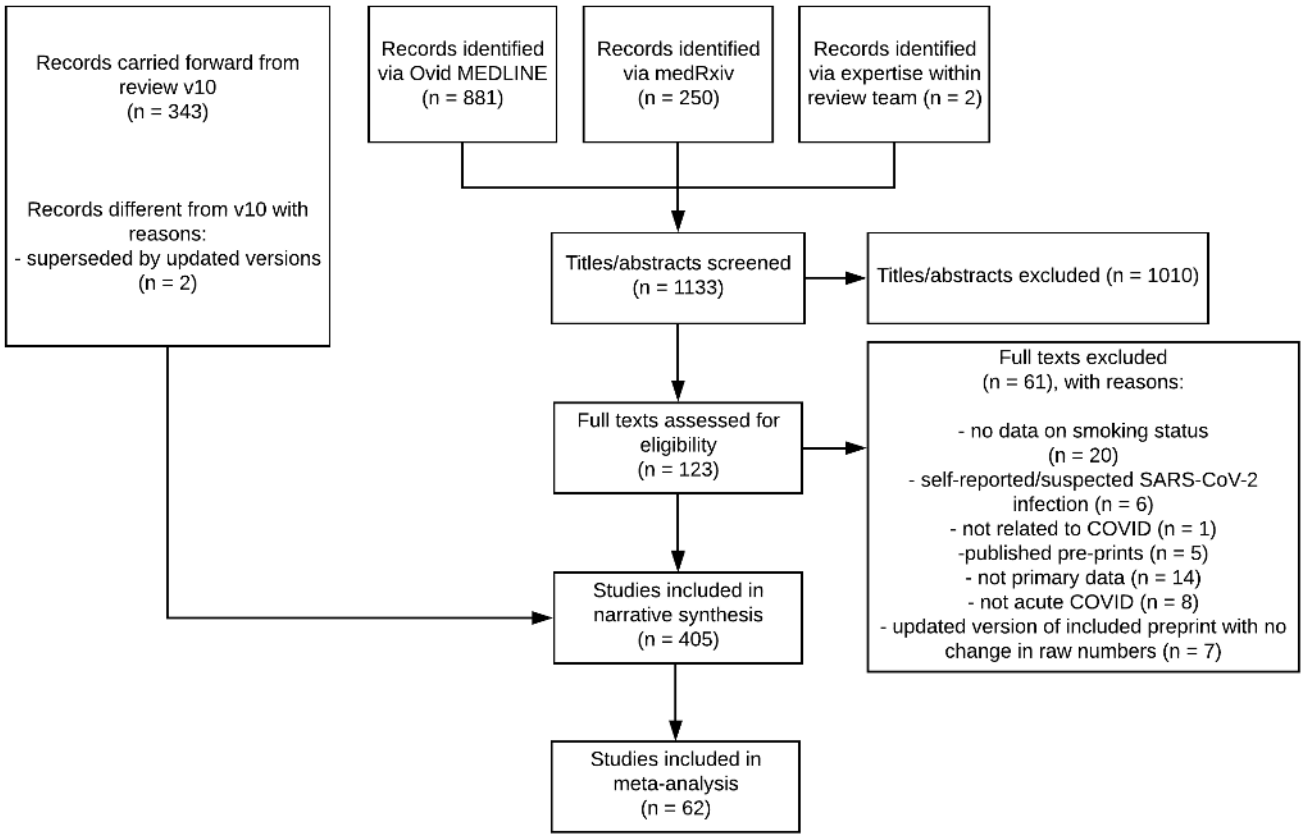

Figure 1. PRISMA flow diagram of included studies.

Characteristics of included studies are presented in Table 1. Studies were conducted across 41 countries. 109 studies were conducted in the USA, 70 in China, 44 in the UK, 28 in Spain, 20 in France, 18 in Mexico, 16 in Italy, 13 in Multiple, 8 in Turkey, 7 in Brazil and Iran, 5 in Israel and Switzerland, 4 in Finland and India, with 3 each from Australia, Austria, Japan, Saudi Arabia, and South Korea and a single study from 10 further countries. The majority of studies used observational designs (see Supplementary table S1). 256 (63.2%) were conducted in hospital settings, 106 studies (26.2%) included individuals from community and hospital settings, 40 studies (9.9%) were conducted exclusively in the community, with one study each conducted in a homeless shelter and a quarantine centre, and one study that did not state the study setting. Studies had a median of 502 (interquartile range = 146-2038) participants. The majority of studies (87.8%) used reverse transcriptase polymerase chain reaction (RT-PCR) for confirmation of SARS-CoV-2 infection, 12.2% used an antibody test to confirm prior infection and 6.8% of studies relied on a combination of RT-PCR or antibody assays.

Smoking status

Categorisation of smoking status was heterogeneous (see Table 1). 236 studies collected data on smoking status through routine electronic health records (EHRs), 129 studies used a bespoke case report form for COVID-19 and 40 studies did not state the source for information on smoking status. None of the studies verified smoking status biochemically. Notably,

only 121 (29.9%) studies reported current, former and never smoking status (see Supplementary table S2a), with a further 26 studies reporting only ever and never smoking status (see Supplementary table S2b). The remaining 252 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). 133 studies explicitly reported the proportion with missing data on smoking status, which ranged from 0% to 97.6%.

Use of alternative nicotine products

Eight 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 (Crooks et al., 2020; Ebinger et al., 2020; Gallichotte et al., 2020; Girardeau et al., 2020; Islam et al., 2020; Kantele et al., 2020; Miyara et al., 2020; Rimland et al., 2020). One additional study grouped together current smokers and vapers (Schubl et al., 2020).

Quality appraisal

Three studies were performed in random or representative population samples and were rated as ‘good’ quality, and 94 studies were rated as ‘fair’ quality, of which 62 studies reported results stratified by smoking status for the outcomes of interest and could be included in meta-analyses. The remaining 308 studies were rated as ‘poor’ quality (see Table 1).

Table 1. **All studies included in narrative review and meta-analysis**

ref	Lead author	Date published	Country	Sample size	Study setting	Median (IQR)	Female %	Current smoker %	Former smokers %	Current/former smokers %	Ne sm %
Huang et al. (2020)	Huang, Wang	2020-01-24	China	41	Hospital	49 (41-58)	27.0	7.3	-	-	-
Li et al. (2020)	Li	2020-02-12	China	17	Hospital	45 (33-57)	47.1	17.6	-	-	-
Zhang et al. (2020)	Zhang, Dong	2020-02-19	China	140	Hospital	57^ (25-87)	46.3	1.4	5.00	-	-
Yang et al. (2020)	Yang, Yu	2020-02-24	China	52	Hospital	60 (47-73)	37.0	3.8	-	-	-
Guan et al. (2020)	Guan, Ni	2020-02-28	China	1,099	Hospital	47 (35-58)	41.9	12.5	1.91	-	84.
Liu et al. (2020)	Liu, Tao	2020-02-28	China	78	Hospital	38 (33-57)	50.0	-	-	6.41	-
Qi et al. (2020)	Qi	2020-03-03	China	267	Hospital	48 (35-65)	45.2	19.9	-	-	-
Huang et al. (2020)	Huang, Yang	2020-03-05	China	36	Hospital	69 (60-78)	30.6	-	-	11.11	-
Xu et al. (2020)	Xu	2020-03-08	China	53	Hospital	NA	47.2	11.3	-	-	-
Zhou et al. (2020)	Zhou, Yu	2020-03-11	China	191	Hospital	56 (46-67)	38.0	5.8	-	-	-

Liu et al. (2020)	Liu, Ming	2020-03-12	China	41	Hospital	39 (30-48)	58.5	9.8	-	-	-
Mo et al. (n.d.)	Mo	2020-03-16	China	155	Hospital	54 (53-66)	44.5	3.9	-	-	-
Shi et al. (2020)	Shi, Yu	2020-03-18	China	487	Hospital	46 (27-65)	46.8	-	-	8.21	-
Zhang et al. (2020)	Zhang, Cai	2020-03-20	China	645	Hospital	NA	49.1	6.4	-	-	-
Dong et al. (2020)	Dong, Cao	2020-03-20	China	9	Hospital	44 (30-46)	66.7	11.1	-	-	-
Wan et al. (2020)	Wan	2020-03-21	China	135	Hospital	47 (36-55)	46.7	6.7	-	-	-
Jin et al. (2020)	Jin	2020-03-24	China	651	Hospital	46 (32-60)	49.2	6.3	-	-	-
Wang et al. (2020)	Wang, Pan	2020-03-24	China	125	Hospital	41 (26-66)	43.2	-	-	12.80	-
Lian et al. (2020)	Lian	2020-03-25	China	788	Hospital	NA	38.5	6.9	-	-	-
Hu et al. (2020)	Hu	2020-03-25	China	323	Hospital	61^ (23-91)	48.6	-	-	11.76	-
Guan et al. (2020)	Guan, Liang	2020-03-26	China	1,590	Hospital	49 (33-64)	42.7	-	-	6.98	93.
Chen et al. (2020)	Chen	2020-03-26	China	548	Hospital	62 (44-70)	37.6	4.4	2.55	-	-
Guo et al. (2020)	Guo	2020-03-27	China	187	Hospital	59 (45-73)	51.3	9.6	-	-	-
CDCMMWR (2020)	Chow (US CDC)	2020-03-31	USA	7,162	Community and Hospital	NA	-	1.3	2.30	-	-
Kim et al. (2020)	Kim	2020-04-01	South Korea	28	Hospital	43 (30-56)	46.4	17.9	-	-	-
Feng et al. (2020)	Feng	2020-04-10	China	476	Hospital	53 (40-64)	43.1	9.2	-	-	-
Rentsch et al. (2020)	Rentsch	2020-04-14	USA	3,528	Community and Hospital	66 (60-70)	4.6	27.2	30.60	-	36.
Goyal et al. (2020)	Goyal	2020-04-17	USA	393	Hospital	62.2 (49-74)	39.3	5.1	-	-	-
Zheng et al. (2020)	Zheng, Gao	2020-04-19	China	66	Hospital	47^ (NA)	25.8	12.1	-	-	-
Gold et al. (2020)	Gold (US CDC)	2020-04-20	USA	305	Hospital	NA	50.5	5.2	-	-	-
Argenziano et al. (2020)	Argenziano	2020-04-22	USA	1,000	Hospital	63 (50-75)	40.4	4.9	17.90	-	77.
Richardson et al. (2020)	Richardson	2020-04-22	USA	5,700	Hospital	63 (52-75)	39.7	-	-	9.79	52.
Fontanet et al. (2020)	Fontanet	2020-04-23	France	661	Community and Hospital	37 (16-47)	62.0	10.4	-	-	-
Shi et al. (2020)	Shi, Ren	2020-04-23	China	134	Hospital	46 (34-58)	51.5	-	-	10.45	-

Hadjadj et al. (2020)	Hadjadj	2020-04-23	France	50	Hospital	55 (50-63)	22.0	2.0	18.00	-	80.
Liao et al. (2020)	Liao, Feng	2020-04-24	China	1,848	Hospital	55 (48-61)	54.7	-	-	0.43	-
Gil-Agudo et al. (2020)	Gil-Agudo	2020-04-24	Spain	7	Hospital	68 (34-75)	28.6	-	-	42.86	57.
Yao et al. (2020)	Yao	2020-04-24	China	108	Hospital	52 (37-58)	60.2	3.7	-	-	-
Zuo et al. (2020)	Zuo, Yalavarthi	2020-04-24	USA	50	Hospital	61 (46-76)	34.0	-	-	36.00	-
Solís and Carreño (2020)	Solis	2020-04-25	Mexico	650	Hospital	46 (NA)	42.1	9.4	-	-	-
Yu et al. (2020)	Yu, Cai	2020-04-27	China	95	Hospital	NA	44.2	8.4	-	-	-
Ziehr et al. (2020)	Ziehr	2020-04-29	USA	66	Hospital	58 (23-87)	35.0	-	-	33.33	63.
Zheng et al. (2020)	Zheng, Xiong	2020-04-30	China	73	Hospital	43^ (NA)	45.2	-	-	10.96	89.
Kalan et al. (2020)	Kalan	2020-05-01	Iran	193	Hospital	52.6^ (37-67)	36.3	7.3	-	-	85.
Kolin et al. (2020)	Kolin	2020-05-05	UK	1,474	Community and Hospital	58 (49-67)	46.6	14.5	40.16	-	44.
Borobia et al. (2020)	Borobia	2020-05-06	Spain	2,226	Hospital	61 (46-78)	52.0	7.1	-	-	-
Giacomelli et al. (2020)	Giacomelli	2020-05-06	Italy	233	Hospital	61 (50-72)	31.9	-	-	30.04	70.
Shah et al. (2020)	Shah	2020-05-06	USA	316	Hospital	63 (43-72)	48.1	16.5	17.72	-	42.
Williamson et al. (2020)	The OpenSAFELY Collaborative	2020-05-07	UK	17,425,445	Community and Hospital	NA	50.1	17.0	32.93	-	45.
Allenbach et al. (2020)	Allenbach	2020-05-08	France	152	Hospital	77 (60-83)	31.1	-	-	6.58	-
Robilotti et al. (2020)	Robilotti	2020-05-08	USA	423	Hospital	NA	50.0	2.1	37.59	-	58.
Lubetzky et al. (2020)	Lubetzky	2020-05-08	USA	54	Hospital	57 (29-83)	62.0	-	-	22.22	-
Yin et al. (2020)	Yin, Yang	2020-05-10	China	106	Hospital	73 (61-85)	39.6	-	-	16.98	-
Rica et al. (2020)	de la Rica	2020-05-11	Spain	48	Hospital	66^ (33-88)	33.0	-	-	20.83	-
Cho et al. (2020)	Cho	2020-05-11	UK	1,331	Community and Hospital	NA	49.2	19.0	26.97	-	54.
Yanover et al. (2020)	Yanover	2020-05-13	Israel	4,353	Community and Hospital	35 (22-54)	44.5	11.8	2.96	-	85.
Hamer et al. (2020)	Hamer	2020-05-13	UK	387,109	Hospital	56.2 (48-64)	55.1	9.7	34.84	-	55.
Targher et al.	Targher	2020-05-	China	339	Hospital	48.4^	52.8	8.3	-	-	-

(2020)		13				(NA)					
Carrillo-Vega et al. (2020)	Carillo-Vega	2020-05-14	Mexico	10,544	Community and Hospital	46.5^ (30-62)	42.3	8.9	-	-	-
Regina et al. (2020)	Regina	2020-05-14	Switzerland	200	Hospital	70 (55-81)	40.0	4.5	-	-	-
Almazeedi et al. (2020)	Almazeedi	2020-05-15	Kuwait	1,096	Hospital	41 (25-57)	19.0	4.0	-	-	-
Lusignan et al. (2020)	de Lusignan	2020-05-15	UK	3,802	Community	58 (34-73)	57.6	10.9	46.11	-	29.
Palaiodimos et al. (2020)	Palaiodimos	2020-05-15	USA	200	Hospital	64 (50-73.5)	51.0	-	-	32.50	67.
Mejia-Vilet et al. (2020)	Mejia-Vilet	2020-05-16	Mexico	329	Hospital	49 (41-60)	36.0	-	-	6.99	-
Chen et al. (2020)	Chen, Jiang	2020-05-16	China	135	Hospital	NA	42.2	-	-	9.63	-
Li et al. (2020)	Li, Chen	2020-05-16	China	1,008	Hospital	55 (44-65)	43.6	5.7	-	-	-
Valenti et al. (2020)	Valenti	2020-05-18	Italy	789	Community	40.7^ (NA)	35.0	25.9	-	-	-
Feuth et al. (2020)	Feuth	2020-05-18	Finland	28	Hospital	56 (47-72)	46.0	10.7	28.57	-	60.
Ge et al. (2020)	Ge	2020-05-18	China	51	Hospital	70 (58-79)	27.5	13.7	-	-	-
Parrotta et al. (2020)	Parrotta	2020-05-18	USA	76	Community and Hospital	44.9 (13-71)	61.8	2.6	26.32	-	68.
Shekhar et al. (2020)	Shekhar	2020-05-18	USA	50	Hospital	55.5 (20-85)	54.0	48.0	-	-	-
Rimland et al. (2020)	Rimland	2020-05-19	USA	11	Hospital	59 (48-65)	18.2	9.1	-	-	-
Basse et al. (2020)	Basse	2020-05-19	France	141	Hospital	62 (52-72)	72.0	17.7	-	-	-
Freites et al. (2020)	Freites	2020-05-19	Spain	123	Hospital	59.88^ (44-74)	69.9	3.3	-	-	-
Alshami et al. (2020)	Alshami	2020-05-19	Saudi Arabia	128	Quarantine Centre	39.6^ (24-55)	53.9	15.6	2.34	-	-
Shi et al. (2020)	Shi, Zhao	2020-05-20	China	101	Hospital	71 (59-80)	40.6	-	-	4.95	-
Al-Hindawi et al. (2020)	Al-Hindawi	2020-05-20	UK	31	Hospital	61 (NA)	12.9	3.2	70.97	-	25.
Wu et al. (2020)	Wu	2020-05-21	Italy	174	Hospital	61.2^ (50-71)	30.5	-	-	33.33	-
Kim et al. (2020)	Kim, Garg	2020-05-22	USA	2,491	Hospital	62 (50-75)	46.8	6.0	25.77	-	-
Docherty et al. (2020)	Docherty	2020-05-22	Multiple	20,133	Hospital	72.9 (58-82)	40.0	4.2	21.68	-	44.
Petrilli et al. (2020)	Petrilli	2020-05-22	USA	5,279	Community and Hospital	54 (38-66)	51.5	5.5	17.09	-	61.
Klang et al. (n.d.)	Klang	2020-05-23	USA	3,406	Hospital	NA	61.8	-	-	23.28	-

