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RESEARCH ARTICLE

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Estimation of the COVID-19 mean incubation time: Systematic review, meta-analysis, and sensitivity analysis

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Abstract

Providing sensible estimates of the mean incubation time for COVID-19 is important yet complex. This study aims to provide synthetic estimates of the mean incubation time of COVID-19 by capitalizing on available estimates reported in the literature and exploring different ways to accommodate heterogeneity involved in the reported studies. Online databases between January 1, 2020 and May 20, 2021 are first searched to obtain estimates of the mean incubation time of COVID-19, and meta-analyses are then conducted to generate synthetic estimates. Heterogeneity of the studies is examined via the use of Cochran's Q statistic and Higgin's & Thompson's I^2 statistic, and subgroup analyses are conducted using mixed effects models. The publication bias issue is assessed using the funnel plot and Egger's test. Using all those reported mean incubation estimates for COVID-19, the synthetic mean incubation time is estimated to be 6.43 days with a 95% confidence interval (CI) [5.90, 6.96], and using all those reported mean incubation estimates together with those transformed median incubation estimates, the estimated mean incubation time is 6.07 days with a 95% CI [5.70, 6.45]. The reported estimates of the mean incubation time of COVID-19 vary considerably due to multiple reasons, including heterogeneity and publication bias. To alleviate these issues, we take different angles to provide a sensible estimate of the mean incubation time of COVID-19. Our analyses show that the mean incubation time of COVID-19 between January 1, 2020 and May 20, 2021 ranges from 5.68 to 8.30 days.

KEYWORDS
COVID-19, heterogeneity, mean incubation time, meta-analysis, publication bias, sensitivity analysis

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) has tremendously impacted public health and the economy. Much research has been conducted to understand its clinical characteristics. An interesting question concerns the COVID-19 incubation time, which is defined as the time from infection of SARS-CoV-2 to the onset of clinical symptoms.[1] As the COVID-19 incubation time varies from patient to patient, it is helpful to estimate the mean incubation time of the population.

Understanding the mean incubation time is of great significance for many reasons. Most obviously, knowing the mean incubation time gives us a valuable metric to develop strategies for isolation or quarantine. Having a sensible estimate of the mean incubation time helps us develop practical intervention steps. Moreover, in developing epidemic models, the mean incubation time is an important

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parameter to model transmission features of SARS-CoV-2, and different estimates of this parameter may significantly affect the outcomes.[2]

Due to its importance, many studies have been carried out to estimate the mean incubation time for COVID-19. However, the available studies do not reveal comparable estimates of the mean incubation time, and they vary considerably from 1.8 days in China[3] to 14 days in India.[4] It is difficult to assess which estimate more reasonably reflects the mean incubation time of the population because different studies are carried out for different subjects under different conditions. This article aims to provide synthetic estimates of the mean incubation time of COVID-19 by capitalizing on the reported estimates in the literature and exploring different ways to accommodate heterogeneity involved in the reported studies about COVID-19.

While some meta-analyses have offered synthetic estimates, many of those studies concentrated on early reports before June 2020, and some included only a small number of studies. To overcome those limitations, we conduct a thorough search for a longer study period from January 1, 2020 to May 20, 2021. We carry out meta-analyses from different perspectives to accommodate diverse information on the mean incubation time estimates. Our analyses consider both mean estimates and transformed estimates of the median incubation time. We carry out subgroup analyses and sensitivity analyses to investigate heterogeneity among the reported studies.

The rest of the manuscript is organized as follows. Section 2 presents the data collection procedures and the characteristics of the data. Section 3 describes the general procedures for meta-analyses. Section 4 analyzes the data using the methods described in Section 3, and Section 5 summarizes the analysis results. Section 6 includes discussions, and Section 7 outlines the limitations of the development.

2 | DATA COLLECTION

2.1 | Search strategy and selection criteria

We searched the articles published between January 1, 2020 and May 20, 2021 through four online databases: *Google Scholar*, *Web of Science*, *Scopus*, and *Collabovid*, as well as official journal websites, including *Lancet* and *Journal of American Medical Association*, where *Collabovid* comprises publications from *Elsevier*, *PubMed*, *medRxiv*, *bioRxiv*, and *arXiv*.

We began with an automatic search using the pairwise combinations of phrases from one of the following categories: (1) "*incubation*," "*incubation period*," and "*incubation time*"; (2) "*COVID-19*," "*SARS-CoV-2*," "*2019-nCoV*," "*2019nCoV*," and "*Novel Coronavirus*." This process identifies 611 articles. We conducted a manual examination and removed 93 duplicated articles in the second step. In the third step, we manually checked the references of the remaining 518 articles and found additional 17 papers that are relevant, yielding 535 articles in total. In the fourth step, we manually examined each report of the third step by checking the abstract to see whether the study is about the COVID-19 incubation time. The step excludes 375 articles. In the fifth step, we manually checked the full text for the remaining 160 articles and retained only those studies having the information on the sample size as well as the information about one of the following categories:

(a) having an estimate of the *mean* incubation time, together with its standard error (SE) or a 95% confidence interval (CI);
(b) having an estimate of the *median* incubation time, together with a 95% CI, or an interquartile range (IQR), or a range.

This step excludes 51 studies for not reporting an estimate of the mean or median incubation time, 2 studies for not reporting variability estimates associated with mean or median estimates, and 3 studies for not reporting the sample size. These procedures finally give us 104 papers with the needed estimation information about the mean or median incubation time of COVID-19. A summary of this process of gathering the data is presented in Figure 1, which is prepared using the flow chart template developed for systematic review and meta-analysis, available at the website www.prisma-statement.org.

2.2 | Data extraction and summary

Figure 2 categorizes those selected 104 papers by the estimation feature for mean or median time. Sixty-nine (N_1) studies merely report the information about estimates of the mean incubation time, and 35 (N_2) articles report only the information about estimates of the median incubation time. Those 69 (N_1) papers can be further grouped as 16 (N_{11}) papers containing meta-analysis results each derived from multiple studies, and 53 (N_{12}) papers each reporting results obtained from a single study, where in those 16 (N_{11}) papers, 1 (N_{111}) paper reports two estimates with one synthetic estimate derived from multiple studies using the meta-analysis method and the other estimate obtained from a single new study, and 15 (N_{112}) papers each reports a single estimate obtained from a meta-analysis. Of those 53 (N_{12}) papers, 1 (N_{121}) paper reports three mean estimates, 3 (N_{122}) papers each report two mean estimates, and 49 (N_{123}) papers each report a single estimate. Those 35 (N_2) papers consist of 1 (N_{21}) paper reporting two median estimates and 34 (N_{22}) papers each reporting a single median estimate.

We report those 104 papers searched in Section 2.1 by displaying the key information, including the last name of the first author, the study period, the region of study subjects, and the methodology, together with the sample size, the estimate of the mean or median COVID-19 incubation time, and the SE reported in the article or converted from the reported 95% CIs. Table 1 reports those 16 papers about meta-analysis of estimates of the mean incubation time, Table 2 summarizes these 54 papers which report 59 estimates of the mean incubation time of COVID-19, and Table 3

