Supplementary Materials for "The effect direction should be taken into account when assessing small-study effects"

Comparisons of Sample Sizes in Studies on Dental Research and General Medicine

 Table S1. Summary of sample sizes of studies from the Journal of Evidence-Based Dental Practice (JEBDP) and

 The BMJ. The studies are published or available online between January 1, 2021 and August 10, 2022.

	No. of systematic	No. of included	No. of excluded	Summary of sample sizes				
	reviews	studies	studies ^b	Q1	Median	Q3		
JEBDP	34	519 ^a	3	36	65	152		
BMJ	48	4449	57	58	170	552		

^a424 studies reported the number of participants, 28 studies reported the number of teeth, 55 studies reported the number of implants, and 12 studies reported the number of sites.

^bSome studies were excluded because sample sizes were not specified.

Additional Simulation Results

Table S2. Type I error rates in case 0 (C0) and power in cases 1, 2, and 3 (C1, C2, and C3), expressed as percentages, for various tests for small-study effects in scenario 1. The nominal significance level is 0.1. Note: n is the number of published studies in each metaanalysis; k is the average number of simulated studies in total among all replications to obtain n published studies; I^2 is the average heterogeneity measure among all replications; the compared tests include the two-sided Egger's test (Reg: two-sided), the two-sided modified regression test (Reg-het: two-sided), Begg's rank test (Rank: two-sided), the trim-and-fill method (T & F), the proposed one-sided Egger's test (Reg: one-sided), and the proposed one-sided modified regression test (Reg-het: one-sided).

		π =	= 0			$\pi = 1$				$\pi = 4$			
Test	C0	C1	C2	C3	C0	C1	C2	C3	C0	C1	C2	C3	
n = 15													
k	15.0	24.2	30.0	52.4	15.0	24.2	29.9	52.4	15.0	24.2	29.9	52.4	
I^2	9.9	3.2	1.9	7.9	18.5	9.6	5.7	15.3	74.2	69.0	58.1	68.6	
Reg: two-sided	10.2	16.3	28.1	20.2	10.5	14.6	22.1	17.8	13.3	13.5	13.3	13.7	
Reg-het: two-sided	9.7	15.8	27.8	19.3	9.7	13.7	21.5	17.0	10.5	10.3	10.6	11.2	
Rank: two-sided	8.0	12.2	22.2	15.5	7.6	10.0	16.4	12.7	9.8	9.4	10.0	10.3	
T & F	6.3	14.2	24.3	17.1	6.4	12.1	19.0	14.6	4.6	3.2	7.2	3.4	
Reg: one-sided	9.9	25.2	42.7	31.6	10.5	21.8	33.7	27.7	12.0	14.5	16.7	16.0	
Reg-het: one-sided	9.7	25.0	42.4	30.8	10.1	21.1	33.4	27.0	9.8	12.9	15.2	15.0	
n = 30													
k	30.0	48.4	59.9	104.9	30.0	48.4	59.9	104.6	30.0	48.5	59.9	104.7	
I^2	7.6	1.5	0.7	5.4	18	7.8	3.4	13.9	77.3	73.3	63.3	72.8	
Reg: two-sided	9.9	23.8	46.6	33.8	10.2	19.1	36.4	26.6	13.2	13.6	14.9	13.8	
Reg-het	9.7	23.6	46.5	32.8	9.7	18.6	36.1	25.5	10.0	10.6	12.4	11.6	
Rank: two-sided	8.0	17.0	39.3	25.6	7.3	12.9	29.4	19.3	9.7	9.8	12.4	10.7	
T & F	6.7	19.4	26.2	24.4	6.9	14.9	21.3	18.9	6.3	3.1	5.6	3.3	
Reg: one-sided	10.0	36.5	61.7	48.6	10.1	29.4	50.3	39.7	12.0	15.8	19.5	17.8	
Reg-het: one-sided	9.7	36.4	61.6	48.0	9.4	28.7	50.2	38.8	10.0	14.2	18.6	17.0	
n = 50													
k	50.0	80.6	100.0	174.7	50.0	80.8	99.9	174.5	50.0	80.7	100.1	174.5	
I^2	6.0	0.7	0.2	3.9	17.8	6.5	2.1	13.3	78.5	74.7	65.8	74.4	
Reg: two-sided	10.0	32.9	67.0	47.1	10.3	25.7	51.1	39.1	13.6	14.2	16.6	16.2	
Reg-het	9.8	32.9	66.9	46.6	9.5	24.9	51.0	38.2	10.3	11.1	14.2	13.9	
Rank: two-sided	7.9	26.0	60.8	36.7	7.8	17.1	44.9	30.2	10.8	10.3	15.1	12.7	
T & F	6.7	21.3	29.3	28.3	7.0	18.2	21.6	23.7	7.2	3.2	3.7	3.2	
Reg: one-sided	9.8	47.4	79.0	61.2	10.4	37.6	64.8	53.0	12.2	17.5	22.1	21.1	
Reg-het: one-sided	9.6	47.3	79.0	60.8	9.7	37.1	64.5	52.5	10.6	15.9	21.9	21.1	