Vaquero et al. (2020)	Vaquero-Roncero	2020-05-24	Spain	146	Hospital	66^ (59-72)	32.2	-	-	6.85	-
Ip et al. (2020)	Ip	2020-05-25	USA	2,512	Hospital	64 (52-76)	37.6	3.1	17.83	-	64.
Heili-Frades (2020)	Heili-Frades	2020-05-25	Spain	4,712	Hospital	62 (47-77)	50.5	4.9	17.40	-	-
Berumen et al. (2020)	Berumen	2020-05-26	Mexico	102,875	Hospital	NA	49.1	-	-	9.64	-
Garibaldi et al. (2020)	Garibaldi	2020-05-26	USA	832	Hospital	63 (49-75)	47.0	5.5	22.60	-	-
Soto-Mota et al. (2020)	Soto-Mota	2020-05-27	Mexico	400	Hospital	NA	30.0	-	-	12.00	-
Li et al. (2020)	Li, Long	2020-05-28	China	145	Not Stated	49^ (13-80)	61.0	-	-	5.52	-
Louis et al. (2020)	Louis	2020-05-28	USA	22	Hospital	66.5^ (55-77)	36.4	-	-	45.45	-
Kuderer et al. (2020)	Kuderer	2020-05-28	Multiple	928	Community and Hospital	66 (57-76)	50.0	4.6	35.13	-	50.
Gianfrancesco et al. (2020)	Gianfrancesco	2020-05-29	Multiple	600	Community and Hospital	56 (45-67)	71.0	-	-	21.50	64.
Chaudhry et al. (2020)	Chaudhry	2020-05-29	USA	40	Community and Hospital	52 (45.5-61)	60.0	-	-	15.00	-
Niedzwiedz et al. (2020)	Niedzwiedz	2020-05-29	UK	392,116	Community and Hospital	NA	54.9	9.8	34.81	-	55.
Valle et al. (2020)	del Valle	2020-05-30	USA	1,484	Hospital	62 (52-72)	40.6	5.5	23.32	-	-
Bello-Chavolla et al. (2020)	Bello-Chavolla	2020-05-31	Mexico	177,133	Community and Hospital	42.6 (26-59)	48.9	-	-	9.28	-
Batty et al. (2020)	Batty	2020-06-01	UK	908	Hospital	57.27^ (48-66)	44.3	11.2	-	-	-
Israel et al. (2020)	Israel	2020-06-01	Israel	24,906	Community and Hospital	40 (27-59)	48.7	16.8	12.66	-	70.
Hao et al. (2020)	Hao	2020-06-01	China	788	Hospital	46 (35-56)	48.4	6.9	-	-	-
Lassale et al. (2020)	Lassale	2020-06-01	UK	900	Hospital	57.2^ (48-66)	44.4	11.4	41.89	-	46.
Eugen-Olsen et al. (2020)	Eugen-Olsen	2020-06-02	Denmark	407	Hospital	64 (47-77)	57.7	20.6	36.86	-	39.
Martinez-Portilla et al. (2020)	Martinez-Portilla	2020-06-02	Mexico	224	Community and Hospital	29 (26-33)	100.0	-	-	3.12	-
Raisi-Estabragh et al. (2020)	Raisi-Estabragh	2020-06-02	UK	4,510	Hospital	NA	48.8	-	-	51.80	-
Luo et al. (2020)	Luo	2020-06-02	China	625	Hospital	46 (NA)	47.7	3.0	-	-	-

Boulware et al. (2020)	Boulware	2020-06-03	Multiple	821	Community	40 (33-50)	51.6	3.3	-	-	-
Ikitimur et al. (2020)	Ikitimur	2020-06-03	Turkey	81	Hospital	55^ (38-72)	44.0	-	-	28.40	-
Sierpiński et al. (2020)	Sierpinski	2020-06-03	Poland	1,942	Community	50 (NA)	60.0	6.3	-	-	-
Wang et al. (2020)	Wang, Oekelen	2020-06-05	USA	58	Community and Hospital	67 (NA)	48.0	-	-	36.21	-
Perrone et al. (2020)	Perrone	2020-06-05	Italy	1,189	Hospital	NA	21.2	-	-	21.87	-
Sharma et al. (2020)	Sharma	2020-06-05	India	501	Hospital	35.1^ (18-51)	36.0	-	-	4.19	-
Magagnoli et al. (2020)	Magagnoli	2020-06-05	USA	807	Hospital	70 (60-75)	4.3	-	-	15.86	-
Ramlall et al. (2020)	Ramlall	2020-06-06	USA	11,116	Community and Hospital	52 (34.7-69.5)	55.2	-	-	26.80	73.
Giannouchos et al. (2020)	Giannouchos	2020-06-07	Mexico	236,439	Community and Hospital	42.5^ (25-59)	49.1	9.1	-	-	-
Romão et al. (2020)	Romao	2020-06-08	Portugal	34	Community	41^ (26-66)	67.7	-	-	26.47	-
Cen et al. (2020)	Cen	2020-06-08	China	1,007	Hospital	61 (49-68)	51.0	-	-	8.74	-
Houlihan et al. (2020)	Houlihan	2020-06-09	UK	200	Community	34 (29-44)	61.0	11.0	16.50	-	66.
Lan et al. (2020)	Lan	2020-06-09	USA	104	Community	49^ (34-63)	47.1	-	-	24.04	-
Russell et al. (2020)	Russell	2020-06-09	UK	156	Community and Hospital	65.18^ (50-79)	42.3	7.1	25.00	-	37.
Veras et al. (2020)	Veras	2020-06-09	Brazil	32	Hospital	58.9^ (40-77)	47.0	-	-	25.00	-
Rossi et al. (2020)	Rossi	2020-06-09	France	246	Hospital	68^ (53-83)	39.0	-	-	25.20	-
Martin-Jimenez et al. (2020)	Martin-Jiminez	2020-06-09	Spain	339	Hospital	81.6 (72-87)	39.5	-	-	30.68	-
Rajter et al. (2020)	Rajter	2020-06-10	USA	280	Hospital	59.6^ (41-77)	45.5	5.7	10.71	-	74.
Zhou et al. (2020)	Zhou, He	2020-06-10	China	238	Hospital	55.5 (35-67)	57.0	2.9	-	-	-
Woolford et al. (2020)	Woolford	2020-06-11	UK	4,510	Community and Hospital	70.5 (NA)	51.2	13.0	38.12	-	48.
Hultcrantz et al. (2020)	Hultcrantz	2020-06-11	USA	127	Community and Hospital	68 (41-91)	46.0	-	-	26.77	72.
Hernández-Garduño (2020)	Hernandez, Garduno	2020-06-11	Mexico	32,583	Community and Hospital	45 (34-56)	48.7	-	-	11.02	-
Sterlin et al. (2020)	Sterlin	2020-06-11	France	135	Hospital	61 (50-72)	41.0	3.7	38.52	-	57.

Maraschini et al. (2020)	Maraschini	2020-06-12	Italy	146	Hospital	32.5^ (27-38)	100.0	-	9.59	-	80.
Wang et al. (2020)	Wang, Zhong	2020-06-12	USA	7,592	Community and Hospital	NA	45.1	3.6	17.08	-	51.
McQueenie et al. (2020)	McQueenie	2020-06-12	UK	428,199	Community and Hospital	NA	54.9	-	-	44.36	55.
Miyara et al. (2020)	Miyara	2020-06-12	France	479	Community and Hospital	NA	44.7	6.7	31.60	-	59.
Apea et al. (2021)	Apea	2020-06-12	UK	1,737	Hospital	63.4^ (NA)	30.4	-	-	9.96	-
Garassino et al. (2020)	Garassino	2020-06-12	Multiple	200	Community and Hospital	68 (61.8-75)	30.0	24.0	55.50	-	18.
Zeng et al. (2020)	Zeng	2020-06-16	China	1,031	Hospital	60.3^ (46-74)	47.8	-	-	10.18	-
Suleyman et al. (2020)	Suleyman	2020-06-16	USA	463	Hospital	57.5^ (40-74)	55.9	-	-	34.56	-
Chen et al. (2020)	Chen, Yu	2020-06-16	China	1,859	Hospital	59 (45-68)	50.0	2.4	3.55	-	94.
Kibler et al. (2020)	Kibler	2020-06-16	France	702	Community and Hospital	82^ (75-88)	56.0	3.7	-	-	-
Olivares et al. (2020)	Olivares	2020-06-16	Chile	21	Hospital	61^ (26-85)	76.2	-	-	9.52	-
Elezkurtaj et al. (2020)	Elezkurtaj	2020-06-17	Germany	26	Hospital	70 (61.8-78.3)	34.6	-	-	19.23	-
Zuo et al. (2020)	Zuo, Estes	2020-06-17	China	172	Hospital	61^ (25-95)	44.0	-	-	26.16	-
Killerby (2020)	Killerby	2020-06-17	USA	531	Community and Hospital	51.6 (38-62)	57.1	-	-	17.14	71.
Gu et al. (2020)	Gu	2020-06-18	USA	5,698	Community and Hospital	47^ (26-67)	62.0	7.0	24.68	-	50.
Wei et al. (2020)	Wei	2020-06-18	USA	147	Hospital	52^ (34-70)	41.0	14.3	-	-	-
Crovetto et al. (2020)	Crovetto	2020-06-19	Spain	874	Community and Hospital	33.7^ (28-38)	100.0	1.1	-	-	-
Govind et al. (2020)	Govind	2020-06-20	UK	6,309	Community and Hospital	46.5^ (31-61)	38.3	66.3	26.77	-	5.5
Sisó-Almirall et al. (2020)	Siso-Almirall	2020-06-20	Spain	322	Community and Hospital	56.7^ (38-74)	50.0	-	-	25.16	-
Salton et al. (2020)	Salton	2020-06-20	Italy	173	Hospital	64.4^ (NA)	34.9	-	-	29.48	-
Duan et al. (2020)	Duan	2020-06-22	China	616	Hospital	64 (53-70)	57.5	3.7	-	-	-

Lenka et al. (2020)	Lenka	2020-06-22	USA	32	Hospital	62.2^ (51-73)	37.5	-	-	50.00	-
Fisman et al. (2020)	Fisman	2020-06-23	Canada	21,922	Community and Hospital	NA	57.0	-	-	2.35	-
Madariaga et al. (2020)	Madariaga	2020-06-23	USA	103	Community and Hospital	41.8^ (27-55)	48.5	-	-	25.24	74.
Jin et al. (2020)	Jin, Gu	2020-06-25	China	6	Hospital	60.5^ (51-75)	33.3	33.3	-	-	-
Mendy et al. (2020)	Mendy	2020-06-27	USA	689	Community and Hospital	49.5 (35.2-67.5)	47.0	-	-	24.67	-
Sigel et al. (2020)	Sigel	2020-06-28	USA	493	Hospital	60 (55-67)	24.1	-	-	28.60	-
Souza et al. (2020)	de Souza	2020-06-28	Brazil	8,443	Hospital	NA	53.0	-	-	1.68	-
Nguyen et al. (2020)	Nguyen	2020-06-29	USA	689	Community and Hospital	55 (40-68)	57.0	-	-	24.82	-
Melo et al. (2020)	de Melo	2020-06-29	Brazil	181	Hospital	55.3^ (34-76)	60.8	9.9	12.15	-	38.
Auvinen et al. (2020)	Auvinen	2020-06-29	Finland	61	Hospital	53 (41-67)	36.0	18.0	27.87	-	54.
Magleby et al. (2020)	Magleby	2020-06-30	USA	678	Hospital	68 (50-81)	38.9	-	-	28.61	-
Hewitt et al. (2020)	Hewitt	2020-06-30	Multiple	1,564	Hospital	74 (61-83)	42.3	7.7	38.55	-	52.
Mohamud et al. (2020)	Mohamud	2020-07-02	USA	6	Hospital	65.8^ (55-78)	16.7	-	-	16.67	-
Trubiano et al. (2020)	Trubiano	2020-07-02	Australia	2,935	Community and Hospital	39 (29-53)	63.5	-	-	8.82	-
Patel et al. (2020)	Patel	2020-07-03	USA	129	Hospital	60.8^ (47-74)	45.0	37.2	-	-	-
Merzon et al. (2020)	Merzon	2020-07-03	Israel	7,807	Community and Hospital	46.2^ (NA)	58.6	-	-	16.18	-
Bello-Chavolla et al. (2020)	Bello-Chavolla, Antonio-Villa	2020-07-04	Mexico	60,121	Community and Hospital	45.5^ (29-61)	47.0	-	-	10.48	-
Zacharioudakis et al. (2020)	Zacharioudakis	2020-07-04	USA	314	Hospital	64 (54-72)	34.7	-	-	22.78	-
Antonio-Villa et al. (2020)	Antonio-Villa	2020-07-04	Mexico	34,263	Community and Hospital	40^ (29-50)	62.9	9.7	-	-	-
Kimmig et al. (2020)	Kimmig	2020-07-06	USA	111	Hospital	63^ (48-78)	44.1	7.2	36.04	-	56.
Senkal (2020)	Senkal	2020-07-07	Turkey	611	Hospital	57^ (18-98)	40.6	11.3	-	-	-
Xie et al. (2020)	Xie	2020-07-07	China	619	Hospital	NA	52.0	-	-	8.24	-

Elmunzer et al. (2020)	Elmunzer	2020-07-09	Multiple	1,992	Hospital	60^ (43-76)	43.0	6.3	28.56	-	59.
Alizadehsani et al. (2020)	Alizadehsani	2020-07-09	Iran	319	Hospital	45.48^ (26-63)	55.5	-	-	0.31	-
Maucourant et al. (2020)	Maucourant	2020-07-10	Sweden	27	Hospital	57 (18-78)	22.2	11.1	25.93	-	40.
Fan et al. (2020)	Fan	2020-07-11	UK	1,425	Community and Hospital	NA	46.7	12.2	40.07	-	46.
Shi et al. (2020)	Shi, Resurreccion	2020-07-11	UK	1,521	Community and Hospital	61.5^ (57-66.8)	45.9	-	-	54.90	-
REACT Study Investigators et al. (2020)	Riley	2020-07-11	UK	120,620	Community and Hospital	NA	54.0	2.2	-	-	-
Hippisley-Cox et al. (2020)	Hippisley-Cox	2020-07-13	UK	8,275,949	Community and Hospital	48.5^ (30-66)	50.3	17.2	21.44	-	57.
Zhang et al. (2020)	Zhang, Cao	2020-07-14	China	289	Hospital	57 (22-88)	46.6	3.5	6.23	-	-
Eiros et al. (2020)	Eiros	2020-07-14	Spain	139	Community and Hospital	52 (41-57)	72.0	4.3	50.36	-	-
Marcos et al. (2020)	Marcos	2020-07-14	Spain	918	Hospital	72.8^ (58-87)	42.2	6.1	-	15.25	-
Hoertel et al. (2020)	Hoertel, Sanchez, Rico	2020-07-14	France	7,345	Hospital	NA	49.3	8.5	-	-	-
Shi et al. (2020)	Shi, Zuo	2020-07-15	USA	172	Hospital	61.48^ (25-96)	44.0	-	-	26.16	-
Hussein et al. (2020)	Hussein	2020-07-15	USA	502	Hospital	60.9^ (45-76)	52.0	9.0	22.11	-	-
Bian et al. (2020)	Bian	2020-07-15	China	28	Hospital	56^ (42-67)	42.9	7.1	-	-	-
Zhan et al. (2020)	Zhan	2020-07-16	China	75	Hospital	57 (25-75)	48.0	-	-	12.00	-
Omrani et al. (2020)	Omrani	2020-07-16	Qatar	1,409	Community and Hospital	39 (30-50)	17.2	-	-	9.23	-
Gupta et al. (2020)	Gupta	2020-07-16	USA	496	Hospital	70 (60-78)	46.0	-	-	7.26	-
Soares et al. (2020)	Soares	2020-07-16	Brazil	10,713	Community and Hospital	NA	55.0	2.0	-	-	-
Abolghasemi et al. (2020)	Abolghasemi	2020-07-17	Iran	24	Hospital	49^ (29-64)	37.5	-	-	4.17	-
Merkely et al. (2020)	Merkely	2020-07-17	Hungary	10,474	Community	48.7^ (30-66)	53.6	28.0	20.46	-	51.
Fox et al. (2020)	Fox	2020-07-17	UK	55	Community and Hospital	63 (23-88)	31.0	1.8	10.91	-	56.
Pandolfi et al. (2020)	Pandolfi	2020-07-17	Italy	33	Hospital	62 (52-65)	21.1	3.0	24.24	-	72.
Girardeau et al.		2020-07-				30 (29-					