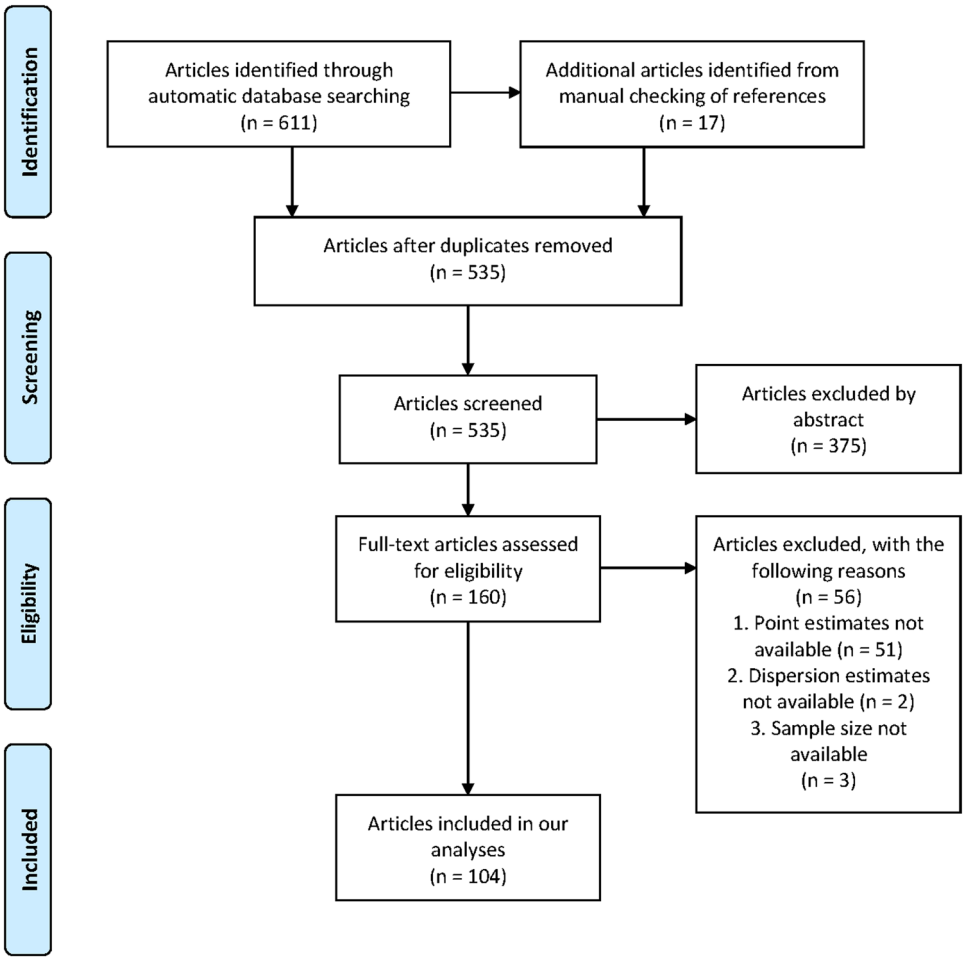

FIGURE 1 Flow diagram for gathering studies about estimation of the mean or median COVID-19 incubation time

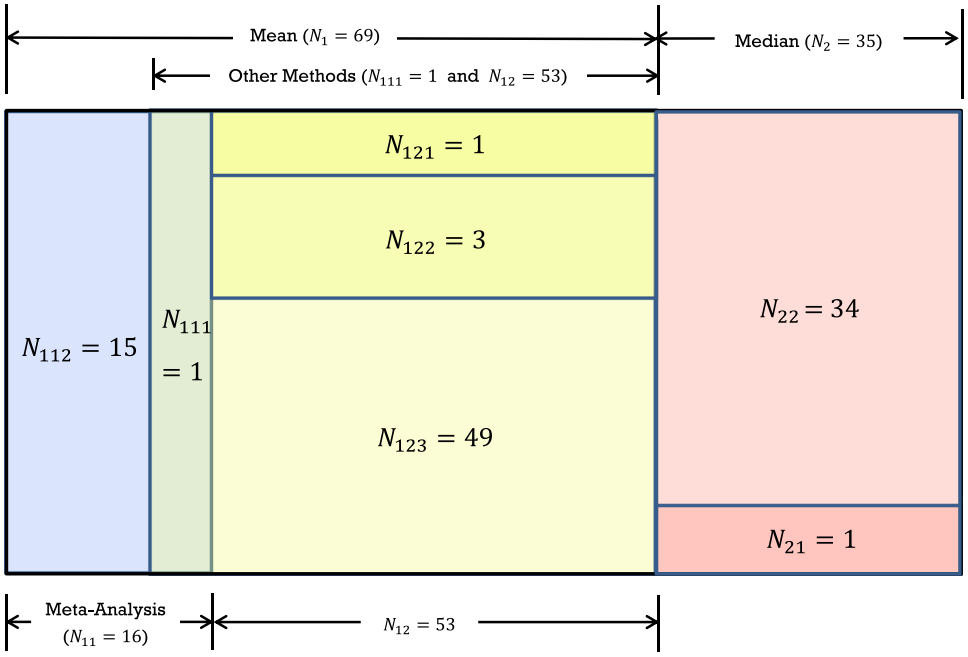

FIGURE 2 The number of papers is classified by the nature of estimates

TABLE 1 A summary of 16 papers reporting meta-analysis results about estimation of the mean incubation time

Author	Period	Region	Methodology	Sample Size	Mean	SD
He et al.	Up to 24 Feb 2020	Worldwide	Meta-analysis	5 studies	5.08	0.16
Li et al.	1 Jan to 6 Apr 2020	Worldwide	Meta-analysis	7 studies (746)	5.30	0.38
Quesada et al.	1 Jan to 21 Mar	Worldwide	Meta-analysis	7 studies (792)	5.60	0.26
Zhang et al.	1 Jan to 24 Feb 2020	Worldwide	Meta-analysis	11 studies (3607)	5.34	0.54
Alene et al.	Up to 31 Mar 2020	Worldwide	Meta-analysis	14 studies (1458)	6.50	0.31
Rai et al.	Up to 31 Mar 2020	Worldwide	Meta-analysis	15 studies	5.74	0.29
Wassie et al.	Up to 2 May 2020	Worldwide	Meta-analysis	18 studies (22595)	5.70	0.33
McAloon et al.	Up to 27 Feb 2020	Worldwide	Meta-analysis (only log normal)	24 studies (1357)	5.80	0.43
Banka et al.	1 Jan to 27 Jul 2020	Worldwide	Meta-analysis (gamma)	31 studies	6.71	0.72
Dhouib et al.	Dec 2019 to Mar 2020	China	Meta-analysis	42 studies	6.20	0.41
Zhang et al.[a]	Up to 8 May 2020	Worldwide	Meta-analysis	42 studies (13272)	6.25	0.26
Khalili et al.	1 Dec 2019 to 11 Mar 2020	Worldwide	Meta-analysis	43 studies	5.68	0.46
Wang et al.	23 Jan to 20 Mar 2020	Worldwide	Meta-analysis	47 studies	5.44	0.26
Pormohammad et al.	Up to 26 Apr 2020	Worldwide	Meta-analysis	53 studies (12609)	6.40	0.31
Wei et al.	1 Dec 2019 to 24 Apr 2020	Worldwide	Meta-analysis (only log normal)	56 studies (4095)	5.80	0.23
Elias et al.	1 Jan 2020 to 10 Jan 2021	Mainly in Asia	Meta-analysis	99 studies	6.38	0.30

Note: The number in brackets under the heading "Sample Size" represents the number of total sample size within all meta-analyses.

[a]This paper (N_{111}) reports one synthetic mean incubation estimate derived from multiple studies using meta-analysis and one mean incubation estimate obtained from a single sample.

shows those 35 studies with 36 reported estimates of the median incubation time, together with the computed estimates of the mean and standard deviation (SD) using the methods described in Supporting Information: Section S2. In sum, 16 (N_{11}) papers with 16 ($N_{111}\cdot 1 + N_{112}\cdot 1$) mean incubation estimates using meta-analysis methods are displayed in Table 1, 54 ($N_{111} + N_{12}$) papers with 59 ($N_{111}\cdot 1 + N_{121}\cdot 3 + N_{122}\cdot 2 + N_{123}\cdot 1$) mean incubation estimates with methods other than meta-analysis are displayed in Table 2, and 35 (N_2) papers with 36 ($N_{21}\cdot 2 + N_{22}\cdot 1$) median incubation estimates are shown in Table 3. These values are summarized in Table 4.

In the papers on meta-analysis reported in Table 1, the size of studies varies from 5 to 99, and the estimates (in days) of the mean incubation time range from 5.08[5] to 6.71.[6] Of all those 16 meta-analyses, 14 are conducted for worldwide studies, 1 is for patients in China, and 1 is for patients in Asia. Regarding the distributional assumption for the incubation time, 2 papers assume a log normal distribution, 1 paper assumes a gamma distribution, and 13 papers make other assumptions.