Table S3. Type I error rates (m = 0) and power (m > 0), expressed as percentages, for various tests for small-study effects in scenario 2. The nominal significance level is 0.1. Note: n is the number of published studies in each meta-analysis; k is the average number of simulated studies in total among all replications to obtain n published studies; I^2 is the average heterogeneity measure among all replications; the compared tests include the two-sided Egger's test (Reg: two-sided), the two-sided modified regression test (Reg-het: two-sided), Begg's rank test (Rank: two-sided), the trim-and-fill method (T & F), the proposed one-sided Egger's test (Reg: one-sided), and the proposed one-sided modified regression test (Reg-het: one-sided).

		$\pi =$: 0		_	$\pi =$: 1		_	$\pi = 4$		
Test	m = 0	$\lfloor n/4 \rfloor$	[n/3]	[n/2]	m = 0	[n/4]	[n/3]	[n/2]	m = 0	$\lfloor n/4 \rfloor$	[n/3]	[n/2]
n = 15												
k	15	18	20	22	15	18	20	22	15	18	20	22
I^2	10.0	2.7	1.5	1.0	18.5	6.9	4.4	2.8	74.2	60.6	54.8	49.7
Reg: two-sided	9.7	23.1	33.3	40.8	10.6	20.5	26.6	32.7	13.2	14.8	15.6	15.2
Reg-het: two-sided	9.3	22.6	33.0	40.5	9.9	19.7	25.9	32.1	9.7	10.8	11.4	11.7
Rank: two-sided	7.8	16.9	23.3	30.1	7.5	13.5	18.6	23.5	9.5	9.8	10.9	11.3
T & F	5.9	34.1	50.0	59.3	6.3	32.8	44.3	53.2	4.9	19.8	26.0	32.0
Reg: one-sided	9.6	36.0	48.1	56.1	10.2	30.9	39.1	46.5	11.9	17.6	19.4	20.7
Reg-het: one-sided	9.3	35.6	47.7	55.9	9.8	30.2	38.5	46.2	9.5	14.7	15.9	17.7
n = 30												
k	30	37	40	45	30	37	40	45	30	37	40	45
I^2	7.6	0.7	0.5	0.2	18.3	3.8	2.2	0.8	77.5	63.1	59.1	52.8
Reg: two-sided	10.1	47.0	58.6	71.2	10.5	36.1	45.3	55.0	13.6	16.8	16.6	18.5
Reg-het	9.7	47.0	58.4	71.1	9.3	36.0	45.0	54.8	9.8	12.8	13.1	14.6
Rank: two-sided	7.4	35.9	47.1	59.8	7.1	27.8	36.0	46.2	9.8	14.3	16.0	18.1
T & F	6.4	77.2	88.1	94.7	6.4	72.7	82.9	91.1	6.5	55.0	65.2	73.4
Reg: one-sided	10.2	61.4	72.2	82.0	10.4	50.1	59.5	68.9	12.0	21.7	23.0	25.0
Reg-het: one-sided	10.0	61.4	72.2	82.1	10.0	50.2	59.5	69.0	10.2	19.5	20.8	22.6
n = 50												
k	50	62	66	75	50	62	66	75	50	62	66	75
I^2	6.1	0.2	0.1	0.0	17.9	2.1	1.3	0.3	78.6	64.5	61.2	54.8
Reg: two-sided	10.3	66.6	77.6	88.5	10.9	54.0	61.8	74.4	13.4	18.1	19.7	21.6
Reg-het	10.0	66.7	77.6	88.5	10.0	54.0	62.1	74.3	9.9	15.5	16.1	18.7
Rank: two-sided	8.3	57.3	69.5	83.4	7.0	46.5	55.4	70.6	9.8	20.6	23.0	28.0
T & F	6.7	95.9	98.5	99.9	6.9	94.3	97.5	99.5	6.8	84.6	89.3	94.7
Reg: one-sided	9.6	78.3	86.8	94.5	10.4	67.1	74.5	84.7	11.6	24.4	27.0	29.8
Reg-het: one-sided	9.5	78.3	86.8	94.5	9.9	67.4	74.7	84.9	10.0	23.2	24.5	28.4