(2020)	Girardeau	17	France	10	Community	33)	50.0	40.0	10.00	-	-
Kurashima et al. (2020)	Kurashima	2020-07-17	Japan	53	Hospital	62.9^ (49-76)	35.8	-	-	50.94	-
McGrail and Edwards (2020)	Edwards	2020-07-19	USA	209	Hospital	62.5 (NA)	38.8	-	-	18.66	-
Martinez-Resendez et al. (2020)	Martinez-Resendez	2020-07-20	Mexico	8	Hospital	57 (48-69)	25.0	-	-	12.50	-
Hoertel et al. (2020)	Hoertel	2020-07-20	France	12,612	Hospital	58.7^ (39-77)	49.6	-	-	9.28	-
Wang et al. (2020)	Wang, Shu	2020-07-20	China	59	Hospital	67.4^ (56-78)	35.6	-	-	15.25	-
Bernaola et al. (2020)	Bernaola	2020-07-21	Spain	1,645	Hospital	NA	38.5	2.5	10.88	-	86.
Schneeweiss et al. (2020)	Schneeweiss	2020-07-22	USA	24,313	Community and Hospital	67^ (53-80)	53.0	-	-	2.88	-
Concha-Mejia and Rincon-Sanchez (2020)	Mejia	2020-07-24	Colombia	72	Community and Hospital	46 (28-64)	47.0	8.3	11.11	-	-
Izquierdo et al. (2020)	Izquierdo	2020-07-24	Spain	71,192	Community and Hospital	42^ (18-66)	59.0	10.0	-	-	-
Santos et al. (2020)	Santos	2020-07-25	USA	23	Community and Hospital	NA	-	-	-	8.70	-
Reiter et al. (2020)	Reiter	2020-07-26	Austria	235	Community	44.2^ (32-55)	70.0	22.6	22.55	-	54.
Motta et al. (2020)	Motta	2020-07-26	USA	374	Hospital	64.7^ (46-82)	41.4	-	-	33.16	66.
Altamimi et al. (2020)	Altamimi	2020-07-27	Qatar	68	Hospital	49^ (40-58)	2.0	16.2	-	-	-
Thompson et al. (2020)	Thompson	2020-07-27	UK	470	Hospital	71 (57-82)	46.0	14.0	27.23	-	58.
Zobairy et al. (2020)	Zobairy	2020-07-28	Iran	203	Community and Hospital	49.2^ (32-65)	44.8	5.9	-	-	-
Zhou et al. (2020)	Zhou, Sun	2020-07-29	China	144	Hospital	47 (38-56)	46.5	9.0	-	-	-
Kumar et al. (2020)	Kumar	2020-07-29	India	91	Hospital	47^ (41-52)	21.0	44.0	-	-	-
Qu et al. (2020)	Qu	2020-07-29	China	246	Hospital	53.6^ (38-68)	53.3	42.3	-	-	-
Higuchi et al. (2020)	Higuchi	2020-07-30	Japan	57	Hospital	52 (35-70)	43.9	12.3	29.82	-	57.
Zhao et al. (2020)	Zhao, Chen	2020-07-30	USA	641	Hospital	60 (NA)	40.1	21.7	-	-	-
Fond et al. (2020)	Fond	2020-07-30	France	1,092	Hospital	62.5 (51-76)	45.7	11.4	-	-	-
Jun et al. (2020)	Jun	2020-08-01	USA	3,086	Hospital	66 (56-77)	40.9	3.7	21.32	-	52.
Morshed et al.		2020-08-				37 (31-					

(2020)	Morshed	02	Bangladesh	103	Community	53)	28.2	31.1	-	-	-
Iversen et al. (2020)	Iversen	2020-08-03	Denmark	28,792	Community and Hospital	44.4^ (31-57)	78.9	16.0	6.52	-	76.
Ebinger et al. (2020)	Ebinger	2020-08-04	USA	6,062	Community	41.5^ (29-53)	67.8	1.7	-	-	-
Hadi et al. (2020)	Hadi	2020-08-05	USA	370	Community and Hospital	48.2^ (34-62)	29.5	-	-	15.14	84.
Tao et al. (2020)	Tao	2020-08-06	China	70	Community	33.2^ (12-53)	48.6	-	-	15.71	-
Klang et al. (2020)	Klang, Soffer	2020-08-09	USA	1,320	Hospital	NA	41.5	-	-	24.70	-
Zhou et al. (2021)	Zhou, Ma	2020-08-10	China	429	Hospital	58.3^ (42-74)	50.6	-	-	8.39	-
Altibi et al. (2020)	Altibi	2020-08-11	USA	706	Hospital	66.7^ (51-81)	43.0	4.0	37.25	-	58.
Izzi-Engbeaya et al. (2020)	Izzi-Engbeaya	2020-08-11	UK	889	Hospital	65.8^ (48-83)	40.0	-	-	21.26	33.
Rizzo et al. (2020)	Rizzo	2020-08-11	USA	76,819	Hospital	54 (38-67)	55.2	6.7	20.78	-	50.
Jehi et al. (2020)	Jehi	2020-08-11	USA	4,536	Community and Hospital	NA	-	7.3	28.48	-	49.
Holman et al. (2020)	Holman	2020-08-13	UK	10,989	Community and Hospital	NA	38.8	5.5	42.62	-	49.
Ouyang et al. (2020)	Ouyang	2020-08-14	China	217	Hospital	46.5^ (30-62)	53.5	16.6	-	-	-
Valenzuela et al. (2020)	Valenzuela	2020-08-14	Chile	29	Hospital	56.9^ (43-70)	6.9	17.2	-	-	-
Monteiro et al. (2020)	Monteiro	2020-08-14	USA	112	Hospital	61 (45-74)	34.0	6.2	17.86	-	68.
Philipose et al. (2020)	Philipose	2020-08-14	UK	466	Hospital	67 (6-97)	41.8	6.0	73.18	-	16.
Weerahandi et al. (2020)	Weerahandi	2020-08-14	USA	394	Community	63 (55-70)	37.0	5.3	25.89	-	55.
Parra-Bracamonte et al. (2020)	Parra-Bracamonte	2020-08-14	Mexico	331,298	Community and Hospital	44 (33-56)	46.2	-	-	7.39	-
Peters et al. (2020)	Peters	2020-08-15	Netherlands	1,893	Hospital	66.8^ (52-81)	39.4	4.9	-	-	-
Islam et al. (2020)	Islam	2020-08-18	Bangladesh	1,016	Community and Hospital	37 (28-49)	35.9	18.2	-	-	-
Chand et al. (2020)	Chand	2020-08-19	USA	300	Hospital	58.2^ (45-70)	39.3	22.3	-	-	-
Aksu et al. (2020)	Aksu	2020-08-19	Turkey	123	Community and Hospital	49.7^ (36-63)	33.3	11.4	-	-	-
Alkurt et al. (2020)	Alkurt	2020-08-20	Turkey	932	Community and	34.8^ (25-44)	64.4	24.5	-	-	-

					Hospital						
Ward et al. (2020)	Ward	2020-08-21	UK	99,908	Community	NA	56.1	10.6	-	-	-
Salerno et al. (2020)	Salerno	2020-08-22	USA	15,920	Hospital	49 (30-65)	57.0	-	-	36.78	55.
Rashid et al. (2020)	Rashid	2020-08-22	UK	517	Hospital	72.8^ (59-86)	31.9	9.9	29.01	-	29.
Pan et al. (2020)	Pan	2020-08-22	USA	12,084	Community and Hospital	45.5^ (27-63)	54.3	-	-	17.51	-
Fillmore et al. (2020)	Fillmore	2020-08-24	USA	22,914	Community and Hospital	NA	-	37.5	40.65	-	15.
Zhou et al. (2020)	Zhou, Qin	2020-08-25	China	51	Hospital	57.37^ (42-72)	29.4	-	-	78.43	21.
Ibrahim et al. (2020)	Ibrahim	2020-08-27	USA	38	Hospital	63^ (51-75)	47.0	10.5	-	-	-
Oliveira et al. (2020)	Oliveira	2020-08-31	USA	131	Hospital	61 (49.5-71.5)	64.9	-	-	17.56	26.
Yoo et al. (2020)	Yoo	2020-08-31	USA	4,840	Hospital	66.4 (54.9-77.8)	43.5	4.4	21.38	-	53.
Zhan et al. (2020)	Zhan, Liu	2020-08-31	China	405	Hospital	56^ (17-95)	54.1	-	-	11.36	88.
Mohamed-Hussein et al. (2020)	Hussein, Galal	2020-09-01	Egypt	444	Community	33.1^ (21-45)	56.8	13.1	9.01	-	77.
Villar-Garcia et al. (2020)	Vilar-Garcia	2020-09-01	Spain	7,699,568	Community and Hospital	43 (24-59)	50.9	17.1	-	-	-
Ibarra-Nava et al. (2020)	Ibarra-Nava	2020-09-01	Mexico	416,546	Community and Hospital	NA	46.9	7.4	-	-	-
Rubio-Rivas et al. (2020)	Rubio-Rivas	2020-09-01	Spain	186	Hospital	64.3^ (51-77)	30.6	4.3	20.43	-	75.
Mamtani et al. (2020)	Mamtani	2020-09-02	USA	403	Hospital	55^ (41-68)	32.3	9.7	12.66	-	68.
Ren et al. (2020)	Ren	2020-09-02	China	432	Hospital	NA	57.9	10.0	-	-	90.
Mutambudzi et al. (2020)	Mutambudzi	2020-09-03	UK	120,075	Community and Hospital	NA	54.2	11.7	26.39	-	61.
Yan et al. (2020)	Yan	2020-09-07	China	578	Hospital	49.2^ (35-63)	49.3	9.2	-	-	-
Mancilla-Galindo et al. (2020)	Mancilla-Galindo	2020-09-08	Mexico	183,779	Community and Hospital	45^ (28-61)	46.0	7.6	-	-	-
Ullah et al. (2020)	Ullah	2020-09-08	UK	212	Community and Hospital	66.7 (54.2-80.5)	44.8	11.3	48.11	-	37.
Hamadah et al. (2020)	Hamadah	2020-09-10	Kuwait	1,123	Hospital	40 (1-93)	18.7	3.9	-	-	-
					Community						

Dashti et al. (2020)	Dashti	2020-09-13	USA	12,347	and Hospital	47 (32-62)	53.3	4.6	15.87	-	57.
Sami et al. (2020)	Sami	2020-09-14	Iran	490	Community and Hospital	56.6^ (41-71)	39.0	14.1	-	-	-
Pongpirul et al. (2020)	Pongpirul	2020-09-16	Thailand	193	Community and Hospital	37 (29-53)	41.5	-	-	15.03	66.
Burrell et al. (2020)	Burrell	2020-09-16	Australia	204	Hospital	63.5 (53-72)	31.4	-	-	13.24	-
Nicholson et al. (2020)	Nicholson	2020-09-17	USA	1,042	Hospital	64 (53-75)	43.2	8.3	22.17	-	37.
Ariza et al. (2020)	Ariza	2020-09-18	Colombia	351	Community and Hospital	30.5 (NA)	54.0	6.8	-	-	-
Carrat et al. (2020)	Carrat	2020-09-18	France	14,628	Community	NA	60.3	12.0	40.83	-	45.
Favara et al. (2020)	Favara	2020-09-20	UK	434	Community	40 (19-66)	82.0	8.5	-	-	-
Invernizzi et al. (2020)	Invernizzi	2020-09-20	Italy	54	Hospital	49.9^ (34-65)	29.7	-	-	24.07	-
Zhu et al. (2020)	Zhu	2020-09-21	China	432	Community and Hospital	49 (35-60)	47.9	14.4	-	-	-
O'Reilly et al. (2020)	O'Reilly	2020-09-21	Australia	1,334	Hospital	NA	-	-	-	28.49	-
Meini et al. (n.d.)	Meini	2020-09-23	Italy	461	Hospital	NA	51.2	10.4	25.81	-	63.
Silva Neto et al. (2020)	da Silva Neto	2020-09-23	Brazil	91	Community and Hospital	49^ (29-68)	49.4	-	-	19.78	-
Ioannou et al. (2020)	Ioannou	2020-09-23	USA	88,747	Community and Hospital	NA	9.0	20.6	37.55	-	29.
Torres-Macho et al. (2020)	Torres-Macho	2020-09-23	Spain	1,968	Hospital	NA	44.0	-	-	23.37	-
Li et al. (2020)	Li, Cai	2020-09-28	China	98	Hospital	68.5 (63-75)	58.2	-	-	11.22	-
Wang et al. (2020)	Wang	2020-09-29	USA	1,078	Hospital	NA	38.2	3.7	24.86	-	49.
Lopez-Medrano et al. (2020)	Lopez-Medrano	2020-09-30	Spain	261	Hospital	NA	43.7	-	-	37.16	-
Collard et al. (2020)	Collard	2020-10-01	Netherlands	1,604	Hospital	65.7^ (50-80)	39.5	4.9	-	-	-
Makaronidis et al. (2020)	Makaronidis	2020-10-01	UK	567	Community	39.4^ (27-51)	69.1	9.3	-	-	-
Yadaw et al. (2020)	Yadaw	2020-10-01	USA	5,051	Community and Hospital	NA	-	3.6	15.92	-	51.
Talavera et al. (2020)	Talavera	2020-10-01	Spain	576	Hospital	67.2^ (52-81)	43.4	-	-	20.49	-
		2020-10-			Community						

Jakob et al. (2020)	Jakob	01	Multiple	2,155	and Hospital	NA	40.3	6.6	7.29	-	34.
Incerti et al. (2020)	Incerti	2020-10-02	USA	13,658	Hospital	62 (49-75)	48.1	6.3	22.64	-	45.
Luo et al. (2020)	Luo, Rizvi	2020-10-03	USA	102	Hospital	68 (61-75)	52.0	-	-	26.47	-
Alharthy et al. (2020)	Alharthy	2020-10-03	Saudi Arabia	352	Hospital	50.6^ (37-63)	12.8	49.4	-	-	-
Robinson et al. (2021)	Robinson	2020-10-05	USA	3,248	Hospital	51^ (34-68)	72.0	4.0	17.64	-	61.
Adrish et al. (2020)	Adrish	2020-10-05	USA	1,173	Hospital	NA	38.6	14.0	14.66	-	71.
Erber et al. (2020)	Erber	2020-10-06	Germany	4,554	Community	38.5^ (NA)	70.4	-	-	18.02	-
Chaudhary et al. (2020)	Chaudhary	2020-10-06	Nepal	220	Hospital	31.5 (25-37)	17.7	11.4	7.73	-	80.
Raines et al. (2021)	Raines	2020-10-07	USA	453	Community and Hospital	60.8^ (46-74)	10.7	-	-	52.98	41.
Roederer et al. (2021)	Roederer	2020-10-09	France	818	Community	NA	20.4	36.9	8.80	-	53.
Zinellu et al. (2021)	Zinellu	2020-10-11	Italy	105	Hospital	72 (59.5-80)	33.3	30.5	10.48	-	59.
Ramachandran et al. (2020)	Ramachandran	2020-10-12	USA	188	Hospital	NA	-	18.6	-	-	-
Lamure et al. (2020)	Lamure	2020-10-12	France	89	Hospital	67 (19-92)	34.0	5.6	32.58	-	48.
Ghinai et al. (2020)	Ghinai	2020-10-12	USA	1,435	Homeless Shelters	NA	27.6	36.6	17.49	-	33.
Best et al. (2020)	Best	2020-10-12	USA	3,471	Hospital	63.5^ (47-79)	51.2	-	-	28.64	-
Savarraj et al. (2020)	Savarraj	2020-10-18	USA	48	Hospital	50^ (33-67)	48.0	10.4	-	-	-
Israel et al. (2020)	Israel, Schaffer	2020-10-18	Israel	26,959	Hospital	NA	50.6	6.8	15.22	-	77.
El-Solh et al. (2020)	El-Solh	2020-10-20	USA	7,816	Hospital	69 (60-74)	5.5	-	-	45.25	-
Perico et al. (2020)	Perico	2020-10-22	Italy	423	Community	44.3^ (34-54)	36.4	21.7	17.97	-	60.
Zhou et al. (2020)	Zhou, Song	2020-10-22	China	124	Hospital	67 (30-86)	48.0	19.1	-	-	-
Chudasama et al. (2020)	Chudasama	2020-10-23	UK	1,706	Community and Hospital	68 (48-85)	42.5	13.8	40.97	-	45.
Salama et al. (2021)	Salama	2020-10-23	Multiple	377	Hospital	55.9^ (41-70)	40.8	5.8	16.98	-	77.
Wang et al. (2020)	Wang, Zheutlin	2020-10-26	USA	3,273	Hospital	65 (53-77)	42.7	3.5	20.68	-	53.
Zhou et al. (2020)	Zhou, He, Yang	2020-10-27	China	1,087	Hospital	NA	51.7	-	-	85.00	15.
Hoertel et al.	Hoertel, Sanchez	2020-10-									