To visualize the summarized results in Table 1, we display the estimate of the mean incubation time against the number of studies included in each meta-analysis in Figure 3, together with the 95% CIs. The results from these meta-analyses having the same number of studies are shown in orange to avoid overlapping in the display. Half of the meta-analyses include less than 25 studies, and 13 out of 16 meta-analyses contain fewer than 50 studies.

Among the studies reported in Table 2, the sample size varies from 6 to 11545, and the estimates of the mean incubation time range from 1.8 to 14 days. Forty-one (74.55%) studies are conducted inside China, in which 9 (16.36%) estimates are obtained from study subjects inside Hubei province, China. In terms of the methodology, 14 (25.45%) analyses are descriptive, 37 (67.27%) studies are derived from parametric models, and the rest are obtained from non-parametric models. For those studies not reporting the SD but reporting a 95% CI of the mean incubation time, the length L of the 95% CI is used to estimate SD:

$$\mathrm{SD} = \frac{L}{2 \cdot t_{0.975,n-1}}, \tag{1}$$

where $t_{0.975,n-1}$ is the 97.5th percentile of the student's t distribution with $(n - 1)$ degrees of freedom, and n is the sample size of the study.[7] Reported and estimated SDs are shown in the last column of Table 2.

Among the studies reported in Table 3, the reported sample size varies from 6 to 2907, and the estimates of the median incubation time range from 2.87 to 10.00 days. Twenty-three (64.86%) studies are conducted inside China, of which 4 (11.11%) are inside Hubei province, China. In terms of the methodology, 24 (66.67%) analyses are descriptive, 11 (30.56%) studies are derived from parametric models, and 1 study (2.78%) uses a nonparametric model. To estimate the SD, Equation (1) is applied to those studies with a 95% CI reported. For analyses with only IQR or range, those quantities are

TABLE 2 A summary of 59 estimates of the mean incubation time from 54 papers

Author	Period	Region	Methodology	Sample Size	Mean	SD
Shen et al.	8 Jan to 26 Feb 2020	Changsha, China	Descriptive analysis	6	7.17	1.96
Huang et al.	23 Jan to 20 Feb 2020	Anhui, China	Descriptive analysis	6	2.17	0.48
Kim et al.	4 Feb to 7 Apr 2020	Korea	Descriptive analysis	7	10.86	2.18
Won et al.	20 Jan to 10 Feb 2020	Korea	Log normal	9	5.53	0.99
Li et al.	Up to 22 Jan 2020	Wuhan, China	Log normal	10	5.20	0.65[a]
Viego et al.	20 Mar to 8 May 2020	Argentina	Log normal	12	7.50	1.80
Wang et al.	5 Jan to 12 Feb 2020	Wuhan, Hubei, China	Log normal	14	4.50	0.79[a]
Gupta et al.	1 Mar to 4 Jun 2020	India	SVM	19	14.00	0.46
Bui et al.	23 Jan to 13 Apr 2020	Vietnam	Weibull	19	6.40	0.70
Sanche et al.	15–30 Jan 2020	China	Descriptive analysis	24	4.20	0.39[a]
Liu et al.	28 Jan to 12 Apr 2020	Taiwan	Descriptive analysis	27	6.00	0.60
Zhou et al.	27 Jan to 10 Feb 2020	Jiangxi, China	Descriptive analysis	30	5.30	0.73
Xiao et al.[b]	Up to 12 Feb 2020	Hefei, Anhui, China	Descriptive analysis	41	5.61	0.57
Cheng et al.[c]	15 Jan to 18 Mar 2020	Taiwan	Gamma	44	4.10	3.82
Liao et al.	Up to 20 Mar 2020	Chongqing, China	Weibull	46	6.60	1.29[a]
Shi et al.	18 Jan to 2 Mar 2020	Wuxi, Jiangsu, China	Log normal	46	4.77	0.58[a]
Lee et al.[c]	20 Feb to 3 Mar 2020	Busan, South Korea	Log normal	47	3.00	1.96
Zhang et al.	19 Jan to 17 Feb 2020	Outside Hubei, China	Log normal	49	5.20	2.64[a]
Jiang et al.	Up to 8 Feb 2020	Wuhan, China	Weibull	50	4.90	0.27[a]
Linton et al.[d]	Up to 31 Jan 2020	Except Wuhan, China	Log normal	52	5.00	0.42
Leung[d]	20 Jan to 7 Feb 2020	Non-travelers to Hubei	Weibull	54	7.20	0.55
Bao et al.	Jan to Feb 2020	China	Log normal	57	5.40	0.45[a]
Men et al.	29 Dec 2019 to 5 Feb 2020	Outside Hubei, China	Nonparametric MC	59	5.84	0.38
Backer et al.	20–28 Jan 2020	Travelers to Wuhan, China	Weibull	88	6.40	0.25
Song et al.	15–30 Jan 2020	China	Gamma	90	5.01	0.35[a]
Tindale et al.[d]	23 Jan to 26 Feb 2020	Singapore	Gamma	93	5.99	0.55[a]
Leung[d]	20 Jan to 7 Feb 2020	Travelers to Hubei, China	Weibull	98	1.80	0.08
Ren et al.	Up to 23 Jan 2020	Outside Hubei, China	Log normal	98	5.30	0.35[a]
Xia et al.	Up to 25 Jan 2020	Outside Hubei, China	Weibull	106	4.90	0.25[a]
Du et al.[c]	5 Jan to 5 Feb 2020	Outside Hubei, China	Gamma	109	5.06	2.08
Jiang et al.	22 Jan to 15 Feb 2020	Outside Hubei, China	Log normal	110	8.08	0.40
Ryu et al.[c]	20 Jan to 21 Apr 2020	South Korea	Log normal	131	4.70	3.92
Yu et al.	Up to 19 Feb 2020	Shanghai, China	Gamma	132	7.20	0.38[a]
Tindale et al.[d]	21 Jan to 22 Feb 2020	Tianjin, China	Gamma	135	8.68	0.50[a]
Kong	10 Jan to 6 Feb 2020	Travelers to Hubei, China	Cumulative frequency	136	8.50	0.35[a]
Pak et al.	Dec 2019 to Mar 2020	Outside Wuhan, China	Log logistic	156	5.30	0.51[a]
Hong et al.	Up to 9 Mar 2020	Ningbo, Zhejiang, China	Descriptive analysis	157	5.70	0.23
Linton et al.[d]	Up to 31 Jan 2020	China	Log normal	158	5.60	0.22
Tan et al.	23 Jan to 2 Apr 2020	Singapore	Descriptive analysis	164	5.54	0.18[a]

TABLE 2 (Continued)

Author	Period	Region	Methodology	Sample Size	Mean	SD
Xiao et al.[b]	Up to 12 Feb 2020	Shenzhen, China	Descriptive analysis	176	9.27	0.35
Dai et al.	20 Jan to 29 Feb 2020	Shiyan, Hubei, China	Weibull	180	6.50	0.30[a]
Farooq	4 Jan to 24 Feb 2020	Outside Hubei, China	Log normal	181	5.10	0.33[a]
You et al.	Up to 31 Mar 2020	Outside Hubei, China	Descriptive analysis	198	8.00	0.34
Xiao et al.[b]	Up to 12 Feb 2020	Shenzhen and Heifei, China	Descriptive analysis	217	8.58	0.32
Böhm et al.	20 Jan to 19 Mar 2020	Bavaria, Germany	Log normal	256	4.60	0.19
Tian et al.	20 Jan to 10 Feb 2020	Beijing. China	Descriptive analysis	262	6.70	0.32
Patrikar et al.	Up to 10 Mar 2020	India	Normal	268	6.93	0.36
Wang et al.	21 Jan to 14 Feb 2020	Henan, China	Log normal	483	7.40	0.22
Ma et al.	Up to 8 Apr 2020	Worldwide	Gamma	687	7.04	0.16
Huang et al.	Unknown	Outside Wuhan, China	Gamma	787	7.80	0.28[a]
Liu et al.	Up to 23 Jan	Guangdong, China	Descriptive analysis	839	4.80	0.09
Zhang et al.[e]	Up to 8 May 2020	Jiangxi, China	Gamma	930	6.60	0.12
Jing et al.	Up to 15 Feb 2020	Outside Hubei, China	Weibull	1084	8.29	0.31[a]
Jiang et al.	19 Jan to 24 Feb 2020	Zhejiang, China	Weibull	1123	7.75	0.23[a]
Deng et al.	19 Jan to 23 Jan 2020	Travelers to Hubei, China	Gamma	1211	9.10	0.46[a]
Paul et al.	22 Jan to 23 Oct 2020	Canada	Log normal	2258	6.98	0.29[a]
Xiao et al.	Up to 21 Feb 2020	Outside Hubei and Qinghai, China	Weibull	2555	8.98	0.49[a]
Tian et al.	31 Dec 2019 to 19 Feb 2020	China	SEIR model	4031	4.90	0.29[a]
Cheng et al.	19 Jan to 21 Sep 2020	Outside Hubei, China	Log normal	11545	7.10	0.05[a]