Forest Plots of Meta-Analyses Presented in the Main Content

Comparison	Total	Mean	CAL SD	Total	Mean	iBL SD	Mean Difference	MD	95%-CI	Weight (common)	Weight (random)
1	22	8.05	2.42	22	8.98	2.40		-0.93	[-2.35; 0.49]	2.7%	3.8%
2	40	10.90	2.50	40	12.40	2.50		-1.50	[-2.60; -0.40]	4.6%	5.7%
3	15	9.60	2.00	15	10.50	2.40		-0.90	[-2.48; 0.68]	2.2%	3.2%
4	15	9.90	1.30	15	10.50	1.50		-0.60	[-1.60; 0.40]	5.5%	6.5%
5	15	10.10	2.40	15	10.90	2.20		-0.80	[-2.45; 0.85]	2.0%	3.0%
6	30	10.30	1.30	30	12.20	1.50		-1.90	[-2.61; -1.19]	11.0%	10.0%
7	30	10.40	1.60	30	12.50	1.00	——	-2.10	[-2.78; -1.42]	12.1%	10.5%
8	177	10.50	2.10	177	11.80	2.30		-1.30	[-1.76; -0.84]	26.2%	14.5%
9	15	9.70	2.50	15	10.30	2.40		-0.60	[-2.35; 1.15]	1.8%	2.7%
10	13	8.50	1.60	13	8.80	1.50	- C	-0.30	[-1.49; 0.89]	3.9%	5.1%
11	50	7.44	2.35	50	7.77	2.50		-0.33	[-1.28; 0.62]	6.1%	7.0%
12	27	9.13	1.97	27	10.30	2.41		-1.17	[-2.34; 0.00]	4.0%	5.2%
13	27	9.17	1.80	27	10.48	2.56		-1.31	[-2.49; -0.13]	4.0%	5.1%
14	10	9.60	1.80	10	10.50	1.80		-0.90	[-2.48; 0.68]	2.2%	3.2%
15	9	8.40	0.70	9	9.50	1.20		-1.10	[-2.01; -0.19]	6.7%	7.5%
16	15	7.20	2.20	15	8.40	1.80		-1.20	[-2.64; 0.24]	2.7%	3.8%
17	14	7.80	1.90	14	8.90	2.30		-1.10	[-2.66; 0.46]	2.3%	3.3%
Common-effect model	524			524				-1.26	[-1.49; -1.02]	100.0%	
Random-effects model							\diamond	-1.19	[-1.49; -0.88]		100.0%
Heterogeneity: $I^2 = 15\%$, τ^2	= 0.11	48, <i>p</i> =	0.28								
							-2 -1 0 1 2				