(2020)	Vernet	27	France	12,210	Hospital	NA	50.1	9.0	-	-	-
Arleo et al. (2020)	Arleo	2020-10-27	USA	70	Community and Hospital	56.6^ (48-65)	80.0	1.4	28.57	-	70.
Bermejo-Martin et al. (2020)	Bermejo-Martin	2020-10-27	Spain	250	Community and Hospital	NA	64.0	6.0	-	-	-
Joubert et al. (2020)	Joubert	2020-10-29	France	74	Community and Hospital	NA	-	5.4	-	-	-
Kortela et al. (2020)	Kortela	2020-11-01	Finland	3,008	Community and Hospital	51 (36-69)	59.6	11.0	14.03	-	29.
Gianfrancesco et al. (2020)	Gianfrancesco, Leykina	2020-11-03	USA	1,324	Community and Hospital	NA	75.9	-	-	26.66	68.
Gallichotte et al. (2020)	Gallichotte	2020-11-05	USA	239	Community	41^ (16-76)	-	20.1	16.74	-	57.
Lin et al. (2020)	Lin	2020-11-05	USA	2,821	Hospital	62.7^ (NA)	45.0	2.9	12.51	-	3.3
Kim et al. (2020)	Kim, Han	2020-11-09	South Korea	4,787	Hospital	55 (38-68)	60.1	5.5	2.84	-	91.
Galal et al. (2020)	Galal	2020-11-12	Egypt	430	Community	37.4^ (24-50)	63.7	6.0	7.67	-	86.
Sourij et al. (2020)	Sourij	2020-11-16	Austria	238	Hospital	71.1^ (58-83)	36.1	1.7	15.97	-	82.
Clavario et al. (2020)	Clavario	2020-11-16	Italy	110	Community	61.7 (53.5-69.2)	40.9	40.9	-	-	-
Saeed et al. (2020)	Saeed	2020-11-16	United Arab Emirates	173	Hospital	NA	34.1	6.4	-	-	-
Mansour et al. (2020)	Mansour	2020-11-16	Iran	353	Hospital	61.7^ (45-78)	42.5	7.1	-	-	-
Cadegiani et al. (2020)	Cadegiani	2020-11-18	Brazil	130	Community	42^ (NA)	0.0	7.7	-	-	-
Ilic et al. (2021)	Ilic	2020-11-19	Serbia	107	Community and Hospital	39.1^ (27-50)	-	29.9	-	-	-
Benaim et al. (2020)	Benaim	2020-11-19	Israel	693	Hospital	59.8 (NA)	47.9	-	-	5.05	-
Ho et al. (2020)	Ho	2020-11-19	UK	235,928	Community and Hospital	NA	-	-	-	45.38	-
Singh et al. (2020)	Singh	2020-11-20	UK	930	Hospital	71.4^ (54-87)	44.8	-	-	19.03	-
Márquez-Salinas et al. (2020)	Marquez-Salinas	2020-11-24	Mexico	1,068	Hospital	53 (44-63)	36.8	-	-	14.98	-
Díez-Manglano et al. (2020)	Diez-Manglanas	2020-11-24	Spain	4,393	Hospital	53^ (NA)	40.8	6.6	-	-	-
Bellan et al. (2020)	Bellan	2020-11-26	Italy	1,697	Hospital	71 (58-80)	41.0	3.2	-	-	-
Woolcott and		2020-11-			Community	42 (34-					

Castilla-Bancayán (2020)	Woolcott	26	Mexico	1,636,050	and Hospital	54)	51.9	-	-	8.76	-
Yao et al. (2021)	Yao, Hasegawa	2020-11-26	Japan	101	Hospital	60^ (17-97)	39.6	-	-	28.71	-
Chen et al. (2020)	Chen, Varathraja	2020-11-29	USA	10,123	Community and Hospital	40 (28-54)	53.6	4.4	9.71	-	45.
Serling-Boyd et al. (2020)	Serling-Boyd	2020-11-30	USA	831	Hospital	NA	76.0	3.0	23.23	-	50.
Simons et al. (2020)	Simons	2020-11-30	UK	446	Hospital	64.9 (52.4-76.2)	35.9	9.4	38.57	-	52.
Dupraz et al. (2020)	Dupraz	2020-11-30	Switzerland	219	Community	NA	54.8	11.0	-	-	-
Barasa et al. (2020)	Barasa	2020-11-30	USA	394	Hospital	NA	47.7	14.7	36.04	-	41.
Ren et al. (2020)	Ren, Guo	2020-11-30	China	481	Hospital	NA	45.7	7.7	0.62	-	91.
Martinez-Lacalzada et al. (2020)	Martinez-Lacalzada	2020-12-01	Spain	10,433	Hospital	65.8^ (49-82)	42.8	5.2	23.77	-	66.
Li et al. (2020)	Li, Long, Zhang	2020-12-03	China	954	Hospital	NA	-	-	-	5.87	94.
Martini et al. (2020)	Martini	2020-12-04	Italy	146	Hospital	NA	49.0	-	-	46.58	53.
O'Gallagher et al. (2020)	O'Gallagher	2020-12-04	UK	1,721	Hospital	71 (56-83)	43.4	6.6	18.48	-	74.
Alguwaihes et al. (2020)	Alguwaihes	2020-12-05	Saudi Arabia	439	Hospital	55 (19-101)	31.7	2.1	-	-	-
Zuo et al. (2020)	Zuo, Warnock	2020-12-05	USA	118	Hospital	61^ (44-78)	46.0	-	-	23.73	-
Zhang et al. (2020)	Zhang, Li	2020-12-06	UK	1,746	Community and Hospital	68.8^ (59-78)	47.1	10.1	35.09	-	44.
Dai et al. (2020)	Dai	2020-12-09	China	1,574	Hospital	57.3^ (41-73)	48.2	-	-	9.21	90.
Vila-Córcoles et al. (2020)	Vila-Corcoles	2020-12-10	Spain	79,083	Community	NA	52.4	-	-	16.12	-
Bisso et al. (2020)	Bisso	2020-12-11	Argentina	168	Hospital	67 (58-75)	34.0	10.7	-	-	-
Rentsch et al. (2020)	Rentsch, Beckman	2020-12-11	USA	4,297	Hospital	68 (58-75)	6.6	36.8	39.31	-	1.9
Thiabaud et al. (2020)	Thiabaud	2020-12-11	Switzerland	3,582	Hospital	68 (54-79)	40.5	-	-	6.62	-
Vila-Corcoles et al. (2020)	Vila-Corcoles, Satue-Gracia	2020-12-11	Spain	282	Community and Hospital	65.9^ (53-78)	50.3	8.9	-	-	-
Lévy et al. (2020)	Levy	2020-12-12	France	61	Hospital	60 (50-69)	20.0	8.2	-	-	-
Kantele et al. (2020)	Kantele	2020-12-13	Finland	1,095	Community and Hospital	38 (31-48)	82.7	16.3	25.84	-	56.

Iftime et al. (2020)	Iftimie	2020-12-14	Spain	468	Hospital	NA	44.9	-	-	7.91	-
Ho et al. (2020)	Ho, Narasimhan	2020-12-15	USA	9,991	Community and Hospital	58^ (39-76)	45.9	4.1	18.08	-	77.
Caliskan and Saylan (2020)	Caliskan	2020-12-16	Turkey	565	Hospital	48 (38-58)	-	20.9	13.98	-	65.
Muñoz et al. (2020)	Munoz	2020-12-16	Spain	314	Community	45 (40-53)	52.5	6.7	-	-	-
Crooks et al. (2020)	Crooks	2020-12-16	UK	2,964	Hospital	NA	52.6	11.7	-	-	-
Núñez-Gil et al. (2020)	Nunez-Gil	2020-12-17	Multiple	2,798	Hospital	67 (53-78)	40.0	6.2	-	-	-
Gori et al. (2020)	Gori	2020-12-17	Italy	1,352	Hospital	68 (58-77)	28.4	3.6	18.42	-	66.
Rowlands et al. (2020)	Rowlands	2020-12-18	UK	580	Community	63.8^ (56-70)	52.2	10.2	38.10	-	51.
Richard et al. (2020)	Richard	2020-12-18	Switzerland	8,344	Community	46.9^ (NA)	53.5	15.2	17.11	-	66.
Schubl et al. (2020)	Schuble*	2020-12-19	USA	1,557	Community	NA	68.9	2.4	-	-	-
Ugur Chousein et al. (2020)	Chousein	2020-12-21	Turkey	114	Hospital	51.1^ (36-66)	32.5	16.7	20.18	-	63.
Modrák et al. (2020)	Modrak	2020-12-22	Czechia	213	Hospital	69 (58-80)	51.0	-	-	13.15	-
Kara Polat et al. (2020)	Polat	2020-12-22	Turkey	1,322	Community	NA	47.6	35.6	15.58	-	48.
Kjetland et al. (2020)	Kjetland	2020-12-24	Norway	7,839	Community and Hospital	45.3^ (33-56)	77.0	-	-	41.00	-
Lewnard et al. (2021)	Lewnard	2021-01-02	USA	1,115	Community	NA	52.6	4.4	14.17	-	81.
Nezhadmoghadam and Tamez-Peña (2021)	Nezhadmoghadam	2021-01-04	Mexico	33,325	Hospital	NA	-	10.2	-	-	-
Covid-19 in pregnancy et al. (2021)	Vousden	2021-01-05	UK	1,148	Community and Hospital	NA	100.0	8.6	-	-	-
Boyd and Martin-Loeches (2021)	Boyd	2021-01-07	Ireland	38	Hospital	NA	26.3	-	-	5.26	-
Paleiron et al. (2021)	Paleiron	2021-01-09	France	1,688	Community	28 (23-35)	13.0	48.3	22.87	-	28.
Ader et al. (2021)	Ader	2021-01-09	Multiple	583	Hospital	63 (54-71)	28.3	3.1	-	-	-
Giannini et al. (2021)	Giannini	2021-01-10	Italy	91	Hospital	74^ (61-87)	45.0	23.1	-	-	-
Shade et al. (2021)	Shade	2021-01-10	USA	3,779	Community and Hospital	NA	47.2	3.3	15.74	-	-
Park et al. (2021)	Park	2021-01-11	South Korea	2,269	Hospital	55.5^ (35-75)	64.1	4.1	-	-	-
Ferrari et al. (2021)	Ferrari	2021-01-	Brazil	198	Community	61 (19-	65.0	-	-	20.71	79

Ferrari et al. (2021)	Ferrari	12	Brazil	130	Community	91)	65.0	-	-	20.74	79.
Zhang et al. (2021)	Zhang, Yang	2021-01-12	UK	1,485	Community and Hospital	68.2^ (59-77)	47.2	48.5	39.19	-	11.
Ebrahimian et al. (2021)	Ebrahimian	2021-01-13	USA	226	Hospital	NA	-	-	-	10.62	-
Vahidy et al. (2021)	Vahidy	2021-01-13	USA	96,473	Hospital	51.2^ (32-69)	59.6	-	-	26.18	73.
Mendes et al. (2021)	Mendes	2021-01-14	Switzerland	265	Hospital	85.9^ (79-92)	57.0	5.7	-	-	-
Saurabh et al. (2021)	Saurabh	2021-01-14	India	911	Community	43.1^ (23-62)	35.2	8.1	0.66	-	91.
Ayoubkhani et al. (2021)	Ayoubkhani	2021-01-15	UK	47,780	Hospital	NA	45.1	8.4	40.94	-	42.
Thakur et al. (2021)	Thakar	2021-01-18	India	250	Hospital	NA	42.4	-	-	49.20	-
Zhong et al. (2021)	Zhong	2021-01-18	China	91	Hospital	47.3^ (30-64)	49.5	-	-	18.68	-
Cummins et al. (2021)	Cummins	2021-01-20	UK	1,781	Community and Hospital	NA	44.8	10.2	-	-	-
Sun et al. (2021)	Sun	2021-01-21	USA	323	Community and Hospital	NA	57.6	-	-	39.32	-
Lowe et al. (2021)	Lowe	2021-01-25	USA	7,102	Hospital	50.3^ (NA)	61.2	2.4	12.81	-	84.
Caglar and Kacer (2021)	Caglar	2021-01-25	Turkey	120	Hospital	57 (47-67)	51.7	-	-	37.50	-
Quan et al. (2021)	Quan	2021-01-27	USA	2,038	Hospital	64^ (47-80)	50.4	-	-	39.74	-
Strangfeld et al. (2021)	Strangfeld	2021-01-27	Multiple	3,729	Community and Hospital	57^ (41-72)	68.0	-	-	20.81	64.
Tardif et al. (2021)	Tardif	2021-01-27	Canada	4,488	Community and Hospital	NA	53.9	9.6	33.60	-	56.
Jafari et al. (2021)	Jafari	2021-01-28	USA	1,979	Hospital	66 (57-74)	32.0	12.1	-	-	-
Prats-Uribe et al. (2021)	Prats-Uribe	2021-01-30	Spain	696	Hospital	63^ (52-73)	30.9	-	-	16.09	74.
Nuño et al. (2021)	Nuno	2021-02-01	USA	4,730	Hospital	61 (46-73)	43.6	10.1	-	-	-
Abajo et al. (2021)	de Abajo	2021-02-03	Spain	625	Hospital	NA	39.4	4.6	29.28	-	39.
Mora et al. (2021)	Mora	2021-02-03	USA	1,058	Community	39.7^ (27-52)	52.5	4.5	14.56	-	80.
Molenaar et al. (2021)	Molenaar	2021-02-03	USA	696	Community and Hospital	33.1^ (NA)	100.0	4.5	-	-	-
Leister et al. (2021)	Leister	2021-02-03	Austria	3,301	Community and Hospital	43.6^ (33-54)	68.0	23.3	-	-	-

Didikoglu et al. (2021)	Didikoglu	2021-02-04	UK	384,816	Community and Hospital	68.3^ (60-76)	54.9	9.8	35.19	-	55.
Estiri et al. (2021)	Estiri	2021-02-04	USA	16,709	Hospital	NA	57.2	-	-	8.62	-
Tavakol et al. (2021)	Tavakol	2021-02-04	Iran	206	Community and Hospital	40.9^ (29-52)	57.8	-	-	12.62	-
Cai et al. (2021)	Cai, Yang	2021-02-05	China	455	Hospital	NA	52.6	7.5	-	-	-
Lohia et al. (2021)	Lohia	2021-02-05	USA	1,871	Hospital	64.1^ (48-80)	48.4	-	-	37.63	-
Vila-Corcoles et al. (2021)	Vila-Corcoles, Satue-Gracia, Vila-Rovira	2021-02-05	Spain	79,083	Community	65.8^ (54-77)	52.4	16.1	-	-	-
International Severe Acute Respiratory and emerging Infections Consortium et al. (2020)	ISARIC	2021-02-11	Multiple	240,149	Hospital	60 (NA)	49.0	-	-	3.63	21.
Gégout petit et al. (2021)	Gegout Petit	2021-02-12	France	2,006	Community	NA	55.0	16.8	-	-	-
Zhang et al. (2021)	Zhang, Wang	2021-02-13	China	172	Hospital	47.9^ (29-66)	46.5	7.0	1.16	91.86	-

* grouped together current smokers and vapers

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, study-based prevalence was typically higher than national estimates. National smoking prevalence estimates used for comparison are presented in Supplementary table 3.

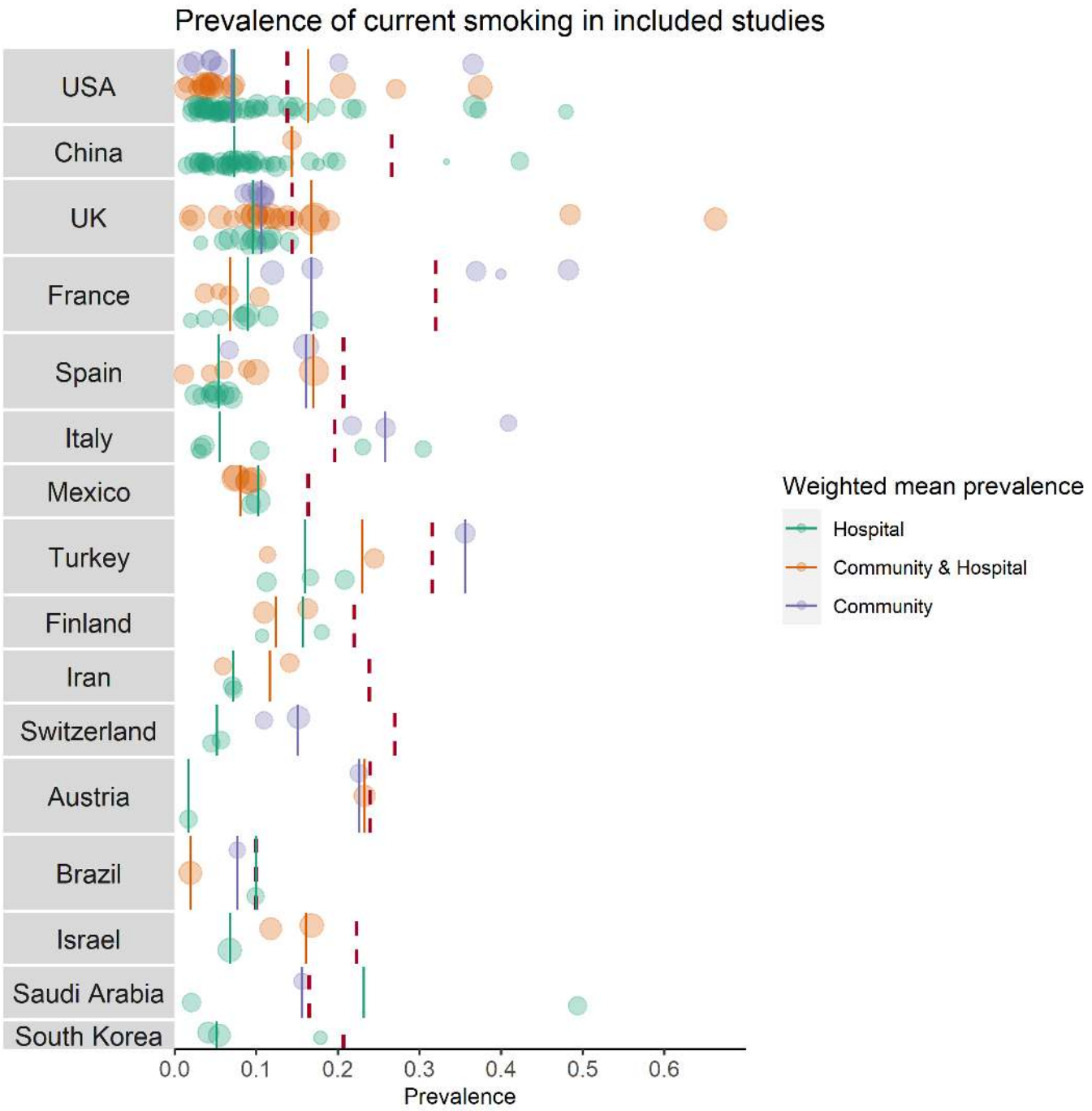

Figure 2a. Weighted mean prevalence of current smoking in included studies, split by country (solid lines). The circles represent individual studies, with colour corresponding to study setting (i.e. community, community and hospital, hospital) and size corresponding to relative study sample size. For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