[a]The SD is transformed from the reported 95% CI.
[b]This paper (N_{121}) reports three mean incubation estimates.
[c]These studies have highly right-skewed 95% CIs of [0.40, 15.80], [0.30, 8.20], [1.20, 12.50], and [0.10, 15.60], respectively.
[d]These papers (N_{122}) each report two mean incubation estimates.
[e]This paper (N_{111}) reports one synthetic mean incubation estimate derived from multiple studies using meta-analysis and one mean incubation.

transformed to obtain estimates of the mean incubation time and SD[8] using the formulas displayed in Supporting Information: Section S2.

3 | META-ANALYSIS: ESTIMATION AND ASSESSMENT PROCEDURES

Our objective is to perform meta-analyses to estimate the mean incubation time of COVID-19 by capitalizing on the results reported in the literature with the study heterogeneity and publication bias taken into account. In this section, we review the associated procedures of meta-analysis.

3.1 | Synthetic estimation under random effects model and fixed effect model

Let μ denote the mean incubation time for the population that is of interest. Suppose that K studies are available to estimate μ independently, and let y_i and σ_i denote the estimate of μ and the associated SE, respectively, for $i = 1, ..., K$.

We are interested in employing a meta-analysis to provide a synthetic estimate of μ using $\{\{y_i, \sigma_i\} : i = 1, ..., K\}$. Under the assumption of the fixed effect model,[9] a synthetic estimate of μ is given by

$$M = \frac{\sum_{i=1}^{K} w_i y_i}{\sum_{i=1}^{K} w_i}, \tag{2}$$

with the associated variance given by

$$V_M = \frac{1}{\sum_{i=1}^{K} w_i}, \tag{3}$$

where $w_i = 1/\sigma_i^2$ is the weight to show the contribution from study i.

In contrast, if assuming the random effects model, we can still obtain a synthetic estimate of μ and the associated variance, denoted M^* and V_{M^*}, respectively, using Equations (2) and (3) with modified weights by replacing w_i in Equations (2) and (3) with $w_i^* = 1/(\sigma_i^2 + T^2)$, where

TABLE 3 A summary of 36 estimates about the median incubation time from 35 papers, together with the derived entries reported in the last two columns

Author	Period	Region	Methodology	Sample Size	Median	Mean	SD
Gao et al.	22 Jan to 11 Mar 2020	Wuxi, Jiangsu, China	Descriptive analysis	6	10.00	8.75	1.43[a]
Cola et al.	20 Mar to 4 Apr 2020	Spain	Descriptive analysis	7	6.50	6.50	1.74[b]
Chaw et al.	28 Feb to 3 Mar 2020	Brunei, Malaysia	Descriptive analysis	8	4.50	4.25	0.87[b]
Yang et al.	25 Jan to 8 Feb 2020	Flight from Singapore to Zhejiang	Descriptive analysis	10	3.00	4.00	1.36[b]
Kong et al.	8–27 Jan 2020	Zhejiang and Shanghai, China	Descriptive analysis	10	6.00	6.33	1.63[b]
Wong et al.	9 Mar to 5 Apr 2020	Brunei, Malaysia	Descriptive analysis	15	5.00	5.00	1.06[b]
Böhmer et al.	21–28 Jan 2020	Bavaria, Germany	Descriptive analysis	16	4.00	3.53	0.41[b]
Chen et al.	24 Jan to 13 Feb 2020	Sichuan, China	Descriptive analysis	18	8.00	8.00	1.52[b]
Ki	20 Jan to 10 Feb 2020	Korea	Descriptive analysis	28	3.00	5.25	0.70[a]
Ejima et al.	Unknown	5 countries	ODE model	30	5.85	5.85	0.42[c]
Pung et al.	2 Jan to 15 Feb 2020	Singapore	Descriptive analysis	37	4.00	4.33	0.38[b]
Wu et al.	17 Jan to 29 Feb	Zhuhai, China	Log normal	48	4.30	4.30	0.47[c]
Yang et al.	Up to 26 Jan 2020	Wuhan, China	Descriptive analysis	52	5.00	5.00	0.42[b]
Xu et al.	10 to 26 Jan 2020	Zhejiang, China	Descriptive analysis	56	4.00	4.00	0.20[b]
Liu et al.	Up to 5 Feb	Shenzhen, China	Descriptive analysis	58	5.00	5.33	0.50[b]
Chun et al.	23 Jan to 31 Mar 2020	South Korea	Log normal	70	2.87	2.87	0.29[c]
Li et al.	21 Jan to 9 Feb 2020	Wenzhou, Zhejiang, China	Descriptive analysis	74	5.00	5.33	0.26[b]
Lou et al.	Up to 9 Feb 2020	Hangzhou, Zhejiang, China	Descriptive analysis	80	5.00	5.67	0.68[b]
Pongpirul et al.	8 Jan to 16 Apr 2020	Thailand	Descriptive analysis	83	5.50	5.50	0.41[b]
Qian et al.	Up to 16 Feb 2020	Zhejiang, China	Descriptive analysis	91	6.00	5.67	0.39[b]
Wen et al.	1 Jan 28 Feb 2020	Shenzhen, China	Log normal	92	5.00	5.43	0.40[b]
Ping et al.	3 Jan to 16 Feb 2020	Guizhou, China	Log normal	93	8.06	8.06	0.62[c]
Cai et al.	Up to 15 Mar 2020	Changsha, China	Descriptive analysis	102	7.00	7.00	0.45[b]
Lauer et al.[d]	4 Jan to 24 Feb 2020	Ouside China	Log normal	108	5.50	5.50	0.66[c]
Zhao et al.	16 Jan to 19 Feb	Jingzhou, Hubei, China	Descriptive analysis	136	6.00	7.00	0.45[b]
Yang et al.	20 Jan to29 Feb 2020	Shiyan, Hubei, China	Weibull	178	5.40	5.40	0.30[c]
Lauer et al.[d]	4 Jan to 24 Feb 2020	Outside Hubei, China	Log normal	181	5.10	5.10	0.33[c]
Bi et al.	14 Jan to 12 Feb 2020	Shenzhen, China	Log normal	183	4.80	4.80	0.30[c]
Jin et al.	17 Jan to 8 Feb 2020	Zhejiang, China	Descriptive analysis	195	5.00	5.33	0.27[b]
Guan et al.	Up to 29 Jan 2020	China	Descriptive analysis	291	4.00	4.33	0.22[b]
Alsofanya et al.	1–31 Mar 2020	Saudi Arabia	Descriptive analysis	309	6.00	6.00	0.32[b]
Guo et al.	15 Jan to 15 Mar 2020	China	Descriptive analysis	341	9.00	9.33	0.28[b]
Li et al.	Up to 18 Mar 2020	Outside Hubei, China	Gamma	646	6.20	6.20	0.20[c]
Lu et al.	1 Jan to 11 Feb 2020	China	Weibull	1158	7.20	7.20	0.15[c]
Li et al.	Up to 10 Dec 2020	Worldwide	Weibull	1765	5.00	5.00	0.10[c]
Nie et al.	19 Jan to 8 Feb 2020	Outside Hubei, China	Descriptive analysis	2907	5.00	5.00	0.08[b]

[a]The mean and SD are transformed by using the Median and range.