Figure S1. Forest plot of the meta-analysis comparing clinical attachment level (CAL) and intraoperative bone level (iBL) of periodontal infrabony defects.

			rBL			iBL				Weight	Weight
Comparison	Total	Mean	SD	Total	Mean	SD	Mean Difference	MD	95%-CI	(common)	(random)
1	22	8 36	2 06	22	8 98	2 40		-0.62	[-1.94·0.70]	3.4%	3 4%
2	40	11 30	2 20	40	12 40	2 50		-1 10	$[-2 \ 13 \ -0 \ 07]$	5.6%	5.6%
3	15	9.00	1.70	15	10.50	2.40		-1.50	[-2.99: -0.01]	2.7%	2.7%
4	15	9.30	2.00	15	10.50	1.50		-1.20	[-2.47; 0.07]	3.7%	3.7%
5	15	10.50	2.10	15	10.90	2.20		-0.40	[-1.94; 1.14]	2.5%	2.5%
6	30	11.20	1.10	30	12.20	1.50		-1.00	[-1.67; -0.33]	13.5%	13.5%
7	30	11.50	1.30	30	12.50	1.00		-1.00	[-1.59; -0.41]	17.4%	17.4%
8	177	10.60	2.60	177	11.80	2.30		-1.20	[-1.71; -0.69]	22.9%	22.9%
9	15	8.10	3.40	15	10.30	2.40		-2.20	[-4.31; -0.09]	1.3%	1.3%
10	13	8.00	2.20	13	8.80	1.50		-0.80	[-2.25; 0.65]	2.9%	2.9%
11	50	7.14	1.95	50	7.77	2.50		-0.63	[-1.51; 0.25]	7.7%	7.7%
12	25	8.84	2.62	27	10.30	2.41		-1.46	[-2.83; -0.09]	3.2%	3.2%
13	26	9.00	3.00	27	10.48	2.56		-1.48	[-2.98; 0.02]	2.6%	2.6%
14	10	8.50	1.60	10	10.50	1.80		-2.00	[-3.49; -0.51]	2.7%	2.7%
15	9	8.30	1.70	9	9.50	1.20		-1.20	[-2.56; 0.16]	3.2%	3.2%
16	15	7.60	2.10	15	8.40	1.80		-0.80	[-2.20; 0.60]	3.1%	3.1%
17	14	6.70	3.10	14	8.90	2.30		-2.20	[-4.22; -0.18]	1.5%	1.5%
Common-effect model	521			524			•	-1.10	[-1.34: -0.85]	100.0%	
Random-effects model							÷	-1.10	[-1.34: -0.85]		100.0%
Heterogeneity: $l^2 = 0\%$, $\tau^2 =$	= 0. p =	0.96									
· · · · · · · · · · · · · · · · · · ·							-4 -2 0 2 4	Ļ			

Figure S2. Forest plot of the meta-analysis comparing radiographic bone level (rBL) and intraoperative bone level (iBL) of periodontal infrabony defects.