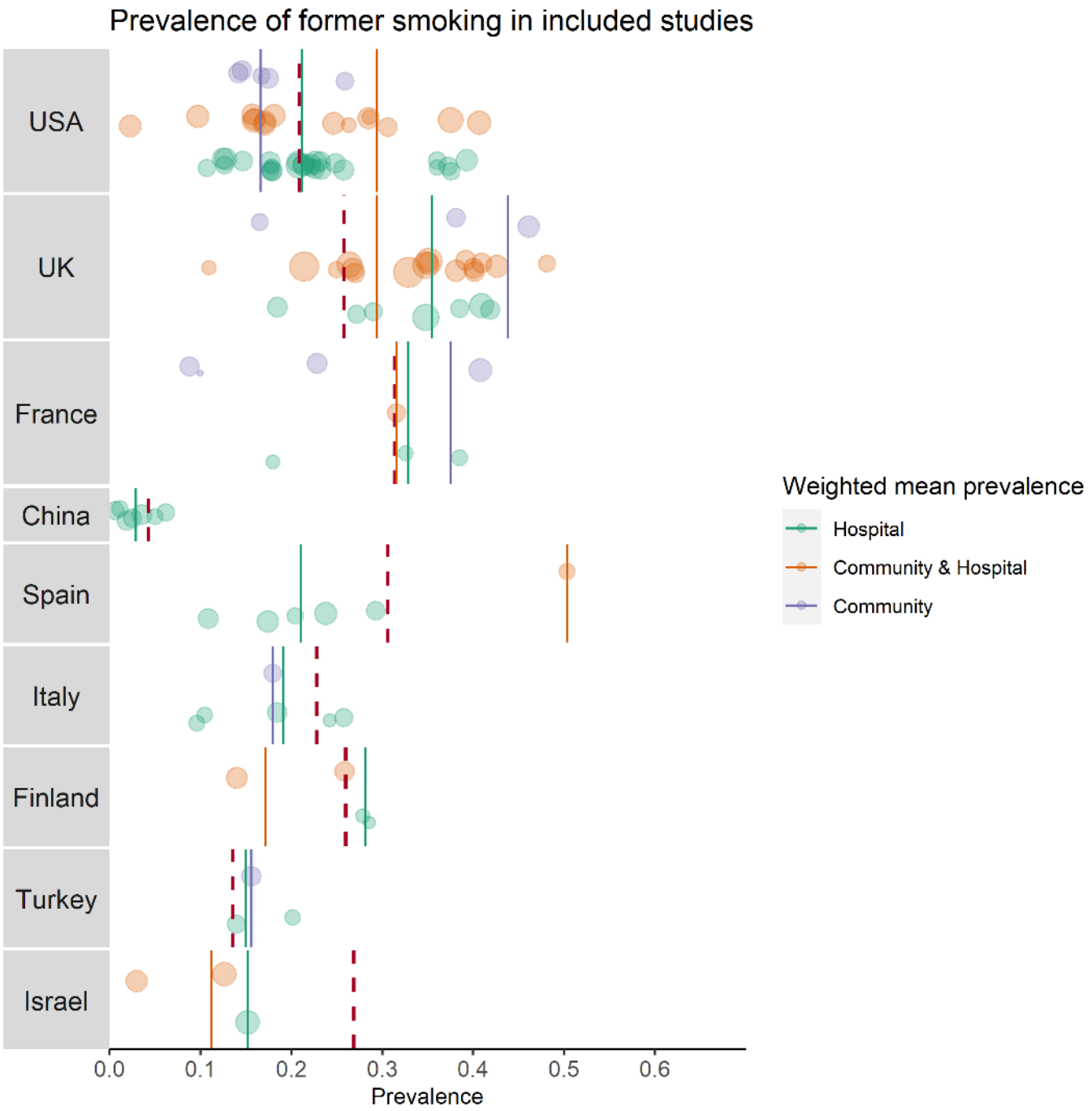

Figure 2b. Prevalence of former smoking in included studies, split by country (solid lines). The circles represent individual studies, with colour corresponding to study setting (i.e. community, community and hospital, hospital) and size corresponding to relative study sample size. For comparison, national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

Four 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 (Rentsch et al., 2020), 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 (Odani, 2018). In the UK Biobank cohort (Niedzwiedz et al., 2020), 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 (Trubiano et al., 2020), 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, $p = 0.045$). In a further study using the UK Biobank cohort (Didikoglu et al., 2021), current (RR = 1.23, 95% CI = 1.19-1.26, $p < 0.001$) and former smokers (RR = 1.20, 95% CI = 1.18-1.23, $p < 0.001$) were more likely to receive a test compared with never smokers.

SARS-CoV-2 infection by smoking status

76 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 3 ‘good’ and 27 ‘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 = 0.71, 95% Credible Interval (CrI) = 0.61-0.82, $\tau = 0.34$). The three good quality studies each reported point estimates less than 1, although the CrI for one of the three studies crossed 1. The probability of current smokers being at reduced risk of infection compared with never smokers (RR ≤0.9) was >99%. Former compared with never smokers were at increased risk of testing positive, but data were inconclusive (RR = 1.03, 95% CrI = 0.95-1.11, $\tau = 0.17$) 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 4%. Results were materially unchanged in sensitivity analyses.

***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/form smoker (%)
Rentsch	3,528	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	1,331	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%)	-
Kolin	1,474	805 (54.61%)	141 (17.52%)	307 (38.14%)	-	354 (43.98%)	3 (0.37%)	669 (45.39%)	72 (10.76%)	285 (42.60%)	-
de Lusignan	3,291	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	102,875	71353 (69.36%)	-	-	7173 (10.05%)	64180 (89.95%)	-	31522 (30.64%)	-	-	2748 (8.72%)
Israel	24,906	20755 (83.33%)	3783 (18.23%)	2671 (12.87%)	-	14301 (68.90%)	-	4151 (16.67%)	406 (9.78%)	483 (11.64%)	-
del Valle	1,108	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	11,116	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	4,510	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	428,199	424355 (99.10%)	-	-	189299 (44.61%)	235056 (55.39%)	-	1311 (0.31%)	-	-	669 (51.03%)
Woolford	4,474	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	32,583	20279 (62.24%)	-	-	2399 (11.83%)	17861 (88.08%)	-	12304 (37.76%)	-	-	1191 (9.68%)
Govind	6,215	6207 (99.87%)	4104 (66.12%)	1669 (26.89%)	-	342 (5.51%)	-	102 (1.64%)	78 (76.47%)	20 (19.61%)	-
Gu	4,699	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%)	-	-
Auvinen	61	33 (54.10%)	10 (30.30%)	8 (24.24%)	-	15 (45.45%)	-	28 (45.90%)	1 (3.57%)	9 (32.14%)	-
Antonio-Villa	34,263	23338 (68.11%)	2293 (9.83%)	-	-	-	21045 (90.17%)	10925 (31.89%)	1023 (9.36%)	-	-
Merzon	7,807	7025 (89.98%)	-	-	1136 (16.17%)	-	5889 (83.83%)	782 (10.02%)	-	-	127 (16.24%)
Trubiano	2,935	2827 (96.32%)	-	-	256 (9.06%)	-	2586 (91.48%)	108 (3.68%)	-	-	3 (2.78%)
Shi, Resurreccion	1,521	1265 (83.17%)	-	-	681 (53.83%)	-	584 (46.17%)	256 (16.83%)	-	-	154 (60.16%)
Riley	120,620	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	10,474	10336 (98.68%)	2904 (28.10%)	2107 (20.39%)	-	5310 (51.37%)	15 (0.15%)	70 (0.67%)	16 (22.86%)	15 (21.43%)	-
Edwards	209	118	-	-	31 (26.27%)	-	87	91	-	-	8 (8.79%)

		(56.46%)					(73.73%)	(43.54%)			
Reiter	235	175 (74.47%)	-	-	93 (53.14%)	82 (46.86%)	-	60 (25.53%)	-	-	13 (21.67%)
Izquierdo	71,192	NA (NA%)	-	-	-	-	-	1006 (1.41%)	111 (11.03%)	-	-
Ward	99,908	94416 (94.50%)	10202 (10.81%)	-	-	-	84214 (89.19%)	5492 (5.50%)	433 (7.88%)	-	-
Ebinger	6,062	5850 (96.50%)	99 (1.69%)	-	-	-	5668 (96.89%)	212 (3.50%)	3 (1.42%)	-	-
Salerno	15,920	14753 (92.67%)	-	-	5517 (37.40%)	8278 (56.11%)	958 (6.49%)	1167 (7.33%)	-	-	339 (29.05%)
Iversen	28,792	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	8,275,949	NA (NA%)	-	-	-	-	-	19486 (0.24%)	1354 (6.95%)	5715 (29.33%)	-
Fillmore	22,914	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%)	-	-
Petrilli	10,620	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	150,200	98567 (65.62%)	-	-	9624 (9.76%)	-	88943 (90.24%)	51633 (34.38%)	-	-	4366 (8.46%)
Ariza	351	322 (91.74%)	21 (6.52%)	-	-	-	301 (93.48%)	29 (8.26%)	3 (10.34%)	-	-
Carrat	14,393	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	4,554	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	88,747	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%)	-
Vila-Corcoles	2,324	1944 (83.65%)	-	-	-	-	-	380 (16.35%)	-	-	27 (7.11%)
O'Reilly	1,334	1284 (96.25%)	-	-	376 (29.28%)	-	908 (70.72%)	50 (3.75%)	-	-	4 (8.00%)
Ghinai	1,435	1004 (69.97%)	412 (41.04%)	155 (15.44%)	-	341 (33.96%)	96 (9.56%)	431 (30.03%)	113 (26.22%)	96 (22.27%)	-
Kortela	2,993	2419 (80.82%)	300 (12.40%)	340 (14.06%)	-	636 (26.29%)	1143 (47.25%)	574 (19.18%)	26 (4.53%)	80 (13.94%)	-
Gallichotte	239	190 (79.50%)	40 (21.05%)	28 (14.74%)	-	110 (57.89%)	-	49 (20.50%)	8 (16.33%)	12 (24.49%)	-

Saeed	173	69 (39.88%)	2 (2.90%)	-	-	-	67 (97.10%)	104 (60.12%)	9 (8.65%)	-	-
Woolcott	1,636,050	878840 (53.72%)	-	-	85816 (9.76%)	-	793024 (90.24%)	757210 (46.28%)	-	-	57451 (7.59%
Barasa	394	277 (70.30%)	49 (17.69%)	105 (37.91%)	-	110 (39.71%)	13 (4.69%)	117 (29.70%)	9 (7.69%)	37 (31.62%)	-
Paleiron	1,688	409 (24.23%)	236 (57.70%)	77 (18.83%)	-	96 (23.47%)	-	1279 (75.77%)	579 (45.27%)	309 (24.16%)	-
Didikoglu	43,428	35695 (82.19%)	3919 (10.98%)	13841 (38.78%)	-	17939 (50.26%)	-	7733 (17.81%)	867 (11.21%)	2966 (38.36%)	-
Kantele	1,095	1059 (96.71%)	176 (16.62%)	272 (25.68%)	-	611 (57.70%)	-	36 (3.29%)	3 (8.33%)	11 (30.56%)	-
Polat	1,322	NA (NA%)	-	-	-	-	-	23 (1.74%)	4 (17.39%)	2 (8.70%)	-
Richard	8,344	6798 (81.47%)	1065 (15.67%)	1171 (17.23%)	-	4456 (65.55%)	106 (1.56%)	531 (6.36%)	47 (8.85%)	83 (15.63%)	-
Schubl	1,557	1392 (89.40%)	33 (2.37%)	-	-	-	1359 (97.63%)	165 (10.60%)	4 (2.42%)	-	-
Nezhadmoghadam	33,325	19958 (59.89%)	2151 (10.78%)	-	-	-	17807 (89.22%)	13367 (40.11%)	1251 (9.36%)	-	-
Mora	1,058	857 (81.00%)	40 (4.67%)	118 (13.77%)	-	698 (81.45%)	1 (0.12%)	201 (19.00%)	8 (3.98%)	36 (17.91%)	-
Molenaar	696	591 (84.91%)	29 (4.91%)	-	-	-	562 (95.09%)	105 (15.09%)	2 (1.90%)	-	-
Vila-Corcoles, Satue-Gracia, Vila-Rovira	4,113	3577 (86.97%)	591 (16.52%)	-	-	-	2986 (83.48%)	536 (13.03%)	41 (7.65%)	-	-
Gegout Petit	2,006	1964 (97.91%)	334 (17.01%)	-	-	1545 (78.67%)	85 (4.33%)	42 (2.09%)	4 (9.52%)	-	-
Leister	3,301	3269 (99.03%)	764 (23.37%)	-	-	-	2505 (76.63%)	32 (0.97%)	5 (15.62%)	-	-

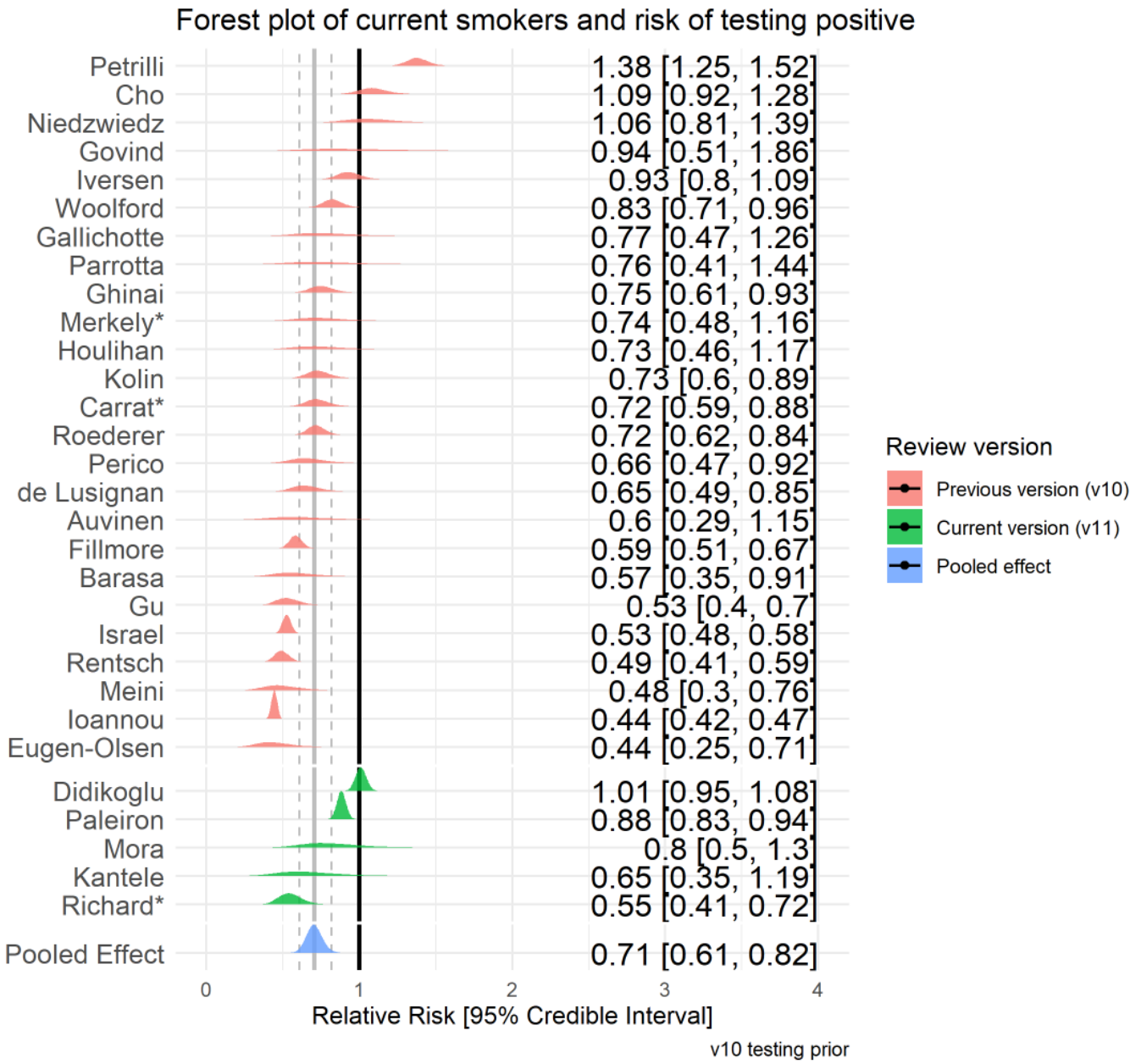

Figure 3. Forest plot for risk of testing positive for SARS-CoV-2 in current vs. never smokers. * Indicates 'good' quality studies. The prior from the previous review version (v10) was RR = 0.69.