[b]The mean and SD are transformed by using the Median and IQR.

[c]The SD is transformed from 95% CI and the mean is approximated by the median.

[d]This paper (N_{21}) reports two median incubation estimate.

$T^2 = \frac{Q-(K-1)}{C}$, with $C = \sum_{i=1}^{K} w_i - \frac{\sum_{i=1}^{K} w_i^2}{\sum_{i=1}^{K} w_i}$ and $Q = \sum_{i=1}^{K} w_i y_i^2 - \frac{\left(\sum_{i=1}^{K} w_i y_i\right)^2}{\sum_{i=1}^{K} w_i}$; Q is called Cochran's heterogeneity statistic.[10, p. 77]

3.2 | Heterogeneity test

To assess heterogeneity among different studies, we consider the following null hypothesis:

$$H_0 : \text{all the } K \text{ studies estimate the same mean incubation time.} \quad (4)$$

To test H_0, we use Cochran's heterogeneity statistic Q to calculate the p value, $P(\chi^2(K-1) > Q)$, where $\chi^2(K-1)$ represents a random variable having the χ^2 distribution with $(K-1)$ degrees of freedom.[11]

Alternatively, we may calculate the I^2 statistics:[12]

$$I^2 = \max\left\{\frac{Q-(K-1)}{Q}, 0\right\}. \quad (5)$$

If $I^2 \leq 50\%$, a fixed effect model is preferred; otherwise, a random effect model is suggested. Substantial heterogeneity is revealed if $I^2 > 75\%$.[13]

TABLE 4 The number of papers and estimates reported in Tables 1–3

	Table 1	Table 2	Table 3	Total
The Number of papers	16	54	35	104
The Number of estimates	16	59	36	111

Both Q and I^2 statistics do not depend on the scale of measurements, but their performance depends on K differently. The Q statistic is more sensitive to small values of K than the I^2 statistic does. When K is smaller than 10, the Q statistic may not perform reliably. I^2 explores the between-study variance on a relative scale whereas Q statistic explains the variance on the absolute scale.[10, p. 119]

3.3 | Forest plot

To visualize the results from a meta-analysis in contrast to the results reported by individual studies, one may employ the forest plot,[14] which can be implemented using the package *meta*[15] in R version 4.1.0. The forest plot displays the key information of each study including the last name of the first author and the estimate of the mean incubation time with a 95% CI, together with the results of the meta-analysis including the synthetic estimate, a 95% CI, an I^2 statistic, a Q statistic (shown as χ^2_{K-1}), and the p value described in Section 3.2.

3.4 | Subgroup analyses

If the test in Section 3.2 suggests evidence to reject H_0, one may further conduct subgroup analyses with different groupings introduced to ameliorate heterogeneity among the studies.[16] The idea is to not regard the K studies coming from the same underlying population but from different subgroups, each having its own effect size (or mean incubation time here). We are interested in assessing whether a true difference of the effect size exists among those subgroups.

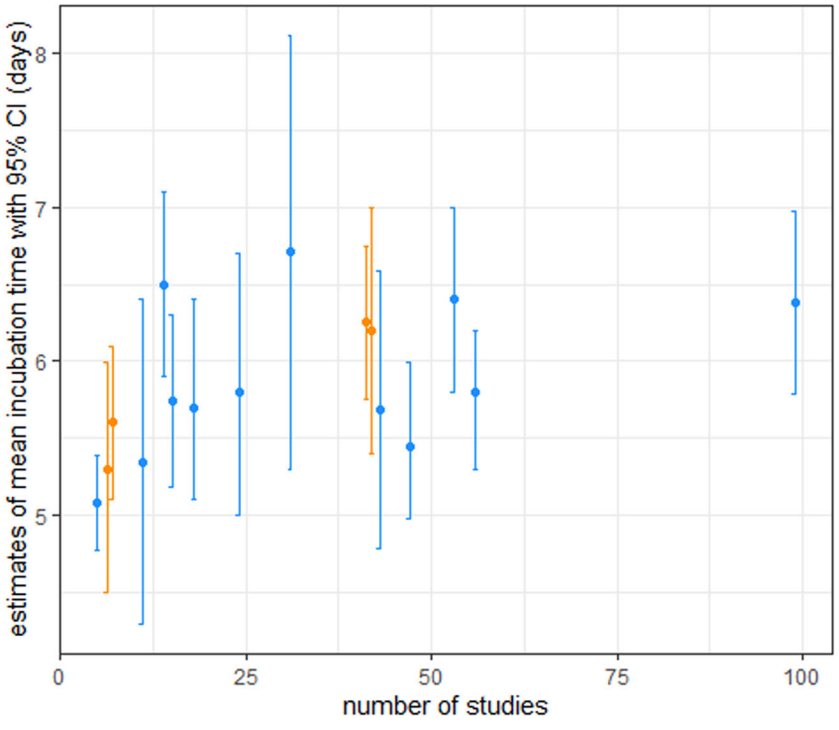

FIGURE 3 The plot shows meta-analysis estimates of the mean incubation time versus the number of studies. Each line segment represents a 95% CI, and a solid dot marks an estimate of the mean incubation time of COVID-19. The first two orange segments represent two meta-analyses having 7 studies and the second two orange segments show two meta-analyses having 42 studies.

To be specific, suppose those K studies are divided into S subgroups. For $i = 1, ..., S$, the procedures for obtaining V_{M^*} and M^* under the random effects model described in Section 3.1 are used to calculate the estimate of the mean incubation time and the associated SE for subgroup i, denoted s_i and τ_i, respectively. Replacing y_i, σ_i and K with τ_i, s_i and S, respectively, in the Q statistic in Section 3.1, we calculate Cochran's heterogeneity statistic, denoted Q^*, for heterogeneity among the S subgroups. Then replacing Q with Q^* and K with S, we apply the test procedure described in Section 3.2 to test for the null hypothesis that S subgroups have the same mean incubation time.

3.5 | Risk of bias assessment

To evaluate the quality of the studies, we assess the risk of bias, defined as the systematic error or deviation from the truth.[17] Here, we adapt the risk of bias tool considered by Hoy et al.[18] in combination with a 10-point checklist to assess the risk of bias for each study. In particular, for items 9 and 10 of the checklist of Hoy et al.[18] that are about the disease prevalence, we change the descriptions to reflect the information on the COVID-19 incubation times following Quesada et al.[19] The resulting checklist includes both external and internal bias assessments related to the sampling method, data collection, case definition, the validity of methodology, and reporting bias, as in line with Wassie et al.[20] The answer to each question in the list is scored as 1 if it has low risk and 0 otherwise, and a total score of all the answers is used to reflect the level of the risk of bias. A total score over 8 indicates low risk of bias, a score below 5 suggests high risk of bias, and a total score between 5 and 8 shows moderate risk of bias. The checklist details are included in Supporting Information: Section S1.

The function *rob.summary* in package *dmetar* [21] in R version 4.1.0 can be used to assess the risk of bias, which typically outputs two summary tables with red and green showing high and low risk of bias, respectively. The first summary table reports the proportion of studies with high or low risk of bias for each question in the checklist. The second summary table, called the *RevMan risk of bias table*,[22] presents the risk of bias results associated with each study for each question, where the rows correspond to the risk assessment items, and the columns refer to the studies.

3.6 | Publication bias

When conducting a meta-analysis, it is helpful to assess potential publication bias incurred in individual studies, and the funnel plot and Egger's test[23] may be employed for this purpose.