Comparison	Total	Mean	CAL SD	Total	Mean	rBL SD	Mean Difference	MD	95%–CI	Weight (common)	Weight (random)
1	22	8.05	2.42	22	8.36	2.06		-0.31	[-1.64; 1.02]	3.4%	4.9%
2	40	10.90	2.50	40	11.30	2.20		-0.40	[-1.43; 0.63]	5.6%	6.8%
3	15	9.60	2.00	15	9.00	1.70		0.60	[-0.73; 1.93]	3.4%	4.9%
4	15	9.90	1.30	15	9.30	2.00		0.60	[-0.61; 1.81]	4.1%	5.5%
5	15	10.10	2.40	15	10.50	2.10		-0.40	[-2.01; 1.21]	2.3%	3.6%
6	30	10.30	1.30	30	11.20	1.10	— —	-0.90	[-1.51; -0.29]	15.9%	11.1%
7	30	10.40	1.60	30	11.50	1.30	——•	-1.10	[-1.84; -0.36]	10.9%	9.6%
8	177	10.50	2.10	177	10.60	2.60		-0.10	[-0.59; 0.39]	24.4%	12.6%
9	15	9.70	2.50	15	8.10	3.40		- 1.60	[-0.54; 3.74]	1.3%	2.3%
10	13	8.50	1.60	13	8.00	2.20		0.50	[-0.98; 1.98]	2.7%	4.1%
11	50	7.44	2.35	50	7.14	1.95		0.30	[-0.55; 1.15]	8.3%	8.4%
12	27	9.13	1.97	25	8.84	2.62		0.29	[-0.98; 1.56]	3.7%	5.2%
13	27	9.17	1.80	26	9.00	3.00		0.17	[-1.17; 1.51]	3.3%	4.8%
14	10	9.60	1.80	10	8.50	1.60		1.10	[-0.39; 2.59]	2.7%	4.1%
15	9	8.40	0.70	9	8.30	1.70		0.10	[-1.10; 1.30]	4.1%	5.6%
16	15	7.20	2.20	15	7.60	2.10		-0.40	[-1.94; 1.14]	2.5%	3.9%
17	14	7.80	1.90	14	6.70	3.10		1.10	[-0.80; 3.00]	1.6%	2.8%
Common-effect model	524			521			4	-0.17	[-0.41; 0.08]	100.0%	
Random–effects model Heterogeneity: $I^2 = 36\%$, τ^2	= 0.18	63, p =	0.07					-0.04	[-0.39; 0.31]		100.0%
							-3 -2 -1 0 1 2 3				

Figure S3. Forest plot of the meta-analysis comparing clinical attachment level (CAL) and radiographic bone level (rBL) of periodontal infrabony defects.

Supplementary Case Studies on COVID-19

We further illustrate the performance of the various methods for assessing small-study effects by three meta-analyses on COVID-19. The first supplementary meta-analysis conducted by Lee et al.¹ investigated the efficacy of COVID-19 vaccines in immunocompromised patients by evaluating the seroconversion among patients with hematological cancers compared with immunocompetent controls after the second dose of COVID-19 vaccine. It consists of 19 studies with risk ratios reported. The second supplementary meta-analysis conducted by Chu et al.² investigated the effect of exposure proximity on the infection of COVID-19, SARS, or MERS. It consists of 32 studies with relative risks reported. The third supplementary meta-analysis conducted by Peckham et al.³ investigated the effect of the risk factor of sex on mortality in patients with COVID-19. It consists of 70 studies with odds ratios reported.

We reperformed the three meta-analyses with complete data; the REML method was used to obtain τ^2 in the random-effects model. Figures S4–S6 present their forest plots. Figure S7 presents the three meta-analyses' contour-enhanced funnel plots for visually assessing small-study effects. Table S4 presents the proposed one-sided regression tests along with the other competitors for assessing small-study effects. The side of missing studies was determined by Egger's regression test. The conclusions are generally consistent with the case studies on dental research presented in the main content.