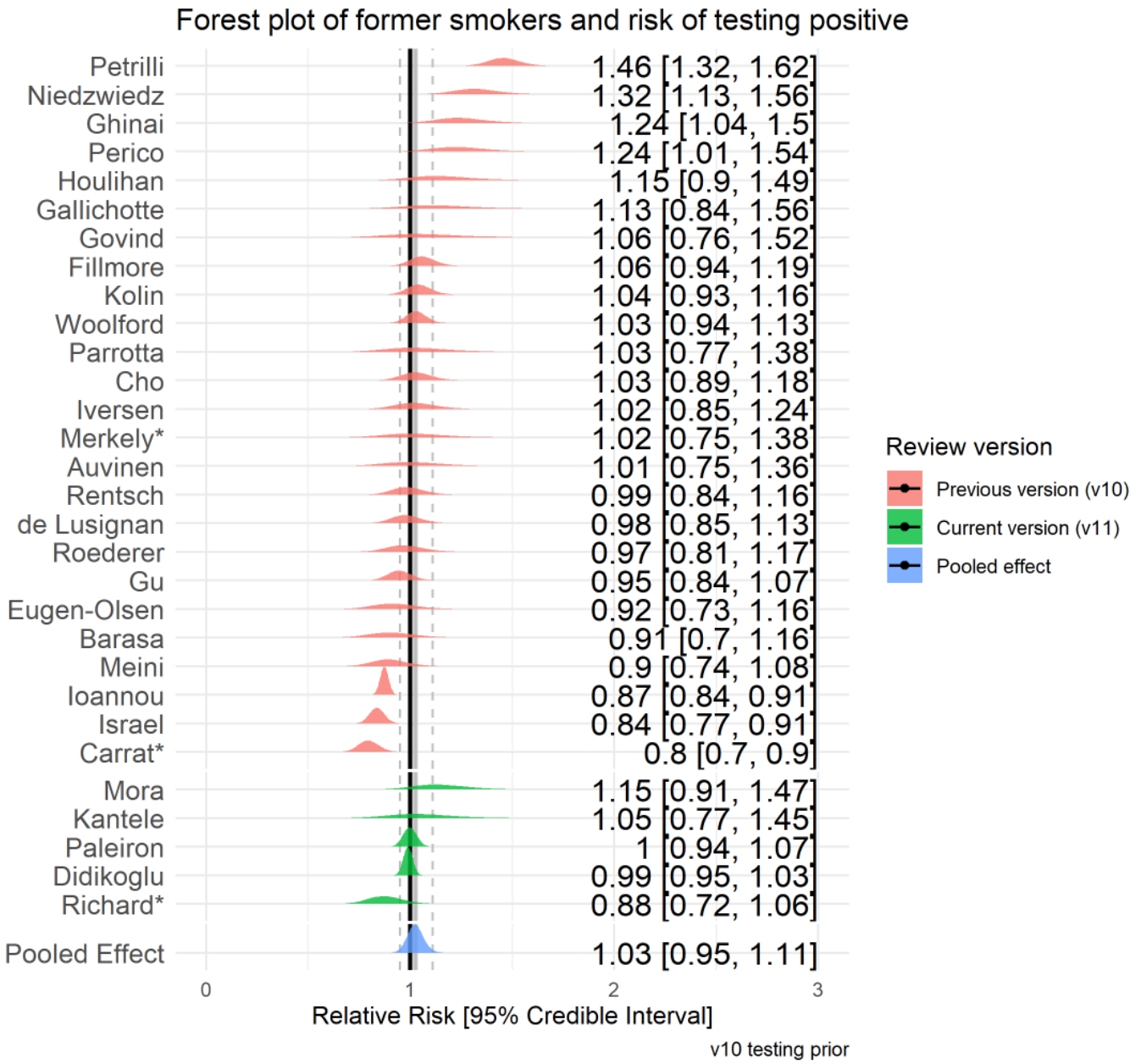

Figure 4. Forest plot for risk of testing positive for SARS-CoV-2 in former vs. never smokers. * Indicates 'good' quality studies. The prior from the previous review version (v10) was RR = 1.02.

Hospitalisation for COVID-19 by smoking status

48 studies examined hospitalisation for COVID-19 disease, stratified by smoking status (see Table 3). Meta-analyses were performed for 16 'fair' quality studies (see Figure 5 and 6). Current (RR = 1.1, 95% CrI = 0.99-1.21, τ = 0.15) and former (RR = 1.19, CrI = 1.1-1.29, τ = 0.13) 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 49% and 98%, respectively. Results were materially unchanged in two sensitivity analyses.

Table 3 COVID-19 hospitalsation 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)	6,637	5143 (77%)	61 (1.19%)	80 (1.56%)	-	-	-	5002 (97.26%)	1494 (22%)	27 (1.81%)	78 (5.22%)	-
Argenziano	1,000	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	9,946	3922 (39%)	408 (10.40%)	-	-	-	-	3514 (89.60%)	6024 (60%)	486 (8.07%)	-	-
Yanover	4,353	4180 (96%)	484 (11.58%)	118 (2.82%)	-	3578 (85.60%)	-	-	173 (3%)	30 (17.34%)	11 (6.36%)	-
Hamer	387,109	386349 (99%)	37333 (9.66%)	134542 (34.82%)	-	214474 (55.51%)	-	-	760 (0%)	93 (12.24%)	313 (41.18%)	-
Heili-Frades	4,712	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	102,875	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	89,756	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 (58%)	-	-	37 (11.90%)	222 (71.38%)	-	52 (16.72%)	220 (41%)	-	-	54 (
Nguyen	689	333 (48%)	-	-	57 (17.12%)	-	-	276 (82.88%)	356 (51%)	-	-	114
Mendy	689	473	-	-	84 (17.76%)	-	-	389	216	-	-	86 (

		(68%)						(82.24%)	(31%)			
Soares	10,713	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	1,006	743 (73%)	52 (7.00%)	-	-	-	691 (93.00%)	-	263 (26%)	16 (6.08%)	-	-
Rizzo	76,819	60039 (78%)	3931 (6.55%)	11379 (18.95%)	-	30042 (50.04%)	-	14687 (24.46%)	16780 (21%)	1254 (7.47%)	4585 (27.32%)	-
Pan	12,084	8548 (70%)	-	-	1263 (14.78%)	-	-	7285 (85.22%)	3536 (29%)	-	-	874
Petrilli	5,279	2538 (48%)	147 (5.79%)	337 (13.28%)	-	1678 (66.12%)	-	376 (14.81%)	2741 (51%)	141 (5.14%)	565 (20.61%)	-
Vilar-Garcia	328,892	291254 (88%)	64792 (22.25%)	-	-	-	-	226462 (77.75%)	37638 (11%)	9526 (25.31%)	-	-
Ibarra-Nava	416,546	302693 (72%)	26773 (8.84%)	-	-	-	-	275920 (91.16%)	113853 (27%)	8875 (7.80%)	-	-
Dashti	12,347	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	26,676	13706 (51%)	944 (6.89%)	2166 (15.80%)	-	10596 (77.31%)	-	-	12970 (48%)	880 (6.78%)	1936 (14.93%)	-
Ioannou	10,131	6624 (65%)	716 (10.81%)	2484 (37.50%)	-	2542 (38.38%)	-	882 (13.32%)	3507 (34%)	419 (11.95%)	1593 (45.42%)	-
Zhang, Li	1,596	576 (36%)	63 (10.94%)	190 (32.99%)	-	318 (55.21%)	-	5 (0.87%)	1020 (63%)	116 (11.37%)	429 (42.06%)	-
Parra-Bracamonte	331,298	235840 (71%)	-	-	16676 (7.07%)	-	-	219164 (92.93%)	95458 (28%)	-	-	751
Jehi	4,536	3578 (78%)	247 (6.90%)	943 (26.36%)	-	1795 (50.17%)	-	593 (16.57%)	958 (21%)	82 (8.56%)	349 (36.43%)	-
Arleo	70	36 (51%)	1 (2.78%)	10 (27.78%)	-	25 (69.44%)	-	-	34 (48%)	0 (0.00%)	10 (29.41%)	-
Kortela	604	246 (40%)	12 (4.88%)	14 (5.69%)	-	55 (22.36%)	-	165 (67.07%)	328 (54%)	14 (4.27%)	66 (20.12%)	-
Didikoglu	7,733	5239 (67%)	554 (10.57%)	1845 (35.22%)	-	2841 (54.23%)	-	-	2494 (32%)	313 (12.55%)	1121 (44.95%)	-
Ho, Narasimhan	9,991	5082 (50%)	189 (3.72%)	744 (14.64%)	-	4148 (81.62%)	-	-	4909 (49%)	217 (4.42%)	1062 (21.63%)	-
Saurabh	911	69 (7%)	6 (8.70%)	0 (0.00%)	-	63 (91.30%)	-	-	842 (92%)	68 (8.08%)	6 (0.71%)	-
Munoz	314	294 (93%)	20 (6.80%)	-	-	-	-	274 (93.20%)	20 (6%)	1 (5.00%)	-	-
Cummins	1,781	586 (32%)	77 (13.14%)	-	-	-	-	509 (86.86%)	1195 (67%)	104 (8.70%)	-	-

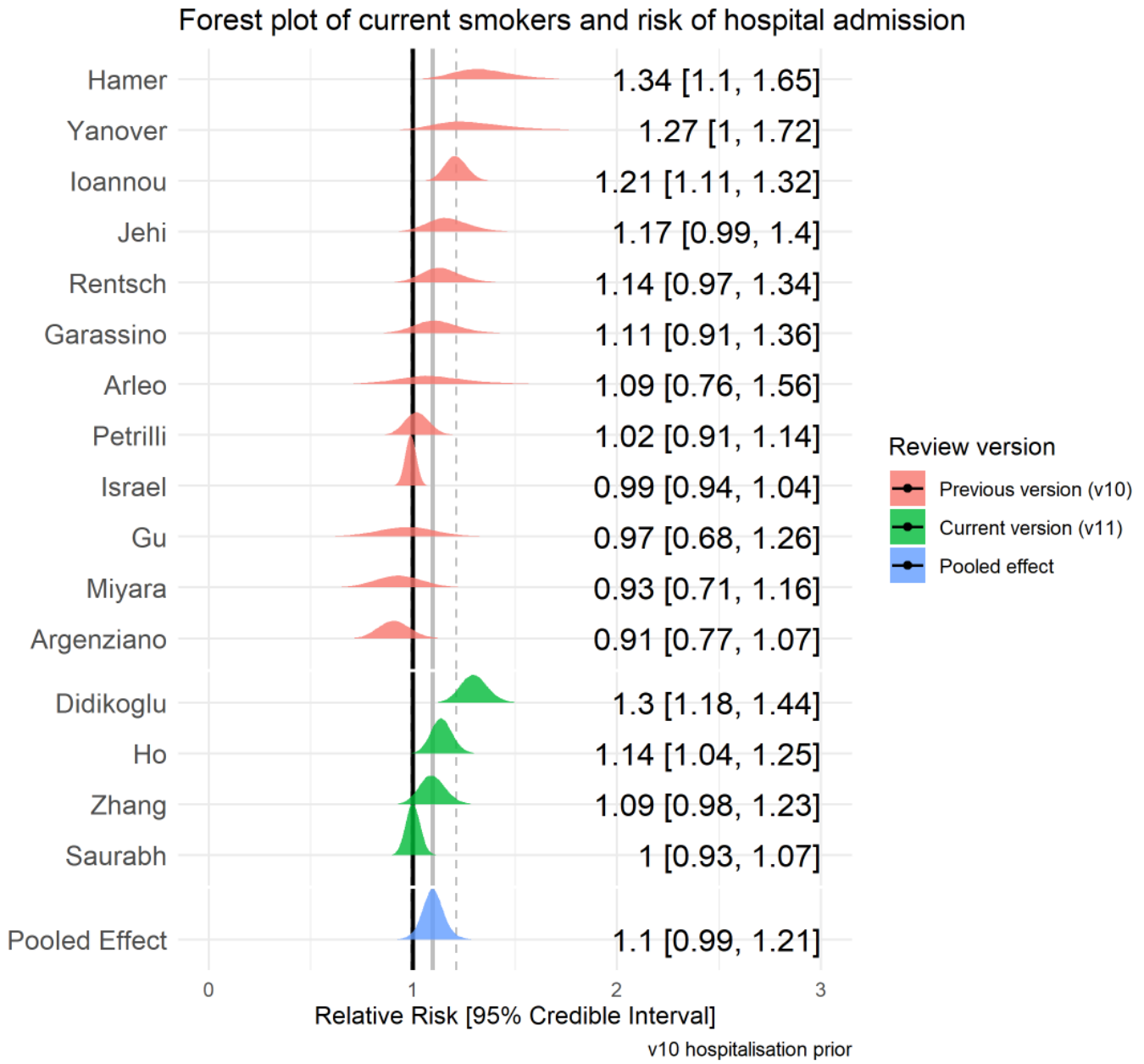

Figure 5. Forest plot for risk of hospitalisation in current vs. never smokers. The prior from the previous review version (v10) was RR = 1.08.

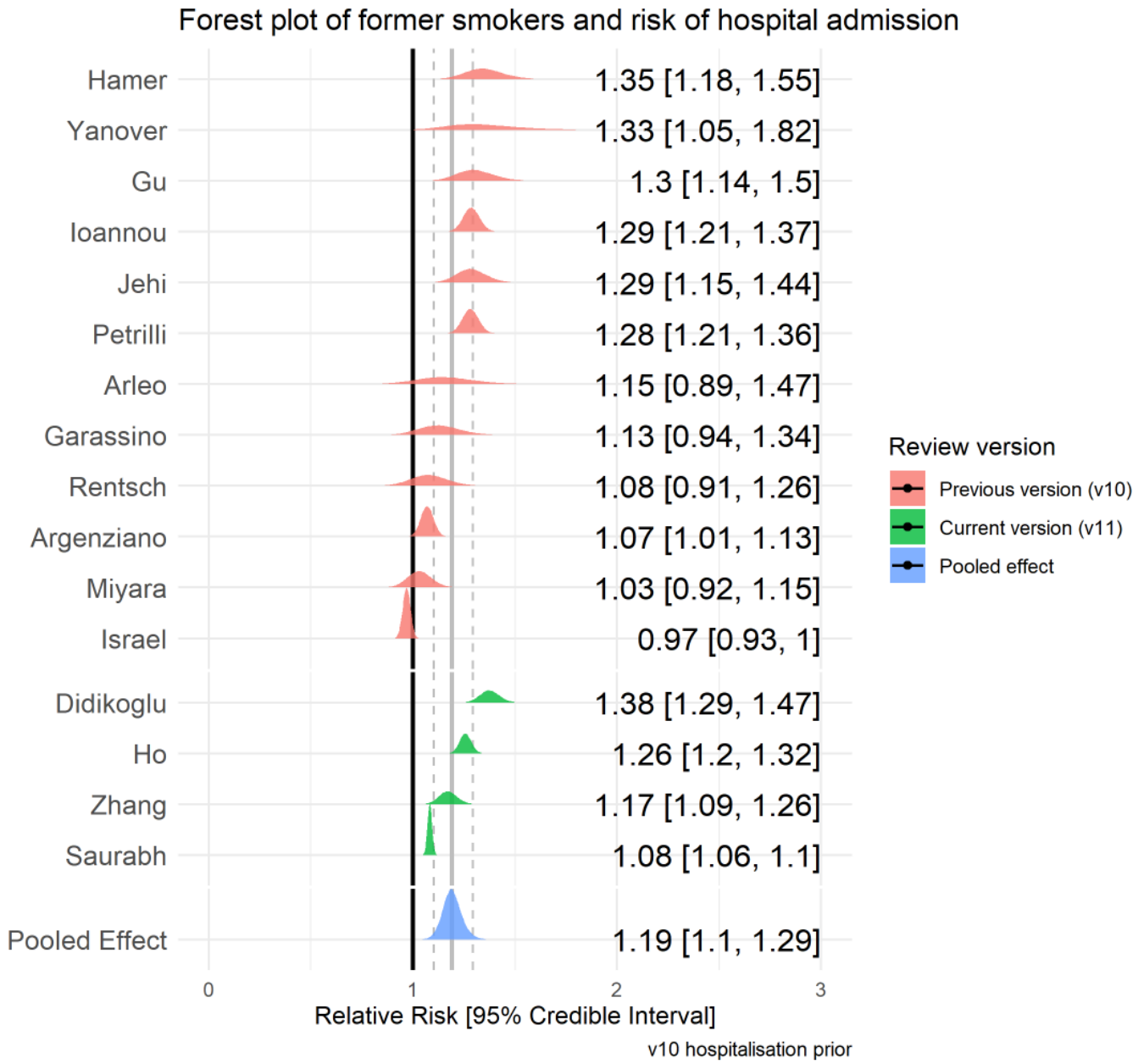

Figure 6. Forest plot for risk of hospitalisation in former vs. never smokers. The prior from the previous version (v10) was RR = 1.18.

Disease severity by smoking status

85 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 11 'fair' quality studies (see Figure 7 and 8). Current (RR = 1.26, 95% CrI = 0.92-1.73, τ = 0.32) and former (RR = 1.8, 95% CrI = 1.27-2.55, τ = 0.46) compared with never smokers were at increased risk of greater disease severity. However, while data for current smokers only were inconclusive, they 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 >99%,

respectively. Results were materially unchanged in two sensitivity analyses.