The funnel plot displays the SE against the effect size for each study. If publication bias is present, the funnel will look asymmetrical. To measure the asymmetry of the funnel plot, one may employ Egger's test, which involves a linear regression equation:[23]

$$\frac{y_i}{\sigma_i} = a + b \cdot \frac{1}{\sigma_i} + \epsilon_i \tag{6}$$

for $i = 1, ..., K$, where a is the intercept, b is the slope, and ϵ_i is the noise term with mean zero. Then assessing no publication bias is reflected by testing the null hypothesis:

$$H_0 : a = 0, \tag{7}$$

for which the test statistic is calculated as:

$$t^* = \frac{se(\hat{a})}{\hat{a}}, \tag{8}$$

where $\hat{a}$ refers to the estimates of a and $se(\hat{a})$ is the associated SE by applying the least-squares method to fit model (6) to the data $\{\{y_i, \sigma_i\} : i = 1, ..., K\}$ described in Section 3.1. Then the p value of testing (7) is given by $2 \cdot P(t(K-2) > |t^*|)$, where $t(K-2)$ represents a random variable having the t distribution with $(K-2)$ degrees of freedom. A small p value indicates the presence of the publication bias.

4 | DATA ANALYSIS

This section applies the procedures described in Section 3 to analyze the data described in Section 2. First, following procedures discussed in Sections 3.5 and 3.6, we evaluate the risk of bias and publication bias for the studies reported in Tables 1 and 2. Next, we conduct three analyses using the procedures in Sections 3.1–3.3. *Analysis 1* is conducted on those studies with only the information about estimates of the mean incubation time, whereas *Analysis 2* is based on the studies with only the information about estimates of the median incubation time. *Analysis 3* combines the studies in *Analyses 1* and *2*, where a transformation described in Section S2 in Supporting Information is used to convert the estimates of the median incubation time to estimates of the mean incubation time. Further, to examine heterogeneity among the studies, we perform subgroup analyses following the discussion in Section 3.4 by grouping the studies differently. Finally, we conduct sensitivity analyses to assess how estimates of the mean incubation time for COVID-19 may be affected by different treatments of the data.

4.1 | Assessing risk of bias and publication bias

The risk of bias assessment and publication bias assessment are conducted using methods described in Sections 3.5 and 3.6, respectively. Figure 4 shows an overall summary for all the 95 estimates in Tables 2 and 3, and Figure 5 displays the RevMan risk of bias table, where the risk status (high or low) for each of 10 questions in the checklist and 95 estimates are shown by rows and columns, respectively. Overall, 5.26% of the estimates have low risk of bias, 43.16% have moderate risk of bias, and 51.58% have high risk of bias. There is no evidence of publication

bias for the estimates considered for *Analyses 1–3*; details of each test are provided in Sections 4.2–4.4.

4.2 | Results of analysis 1

Table 2 contains 4 estimates (marked as an asterisk) with highly right-screwed 95% CIs in the sense that each estimate is much closer to the lower bound than the upper bound, suggesting that the derived SDs based on (1) may be unreliable. Thus, we exclude those estimates and then apply the test procedures described in Section 3.2 to the remaining 55 estimates. The *p* value for Cochran's test is less than 0.01 and I^2 = 99%, both suggesting that the random effects model is preferred when conducting meta-analysis. Figure 6 displays the forest plot of the meta-analysis, showing that the pooled mean incubation estimate for *Analysis 1* is 6.43 days with a 95% CI [5.90, 6.96]. By applying the method in Section 3.6, we obtain the *p* value 0.33 for the Egger test, suggesting no evidence of asymmetry in the funnel plot, displayed in Figure 7.

4.3 | Results of analysis 2

Using the test procedures described in Section 3.2, we assess the 36 transformed results shown in the last two columns of Table 3. The *p* value for Cochran's test is less than 0.01 and I^2 = 95%, both suggesting that the random effects model is preferred when conducting meta-analysis. Using the method in Section 3.1 gives us an approximate synthetic mean incubation estimate to be 5.52 days with a 95% CI [5.06, 5.99]. Applying the method in Section 3.6 yields the *p* value of 0.43 for the Egger test, showing no evidence of publication bias.

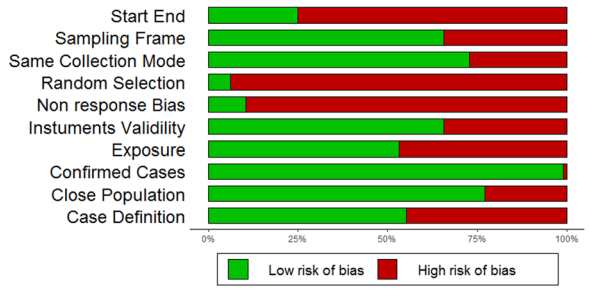

FIGURE 4 Summary of risk of bias

4.4 | Results of analysis 3

Combining the 55 estimates in *Analysis 1* and 36 estimates in *Analysis 2*, we apply the test procedures described in Section 3.2 to those combined 91 estimates and obtain that the *p* value for Cochran's test

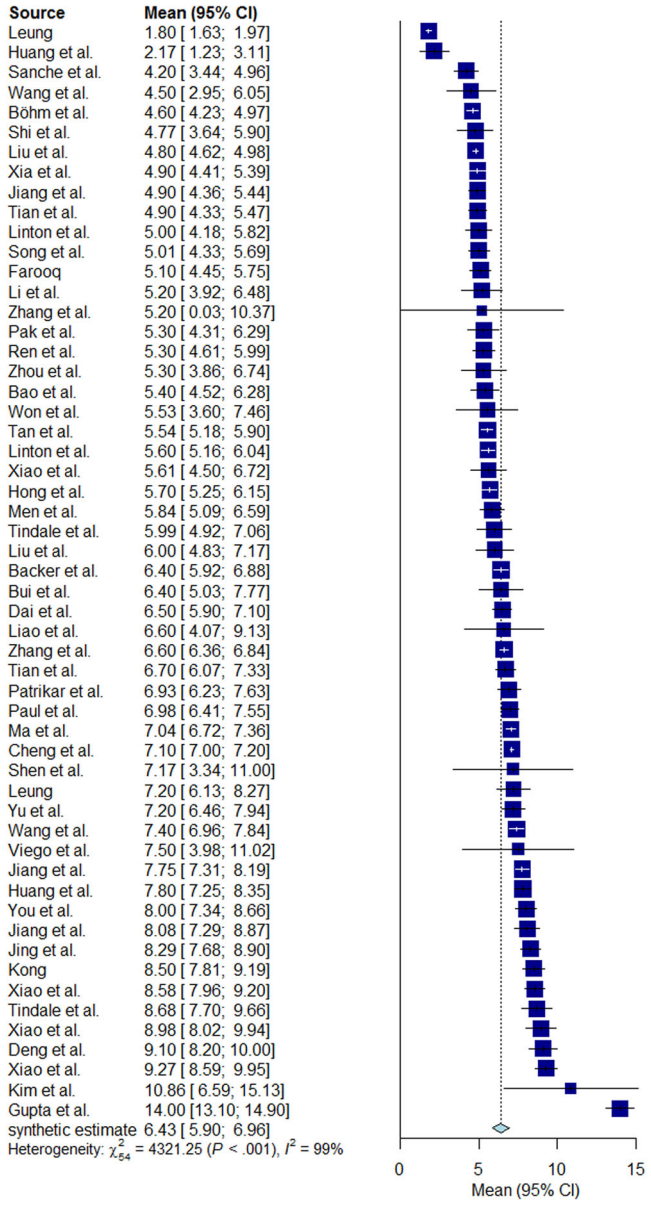

FIGURE 6 Forest plot for Analysis 1

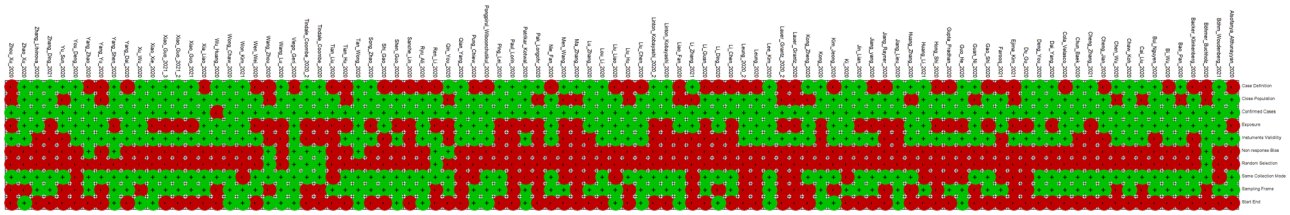

FIGURE 5 RevMan risk of bias table

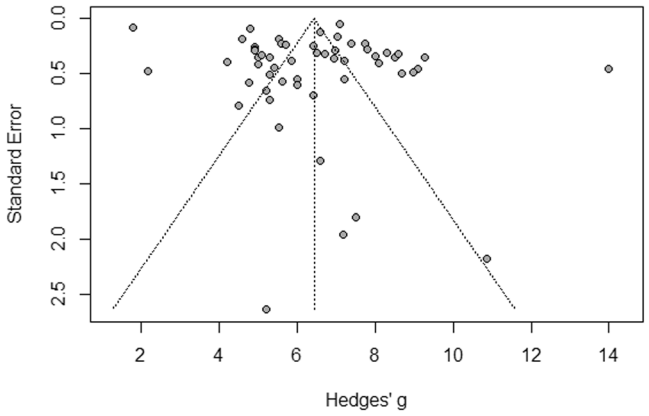

FIGURE 7 Funnel plot for Analysis 1

is less than 0.01 and I^2 = 98%, both suggesting the preference of using random effects model for conducting meta-analysis. Figure 8 displays the forest plot of the meta-analysis, showing that the pooled mean incubation estimate for *Analysis 3* is 6.08 days with a 95% CI [5.71, 6.46]. By applying the method in Section 3.6, we obtain that the *p* value for the Egger test is 0.32, indicating no evidence of asymmetry in the funnel plot, displayed in Figure 9.

4.5 | Results of subgroup analyses

Applying the test procedures described in Section 3.4 to the 55 estimates considered in *Analysis 1*, we further conduct four subgroup analyses using different grouping strategies. Focusing on the region differences related to the reported estimates, we perform two subgroup analyses, where *Subgroup Analysis 1* classifies the estimates into three groups according to being inside or outside China, or mixed, and *Subgroup Analysis 2* divides the estimates into three categories using Hubei province of China (inside or outside Hubei, or mixed). Considering the feature of analysis methods, we perform *Subgroup Analysis 3*, which categorizes the reported estimates into three classes according to whether an estimate was obtained from a descriptive analysis, a parametric model, or a nonparametric model. Using the result suggested in Section 4.1, we classify the estimates into three groups having low, moderate, and high risk of bias, respectively, and conduct *Subgroup Analysis 4*. The results are reported in Table 5, where LBCI and UBCI stand for the lower and upper bounds of a 95% CI for the mean incubation estimate, respectively.

In *Subgroup Analysis 1*, 41 estimates are obtained for study subjects within China, 11 estimates are obtained based on studying subjects outside China, and 3 estimates are based on mixed cases outside and within China (called "Mixed1"). This subgroup analysis suggests a synthetic estimate of the mean incubation time to be 7.18 days with a 95% CI [5.55, 8.80], and 6.23 days with a 95% CI [5.69, 6.78] for subjects outside and within China, respectively.

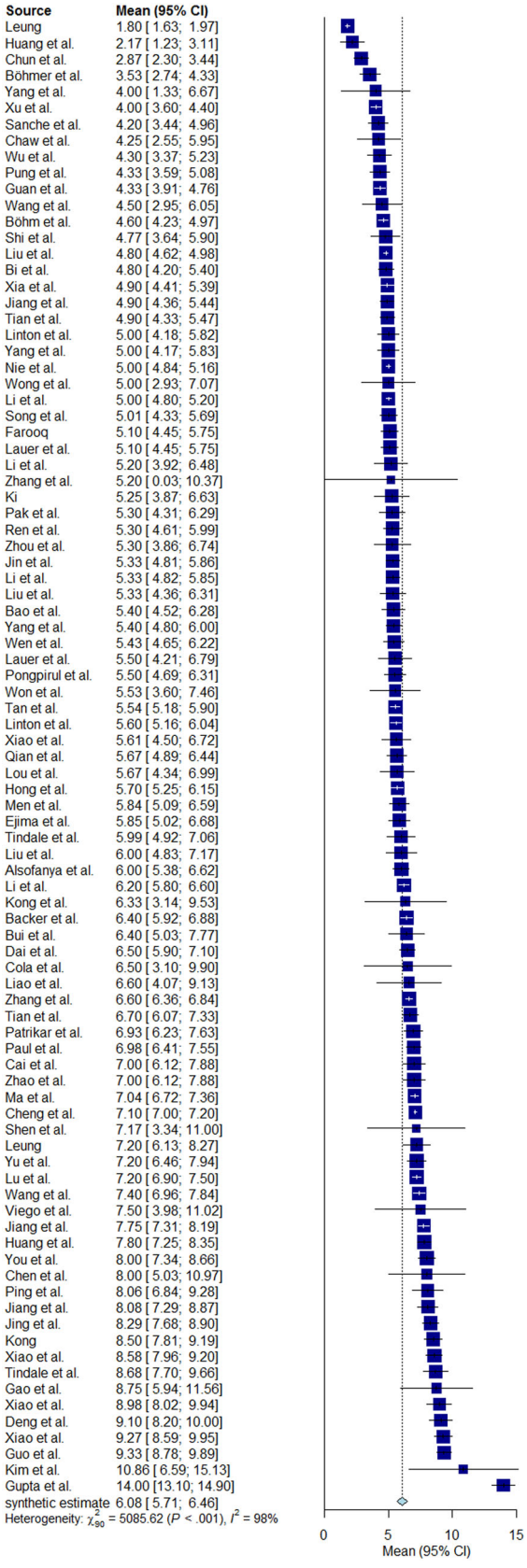

FIGURE 8 Forest plot for Analysis 3

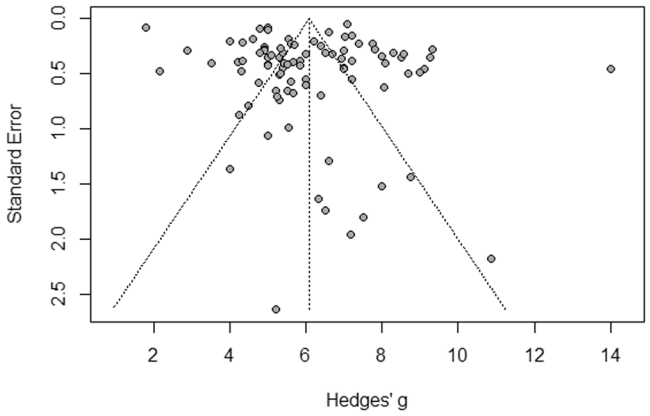

FIGURE 9 Funnel plot for Analysis 3

TABLE 5 Subgroup analysis results

	K	Mean	LBCI	UBCI	I^2
Subgroup Analysis 1					
China	41	6.23	5.69	6.78	99%
Mixed1	3	6.77	5.35	8.19	89%
Outside China	11	7.18	5.55	8.80	97%
Subgroup Analysis 2					
Hubei	9	6.01	4.55	7.47	95%
Mixed2	8	5.68	4.85	6.51	97%
Outside Hubei	38	6.71	6.07	7.35	97%
Subgroup Analysis 3					
Descriptive analysis	14	6.22	5.12	7.33	97%
Nonparametric	4	8.30	4.30	12.30	99%
Parametric	37	6.30	5.80	6.79	99%
Subgroup Analysis 4					
Low risk	2	5.70	4.64	6.76	15%
High risk	29	6.03	5.25	6.82	99%
Moderate risk	24	6.95	6.30	7.60	95%

For *Subgroup Analysis 2*, 9 estimates are obtained from evaluating cases within Hubei province of China, 38 estimates are derived from patients outside Hubei province, and 8 estimates are conducted based on mixed cases outside and inside Hubei province (called "Mixed2"). The synthetic estimate of the mean incubation time outside Hubei province is 6.71 days with a 95% CI [6.07, 7.35], larger than the counterpart inside Hubei province, which is 6.01 days with a 95% CI [4.55, 7.47].