Table 4 **COVID-19 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	1,085	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 (NaN%)	0 (NaN%)	-
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%)	-	-
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%)	-	-	1(
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	2,490	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	89,756	78050 (86%)	6322 (8.10%)	-	-	-	71728 (91.90%)	-	11706 (13%)	1089 (9.30%)	-	-
Cen	1,007	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%)	-
Russell	156	128 (82%)	9 (7.03%)	31 (24.22%)	-	51 (39.84%)	-	37 (28.91%)	28 (17%)	2 (7.14%)	8 (28.57%)	-
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%)	-
Mendy	689	598 (86%)	-	-	133 (22.24%)	-	-	465 (77.76%)	91 (13%)	-	-	37
Jin, Gu	6	2 (33%)	-	-	0 (0.00%)	-	-	2 (100.00%)	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	7,345	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%)	-
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 (NA%)	-	-	-	-	-	-	1286 (NA%)	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%)	-	-
Petrilli	2,729	1739 (63%)	97 (5.58%)	325 (18.69%)	-	1067 (61.36%)	-	250 (14.38%)	990 (36%)	44 (4.44%)	236 (23.84%)	-
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	1,042	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	1,706	NA (NA%)	-	-	-	-	-	-	1706 (100%)	235 (13.77%)	699 (40.97%)	-
Lamure	89	NA (NA%)	-	-	-	-	-	-	25 (28%)	1 (4.00%)	5 (20.00%)	-
Zhou, He, Yang	1,087	990 (91%)	-	-	849 (85.76%)	141 (14.24%)	-	-	97 (8%)	-	-	75
Zhou, Qin	51	NA (NA%)	-	-	-	-	-	-	51 (100%)	-	-	40
Zhan, Liu	405	257 (63%)	-	-	21 (8.17%)	236 (91.83%)	-	-	148 (36%)	-	-	25
Li, Long, Zhang	954	838 (87%)	-	-	34 (4.06%)	804 (95.94%)	-	-	116 (12%)	-	-	22
Jakob	2,155	1400 (64%)	-	-	92 (6.57%)	99 (7.07%)	-	669 (47.79%)	755 (35%)	51 (6.75%)	58 (7.68%)	-
Aksu	123	34 (27%)	3 (8.82%)	-	-	-	31 (91.18%)	-	89 (72%)	11 (12.36%)	-	-

Adrish	1,173	162 (13%)	-	-	36 (22.22%)	-	126 (77.78%)	-	1011 (86%)	-	-	30
Hoertel, Sanchez, Vernet	12,210	11018 (90%)	921 (8.36%)	-	-	-	-	10097 (91.64%)	1192 (9%)	181 (15.18%)	-	-
Vila-Corcoles, Satue-Gracia	282	218 (77%)	-	-	21 (9.63%)	-	-	197 (90.37%)	64 (22%)	-	-	4
Boyd	38	0 (0%)	-	-	-	-	-	-	38 (100%)	-	-	2
Caliskan	565	474 (83%)	96 (20.25%)	45 (9.49%)	-	333 (70.25%)	-	-	91 (16%)	22 (24.18%)	34 (37.36%)	-
Ebrahimian	226	134 (59%)	-	-	12 (8.96%)	-	122 (91.04%)	-	92 (40%)	-	-	12
Ho, Narasimhan	4,909	3859 (78%)	169 (4.38%)	833 (21.59%)	-	-	2857 (74.03%)	-	1050 (21%)	48 (4.57%)	229 (21.81%)	-
Quan	2,038	1452 (71%)	-	549 (37.81%)	-	-	-	903 (62.19%)	586 (28%)	-	-	26
Saurabh	911	783 (85%)	65 (8.30%)	3 (0.38%)	-	715 (91.32%)	-	-	128 (14%)	9 (7.03%)	3 (2.34%)	-
Chousein	114	94 (82%)	17 (18.09%)	17 (18.09%)	-	60 (63.83%)	-	-	20 (17%)	2 (10.00%)	6 (30.00%)	-
Tavakol	206	182 (88%)	-	-	24 (13.19%)	-	158 (86.81%)	-	24 (11%)	-	-	2
Yao, Hasegawa	101	78 (77%)	-	-	17 (21.79%)	-	71 (91.03%)	-	23 (22%)	-	-	12
Cummins	1,195	1043 (87%)	96 (9.20%)	-	-	-	-	947 (90.80%)	152 (12%)	9 (5.92%)	-	-
Nuno	4,730	3536 (74%)	333 (9.42%)	-	-	-	-	3203 (90.58%)	1194 (25%)	147 (12.31%)	-	-

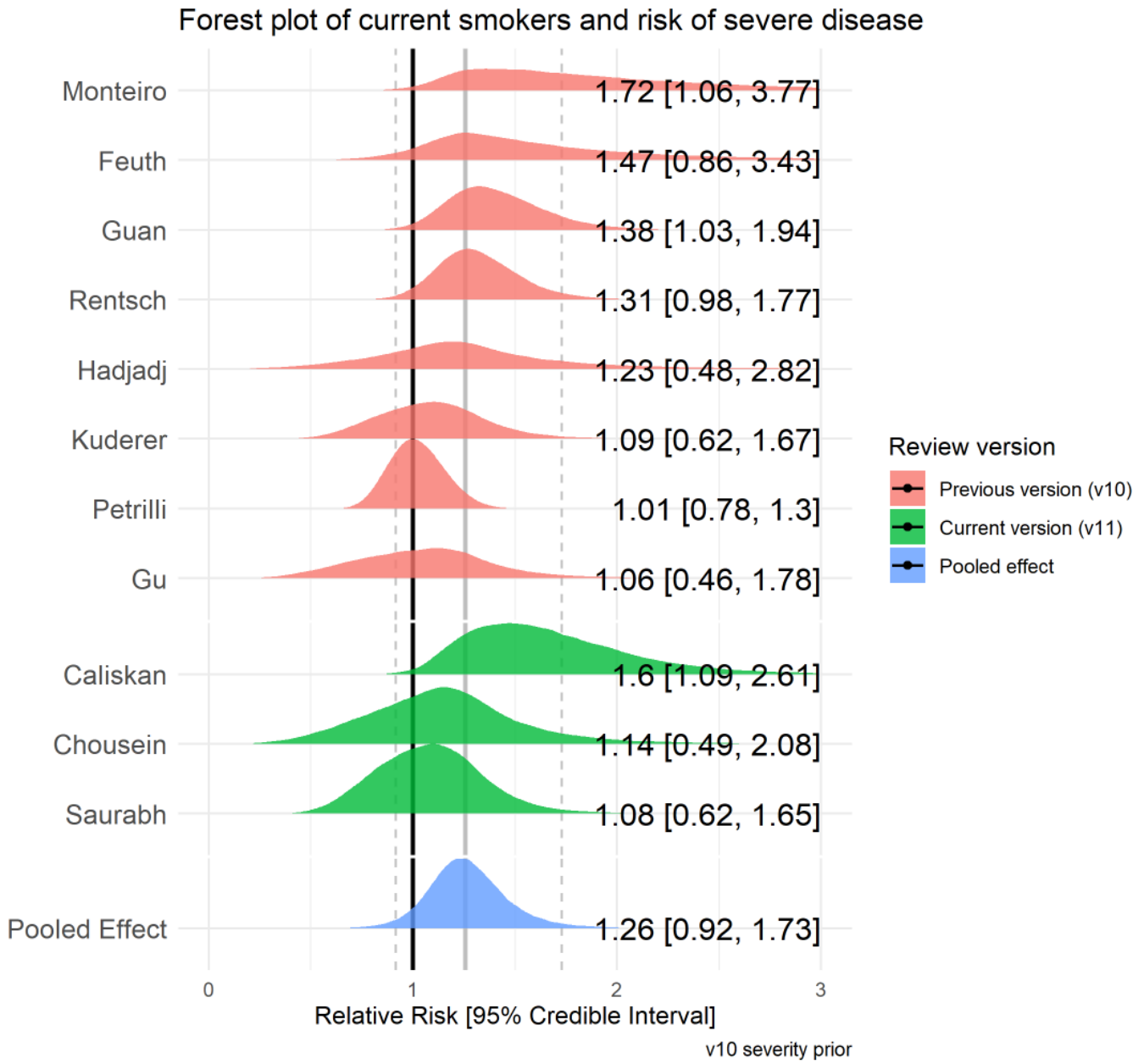

Figure 7. Forest plot for the risk of severe disease in current vs. never smokers. The prior from the previous review version (v10) was RR = 1.26.

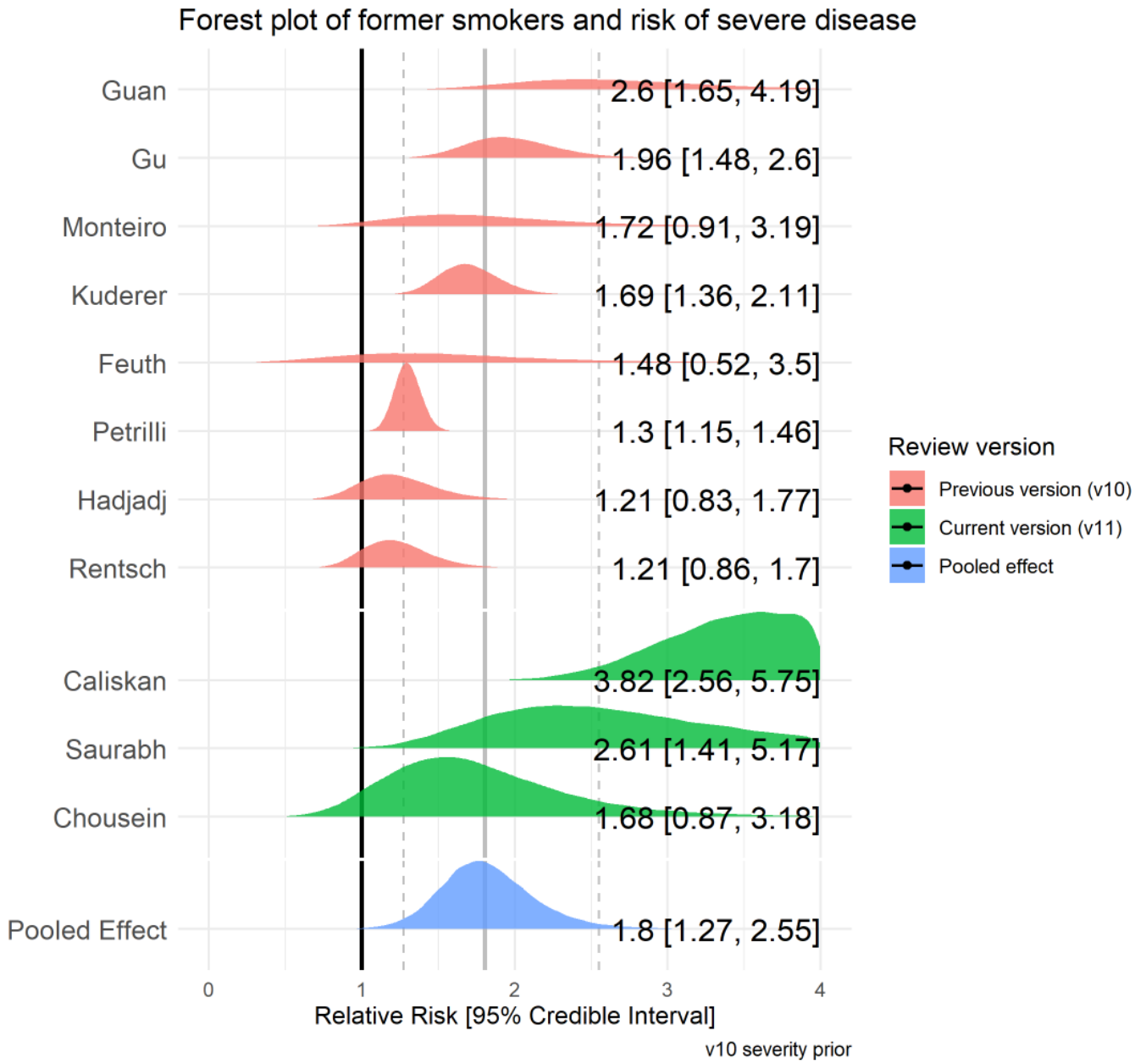

Figure 8. Forest plot for the risk of severe disease in former vs. never smokers. The prior from the previous review version (v10) was RR = 1.52.

Mortality by smoking status

89 studies reported mortality from COVID-19 by smoking status (see Table 5), with 19 'fair' quality studies included in meta-analyses (see Figure 9 and 10). Current (RR = 1.12, 95% CrI = 0.84-1.47, τ = 0.42) and former (RR = 1.56, 95% CrI = 1.23-2, τ = 0.43) 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 60% and >99%, respectively. Results were materially unchanged in two sensitivity analyses.

Table 5 COVID-19 attributed 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 (%)
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	2,226	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%)	-	-
Yao	108	96 (88%)	1 (1.04%)	-	-	-	-	95 (98.96%)	12 (11%)	3 (25.00%)	-
Carillo-Vega	9,946	8983 (90%)	795 (8.85%)	-	-	-	-	8188 (91.15%)	963 (9%)	99 (10.28%)	-
Ge	51	39 (76%)	6 (15.38%)	-	-	-	-	33 (84.62%)	12 (23%)	1 (8.33%)	-
Chen, Jiang	135	NA (NA%)	-	-	-	-	-	-	31 (22%)	-	-
Heili-Frades	4,712	4086 (86%)	210 (5.14%)	659 (16.13%)	-	-	3217 (78.73%)	-	626 (13%)	23 (3.67%)	161 (25.72%)
Kim, Garg	2,490	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%)	-	-
Soto-Mota	400	200 (50%)	-	-	23 (11.50%)	-	-	177 (88.50%)	200 (50%)	-	-
Garibaldi	747	634 (84%)	36 (5.68%)	129 (20.35%)	-	-	-	469 (73.97%)	113 (15%)	6 (5.31%)	36 (31.86%)
Docherty	13,364	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	11,116	10498 (94%)	-	-	2771 (26.40%)	7727 (73.60%)	-	-	618 (5%)	-	-
Wang, Oekelen	57	43 (75%)	-	-	14 (32.56%)	-	-	29 (67.44%)	14 (24%)	-	-
Martinez-Portilla	224	217 (96%)	-	-	7 (3.23%)	-	-	210 (96.77%)	7 (3%)	-	-
Cen	1,007	964 (95%)	-	-	87 (9.02%)	-	-	877 (90.98%)	43 (4%)	-	-
Klang	3,406	2270 (66%)	-	-	492 (21.67%)	-	-	1778 (78.33%)	1136 (33%)	-	-

Wang, Zhong	5,510	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%)	-	-
Zeng	1,031	866 (84%)	-	-	69 (7.97%)	-	-	797 (92.03%)	165 (16%)	-	-
Chen, Yu	1,859	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%)
Zhou, He	-	NA (NA%)	-	-	-	-	-	-	NA (NA%)	-	-
Sigel	88	70 (79%)	-	-	37 (52.86%)	-	-	33 (47.14%)	18 (20%)	-	-
Nguyen	356	308 (86%)	-	-	91 (29.55%)	-	-	217 (70.45%)	45 (12%)	-	-
de Souza	8,443	7826 (92%)	-	-	95 (1.21%)	-	7571 (96.74%)	160 (2.04%)	617 (7%)	-	-
Mendy	532	663 (124%)	-	-	160 (24.13%)	-	-	503 (75.87%)	26 (4%)	-	-
Shi, Resurreccion	256	210 (82%)	-	-	128 (60.95%)	-	-	82 (39.05%)	46 (17%)	-	-
Xie	619	591 (95%)	-	-	43 (7.28%)	-	-	548 (92.72%)	28 (4%)	-	-
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%)	-	-
Soares	1,152	696 (60%)	38 (5.46%)	-	-	-	658 (94.54%)	-	456 (39%)	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	1,645	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%)
Fillmore	1,794	1566 (87%)	408 (26.05%)	758 (48.40%)	-	279 (17.82%)	-	98 (6.26%)	228 (12%)	44 (19.30%)	141 (61.84%)
Pan	3,536	3302 (93%)	-	-	862 (26.11%)	-	-	2440 (73.89%)	234 (6%)	-	-
Zhao, Chen	474	398 (83%)	87 (21.86%)	-	-	-	-	311 (78.14%)	82 (17%)	36 (43.90%)	-
Holman	10,989	NA	-	-	-	-	-	-	10989	609	4684

Hofman	10,989	NA (NA%)	-	-	-	-	-	-	1089 (100%)	60 (5.54%)	464 (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%)	-	-
Vilar-Garcia	328,892	316605 (96%)	71215 (22.49%)	-	-	-	-	245390 (77.51%)	12287 (3%)	3103 (25.25%)	-
Ibarra-Nava	416,546	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%)	-
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	3,401	2892 (85%)	190 (6.57%)	689 (23.82%)	-	1756 (60.72%)	-	257 (8.89%)	509 (14%)	20 (3.93%)	171 (33.60%)
Nicholson	1,040	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	13,658	11495 (84%)	785 (6.83%)	2450 (21.31%)	-	5450 (47.41%)	2810 (24.45%)	-	2163 (15%)	81 (3.74%)	642 (29.68%)
Ioannou	10,131	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	5,051	4635 (91%)	162 (3.50%)	709 (15.30%)	-	2394 (51.65%)	-	1370 (29.56%)	416 (8%)	17 (4.09%)	105 (25.24%)
Zinellu	105	77 (73%)	24 (31.17%)	8 (10.39%)	-	45 (58.44%)	-	-	28 (26%)	8 (28.57%)	3 (10.71%)
Zhang, Li	399	NA (NA%)	-	-	-	-	-	-	399 (100%)	60 (15.04%)	186 (46.62%)
Wang, Shu	59	18 (30%)	-	-	0 (0.00%)	-	-	18 (100.00%)	41 (69%)	-	-
Wang, Zheutlin	2,448	1706 (69%)	57 (3.34%)	315 (18.46%)	-	954 (55.92%)	-	380 (22.27%)	742 (30%)	25 (3.37%)	197 (26.55%)
Torres-Macho	1,968	1643 (83%)	-	-	335 (20.39%)	-	-	1308 (79.61%)	325 (16%)	-	-
Raines	440	408 (92%)	-	-	222 (54.41%)	186 (45.59%)	-	-	32 (7%)	-	-
Parra-Bracamonte	331,298	292988 (88%)	-	-	21269 (7.26%)	-	-	271719 (92.74%)	38310 (11%)	-	-
Li, Long, Zhang	954	876 (91%)	-	-	48 (5.48%)	828 (94.52%)	-	-	78 (8%)	-	-
Bellan	407	285 (70%)	30 (10.53%)	-	-	-	191 (67.02%)	64 (22.46%)	122 (29%)	24 (19.67%)	-
Alharthy	352	239 (67%)	109 (45.61%)	-	-	-	130 (54.39%)	-	113 (32%)	65 (57.52%)	-
Adrish	1,173	783 (66%)	-	-	205 (26.18%)	578 (73.82%)	-	-	390 (33%)	-	-

Hoertel, Sanchez, Vernet	12,210	12210 (100%)	898 (7.35%)	-	-	-	-	9904 (81.11%)	1408 (11%)	204 (14.49%)	-
Sourij	238	180 (75%)	4 (2.22%)	26 (14.44%)	-	150 (83.33%)	-	-	58 (24%)	0 (0.00%)	12 (20.69%)
Simons	446	318 (71%)	30 (9.43%)	109 (34.28%)	-	179 (56.29%)	-	-	128 (28%)	12 (9.38%)	63 (49.22%)
Bisso	168	122 (72%)	13 (10.66%)	-	-	-	-	109 (89.34%)	46 (27%)	5 (10.87%)	-
Caliskan	565	490 (86%)	97 (19.80%)	48 (9.80%)	-	345 (70.41%)	-	-	75 (13%)	21 (28.00%)	31 (41.33%)
Ebrahimian	226	128 (56%)	-	-	9 (7.03%)	-	119 (92.97%)	-	98 (43%)	-	-
Estiri	16,709	15879 (95%)	-	-	1304 (8.21%)	-	-	14575 (91.79%)	830 (4%)	-	-
Ferrari	198	165 (83%)	-	-	27 (16.36%)	138 (83.64%)	-	-	33 (16%)	-	-
Ho, Narasimhan	4,909	3553 (72%)	163 (4.59%)	743 (20.91%)	-	2647 (74.50%)	-	-	1356 (27%)	54 (3.98%)	319 (23.53%)
Mansour	111	83 (74%)	5 (6.02%)	-	-	-	-	78 (93.98%)	28 (25%)	6 (21.43%)	-
Park	2,269	2105 (92%)	92 (4.37%)	-	-	-	-	2013 (95.63%)	164 (7%)	2 (1.22%)	-
Quan	2,038	1587 (77%)	-	-	589 (37.11%)	-	-	998 (62.89%)	442 (21%)	-	-
Saurabh	911	870 (95%)	70 (8.05%)	4 (0.46%)	-	796 (91.49%)	-	-	41 (4%)	4 (9.76%)	2 (4.88%)
Strangfeld	3,729	3339 (89%)	-	-	664 (19.89%)	2190 (65.59%)	-	485 (14.53%)	390 (10%)	-	-
Nezhadmoghadam	13,367	7757 (58%)	686 (8.84%)	-	-	-	-	7071 (91.16%)	5610 (41%)	565 (10.07%)	-
Nuno	4,730	4401 (93%)	427 (9.70%)	-	-	-	-	3974 (90.30%)	329 (6%)	53 (16.11%)	-

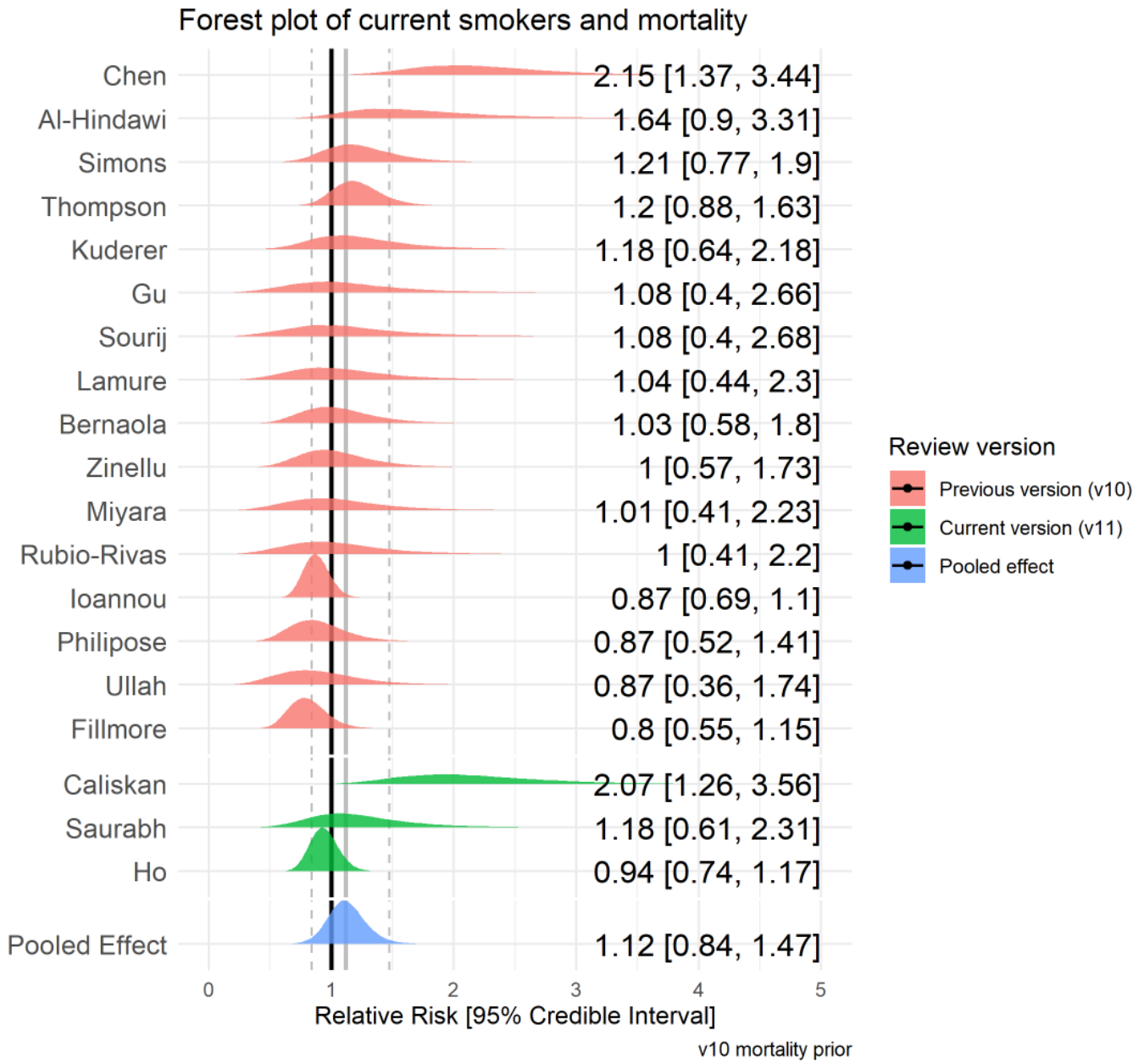

Figure 9. Forest plot for the risk of mortality in current vs. never smokers. The prior from the previous review version (v10) was RR = 1.05.

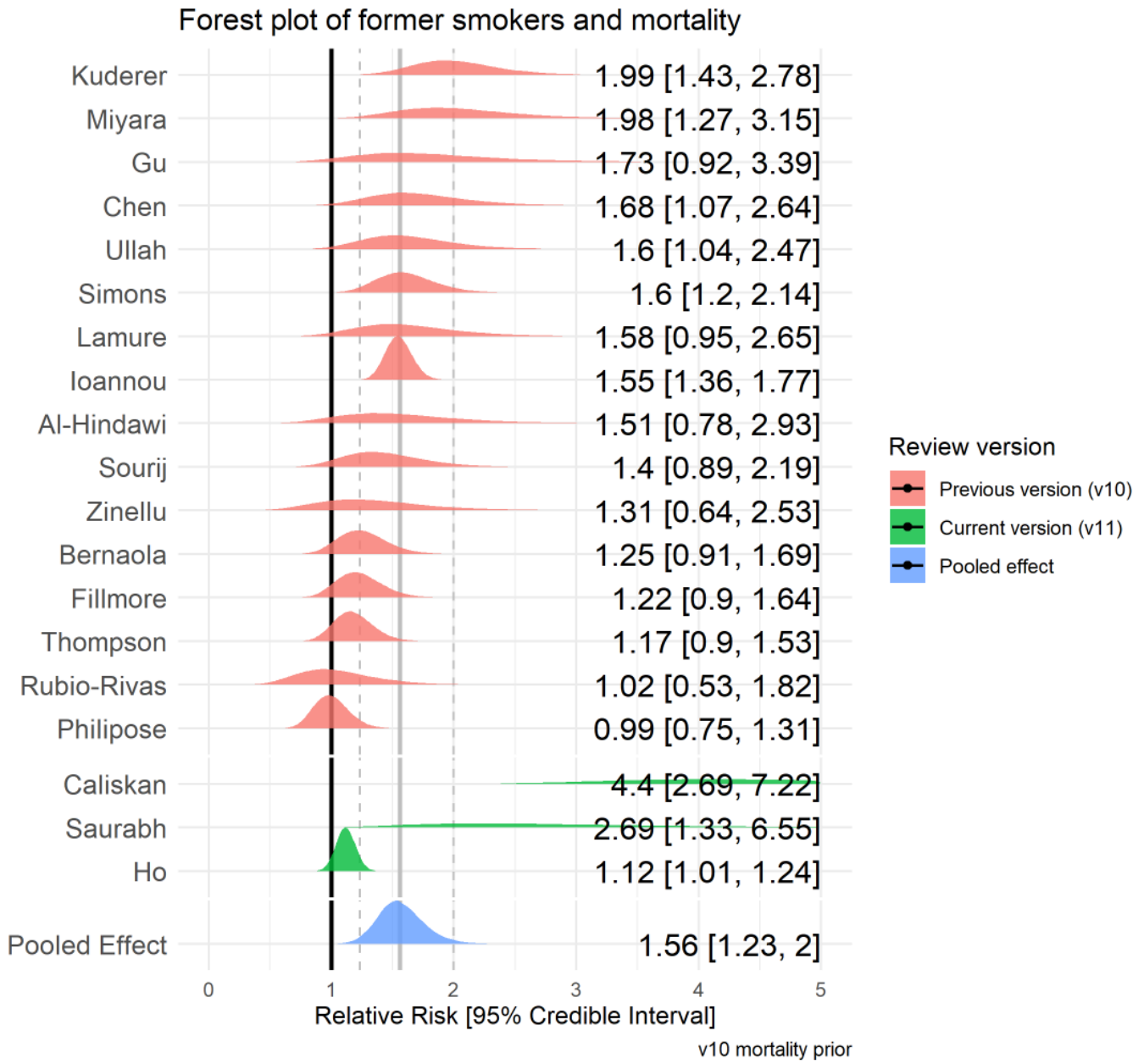

Figure 10. Forest plot for the risk of mortality in former smokers vs. never smokers. The prior from the previous version (v10) was RR = 1.40.

Discussion

This living rapid review found uncertainty in the majority of 405 studies arising from the recording of smoking status. Notwithstanding this uncertainty, compared with overall adult national prevalence estimates, recorded current smoking rates in most studies were lower than expected. In a subset of good and fair quality studies (n = 30), 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 (CMMID COVID-19 working group et al., 2020), 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 and may be confounded with smoking. For example, the household secondary attack rate for COVID-19 is estimated at 17% (Fung et al., 2020).

   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 (Conti et al., 1999). However, as SARS-CoV-2 is an enveloped virus (Schoeman and Fielding, 2019), 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 (Buitrago-Garcia et al., 2020), with some evidence suggesting younger people are more likely to be asymptomatic (Kronbichler et al., 2020). Testing is hence likely limited in some subgroups, with the potential for these groups to include an overrepresentation of current smokers.

   ii) On the other hand, 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 (Hopkinson et al., 2020). 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 (Merkely et al., 2020); 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, two further representative population surveys (Carrat et al., 2020; Richard et al., 2020) reported a current smoking rate of more than 10 percentage points below national prevalence (12% vs. 25% and 15% vs. 27% daily smoking prevalence, respectively) (Andler, 2019; FSO,

2020).

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 (Brown, 2020).

   ii) Diagnostic criteria for SARS-CoV-2 infection and COVID-19 have changed during the course of the pandemic (Organisation, n.d.). 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 (Lusignan et al., 2020).

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 (Griffith et al., 2020), 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) (Murray, 2020).

   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 (Polubriaginof et al., 2018). Known failings of EHRs include implausible longitudinal changes, such as former smokers being recorded as never smokers at subsequent hospital visits (Polubriaginof et al., 2018). 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 (Benowitz et al., 2009). 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 (Mangera et al., 2017).

   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 (Farsalinos, Niaura, et al., 2020).

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.

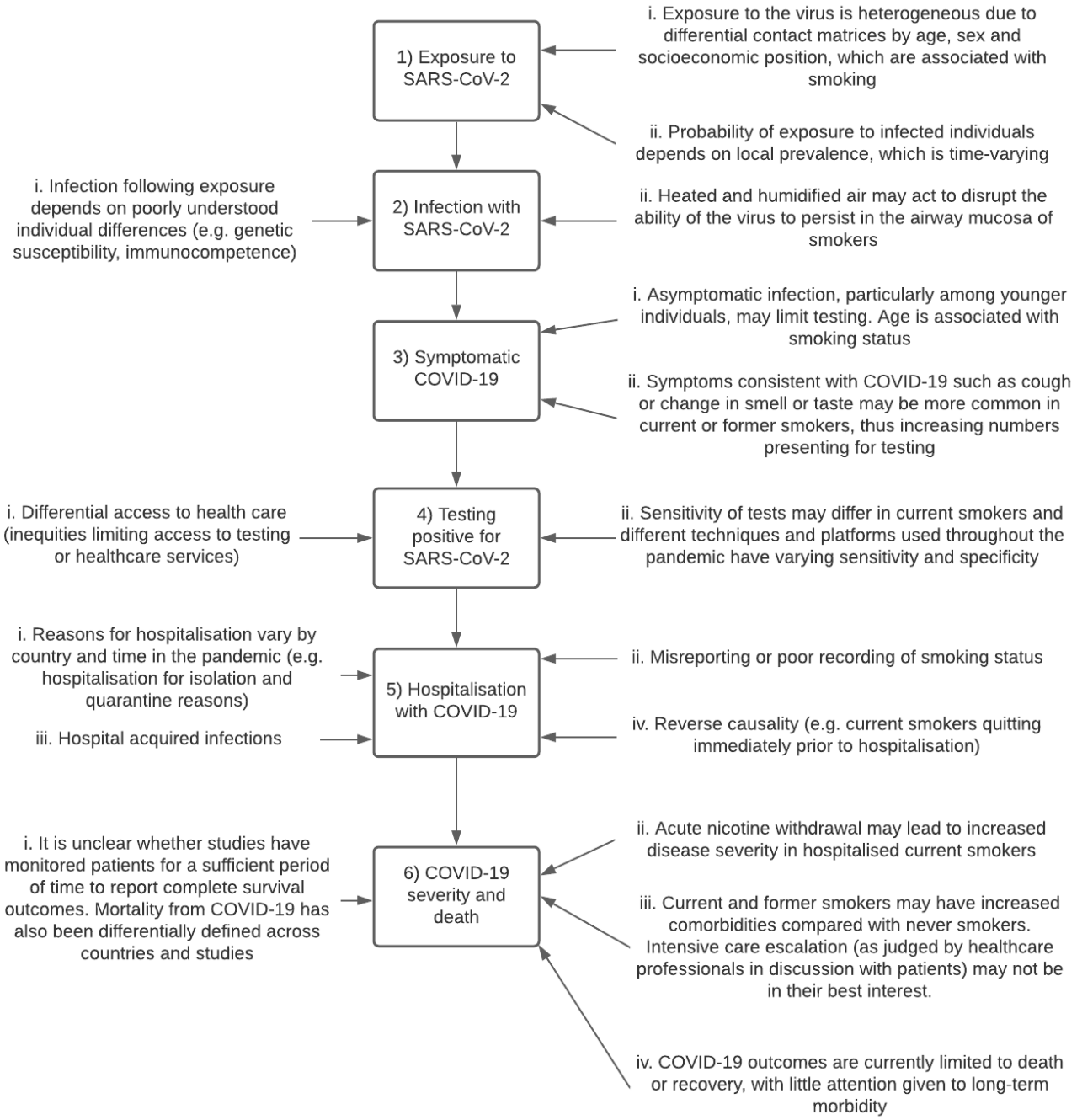

Figure 11. A schematic of some of the interpretation issues for the association of smoking status and COVID-19 infection, hospitalisation, disease severity and mortality. Numbers refer to the issues listed in-text in the above section. Issues presented on the right-hand side relate directly to smoking 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) (Bowyer et al., 2020; Hopkinson et al., 2020; Jackson et al., 2020). We also did not include a large, UK-based, representative seroprevalence study (Ward et al., 2020) 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 (Farsalinos, Barbouni, et al., 2020).

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 (Shahab et al., 2013) 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 (Stead et al., 2013). 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 405 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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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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Review versions

The most up-to-date review version is available here

Previous review versions

- Version 1
- Version 2
- Version 3
- Version 4

- Version 5
- Version 6
- Version 7
- Version 8
- Version 9
- Version 10

Data availability

All data contributing to the current and future review versions are available here

All code required to reproduce the current and future analyses are available here

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