For *Subgroup Analysis 3*, 14 estimates came from descriptive analyses, 4 estimates were obtained from nonparametric models, and 37 utilized parametric models. The group for nonparametric models reveals the largest synthetic estimate as 8.30 days (95% CI [4.30, 12.30]). The rest two groups of descriptive analyses and parametric models output estimates of 6.22 days (95% CI [5.12, 7.33]) and 6.30 days (95% CI [5.80, 6.79]), respectively.

Finally, for *Subgroup Analysis 4*, according to the analysis in Section 4.1, 29 estimates are of high risk of bias, 24 estimates are of moderate risk, and 2 estimates are of low risk of bias. Analysis of the estimates with low risk of bias gives a synthetic estimate of 5.70 days with a 95% CI [4.64, 6.76]; analysis of the estimates of moderate risk produces an estimate of the mean incubation time to be 6.95 days with a 95% CI [6.30, 7.60]; and analysis of the subgroup of high risk results in an estimate of 6.03 days with a 95% CI [5.25, 6.82]. Further, applying the testing procedure for the differences among the groups in Section 3.5, we obtain that p values are 0.48, 0.15, 0.61, and 0.07 for *Subgroup Analyses 1*, *2*, *3*, and *4*, respectively, suggesting no significant difference among the groups in all the four subgroup analyses at level 0.05.

4.6 | Results of sensitivity analyses

To further understand the performance of the meta-analysis, we conduct two sensitivity analyses using the same procedure as for *Analyses 1–3*.

First, we report *Analyses 1* and *3* by adding back those four estimates with highly right-screwed CIs. The resultant synthetic estimates of the mean incubation time corresponding to *Analyses 1* and *3* are 6.37 days (95% CI [5.86, 6.89]) and 6.06 days (95% CI [5.69, 6.42]), respectively, with the estimates being slightly smaller than those reported in Sections 4.2 and 4.4, respectively.

Next, we repeat *Analysis 1* by considering only those 13 estimates with symmetric CIs. The resultant synthetic estimate of the mean incubation time is 6.06 days with a 95% CI [5.27, 6.85].

5 | CONCLUSIONS

In this article, we take different angles to estimate the mean incubation time of COVID-19 by utilizing the estimates reported in the literature for various studies between January 1, 2020 and May 20, 2021. Using the 55 estimates of the mean incubation time of COVID-19, we employ a meta-analysis to output a synthetic estimate of 6.43 days with a 95% CI [5.90, 6.96]. Further combined with 36 estimates transformed from the reported estimates of the median incubation time of COVID-19, a meta-analysis yields a synthetic estimate of the mean incubation time to be 6.08 days with a 95% CI [5.71, 6.46].

Our subgroup analyses suggest that the estimate of the mean incubation time is 7.18 days (95% CI [5.55, 8.80]) and 6.71 days (95% CI [6.07, 7.35]), respectively, for patients outside China and outside Hubei province. For different risk levels, studies with low risk of bias yield the smallest synthetic mean estimate of 5.70 days (95% CI [4.64, 6.76]) among those studies of moderate and high risk. The largest synthetic estimate revealed from those studies based on nonparametric models is 8.30 days with a 95% CI [4.30, 12.30].

Sensitivity analyses show that including or excluding studies with highly skewed CIs may considerably change estimates. While it is difficult to precisely determine the mean incubation time of COVID-19, our analyses here provide insights into understating this unknown quantity by incorporating various features of the available estimates, including heterogeneity, varying sample sizes, publication bias, and differences in estimation methods.

6 | DISCUSSION

While several meta-analyses have been conducted to estimate the mean incubation time of COVID-19, the estimates of these studies vary because the studies often cover different times of the pandemic. Many of those studies examined the publications before June 2020. Our analysis is based on searching for an extended period until May 20, 2021.

We carry out meta-analyses from different perspectives to accommodate diverse information on the mean incubation time estimates. Our analyses consider both mean estimates and those transformed estimates about the median incubation time. We employ subgroup analyses and sensitivity analyses to investigate heterogeneity among the reported studies.

Cheng et al.[24] conducted meta-analyses for the published studies over a period similar to the time window we considered. However, several aspects make our work differ from Cheng et al.[24] First, the search criteria of the two papers are not identical. Unlike our search method described in Section 2.1, Cheng et al.[24] searched the published studies in CNKI, Wanfang, PubMed, and Embase databases. Second, Cheng et al.[24] did not distinguish reported estimates for the mean and median incubation times, but our work treats those estimates differently. Third, Cheng et al.[24] did not perform the quality assessment, whereas our manuscript investigates this aspect of the reported studies. Finally, our paper examines the heterogeneity and publication bias of the associated studies and conducts sensitivity analyses to uncover a more comprehensive picture than Cheng et al.[24] did.

7 | LIMITATIONS

While our study examines the reported estimates of the mean incubation time of COVID-19 from different angles, limitations remain, just like any other available research. Here we outline some issues that warrant further explorations.

Although our search of the literature spans the period from January 1, 2020 to May 20, 2021, the reported estimates of the mean incubation time of COVID-19 are mainly obtained from the studies of those infected cases before March 31, 2020. Therefore, the results here do not reflect the feature that the incubation time of COVID-19 may change with the emerging virus variants. For example, concerning the Delta variant spread in Guangdong province of China from May 2021 to June 2021, Kang et al.[25] estimated the mean incubation time to be 5.80 days with a 95% CI [5.20, 6.40] using the data for 167 patients; and Zhang et al.[26] reported an estimate to be 4.40 days with a 95% CI [3.90, 5.00] using the data for 68 cases. Both studies indicate a shorter mean incubation period than that of SARS-CoV-2 in our analyses. For the Omicron variant identified in November 2021,[27] the mean incubation time of Omicron is expected to be shorter than those revealed from our analyses: the median incubation time was estimated to be 3 days for the SARS-CoV-2 B.1.1.529 (Omicron) variant.[28]

While heterogeneity in the studies may be related to different virus variants, clinical features of study subjects are also responsible for explaining the heterogeneity. Most available studies about the estimation of the mean incubation time of COVID-19 did not report individual characteristics such as age, the sex ratio, and medical conditions of patients, which hinders us in closely exploring the heterogeneity of the studies. The grouping schemes in Section 4.5 are dictated by the available characteristics, such as regions of study subjects, analysis methods, and the risk of bias levels. They do not adequately address heterogeneity, as shown by those large values of I^2 for most subgroup analyses. (Although the value of I^2 for a subgroup analysis is as low as 15%, we cannot over-interpret its ability of explaining heterogeneity due to the small number of the included studies.)

While conducting subgroup analyses aims to address the heterogeneity of the original studies, it is not trivial to decide how to form groups of homogeneous or nearly homogeneous studies. Addressing heterogeneity in meta-analysis is challenging, and a variety of issues may come into play, such as confounding effects, the accuracy of measurements, analysis methods and associated assumptions, whether or not data come from designed studies or observational studies, and so on.

Another critical issue is the validity of the assumptions ubiquitously required by almost all studies. For example, the normality assumption is often made for conducting a meta-analysis. This assumption, however, may not be valid since the distributions of incubation times in some studies may be right-skewed. Most studies using parametric models assume a distribution such as gamma, Weibull, or log normal to describe COVID-19 incubation times. Such distributional assumptions may not hold, and the resultant estimates incur bias.

In addition, the interpretation of the analysis results needs care, especially when the quality of data is an issue. A critical yet tacit assumption is that the data collected for each study truthfully reflect incubation times for the study subjects. Nevertheless, accurately measuring the incubation time of a COVID-19 patient can be difficult, and the issues related to measurement error[29] are worth in-depth explorations. Furthermore, our meta-analyses are carried out by utilizing the estimates of the mean or median incubation time of COVID-19 reported in various literature studies; the development here does not examine the missing values possibly associated with individual studies.

AUTHOR CONTRIBUTIONS

Yijia Weng searches the data, conducts the analysis, and prepares an initial draft. Grace Y. Yi offers ideas for the project and writes the manuscript.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Additional materials and references for this manuscript are reported in the Supporting Information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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