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I	mmunocompro	mised	He	althy				Weight	Weight
Study	Events	Total	Events	Total	Risk Ratio	RR	95%-CI	(common)	(random)
1	20	27	27	28	ا	0.77	[0 61 0 07]	1 5%	5 1%
2	32	37	40	20 40		0.77	[0.01, 0.97]	2.2%	5.9%
3	45	74	196	212	<u> </u>	0.66	[0.55, 0.79]	5.7%	5.5%
4	36	86	197	201		0.43	[0.33: 0.55]	6.6%	5.0%
5	66	167	52	52	- <u>-</u>	0.40	[0.33; 0.48]	4.5%	5.5%
6	13	33	85	85		0.40	[0.27; 0.61]	2.7%	3.8%
7	80	117	35	35	<u>-1</u> 	0.69	[0.61; 0.77]	3.1%	5.9%
8	91	195	26	30		0.54	[0.44; 0.66]	2.5%	5.4%
9	170	263	166	167	÷	0.65	[0.59; 0.71]	11.4%	6.0%
10	3	5	12	12		0.64	[0.34; 1.20]	0.4%	2.5%
11	39	55	36	37	<u>5 m</u>	0.73	[0.61; 0.87]	2.4%	5.6%
12	12	41	40	40		0.30	[0.19; 0.48]	2.3%	3.4%
13	77	92	36	36	+	0.84	[0.77; 0.92]	2.9%	6.0%
14	354	529	269	272	+	0.68	[0.64; 0.72]	20.0%	6.1%
15	118	152	239	272		0.88	[0.80; 0.97]	9.6%	6.0%
16	16	20	24	24		0.80	[0.65; 1.00]	1.3%	5.3%
17	43	96	31	31		0.45	[0.36; 0.56]	2.7%	5.3%
18	67	132	210	214		0.52	[0.44; 0.61]	9.0%	5.6%
19	235	315	107	108		0.75	[0.70; 0.81]	9.0%	6.1%
Common-effect	t model	2436		1896	\$	0.64	[0.62; 0.67]	100.0%	
Random–effect Heterogeneity: / ²	s model = 89%, τ ² = 0.0688	8, <i>p</i> < 0	.01	c		0.62	[0.55; 0.71]		100.0%
				L L	. 0.0 1 2	5			

Figure S4. Forest plot of the meta-analysis in Lee et al.¹ The meta-analysis investigated the efficacy of COVID-19 vaccines in immunocompromised patients after the second dose.

	Fu	rther	Sh	orter				Weight	Weight
Study	Events	Total	Events	Total	Relative Risk R	R	95%-CI	(common)	(random)
aroup - MERS					6 I				
	ß	77/	11	54		15	[0 02· 0 12]	1 2%	5 5%
2	1	10	8	20)5)5	[0.02, 0.12] [0.04· 1.73]	1.1%	2.5%
3	2	29	4	42		22	[0.04, 1.70] [0.14: 3.70]	0.7%	3.3%
4	0	20		25		6	[0.14, 0.70] [0.05: 9.57]	0.7%	1 7%
5	0	5	0	43	0.0	0	[0.00, 0.07]	0.0%	0.0%
6	0	16	0	22				0.0%	0.0%
7	0	12	0	69				0.0%	0.0%
8	0	7	0	27				0.0%	0.0%
Common-effect model	Ŭ	856	0	302	- 01	8	0 10. 0 351	6.2%	0.0%
Bandom-effects model		000		002		22	0.05.093	0.2 /0	13 1%
Heterogeneity: $l^2 = 72\% \tau^2$	= 1 3402	p = 0	01				[0.00, 0.00]		10.170
notorogonoty. 7 = 72,0, t	= 1.0402,	ρ = 0	.01						
group = SARS									
9	1	12	6	19		26	[0.04; 1.93]	0.9%	2.6%
10	4	149	43	294	0.1	8	[0.07; 0.50]	5.9%	5.0%
11	1	12	26	73		23	[0.03; 1.57]	1.5%	2.7%
12	3	123	6	57	0.2	23	[0.06; 0.89]	1.7%	4.0%
13	18	3493	41	647	0.0)8	[0.05; 0.14]	14.1%	6.5%
14	28	314	63	445		53	[0.41; 0.96]	10.6%	6.8%
15	39	965	136	1124	+ 0.3	33	[0.24; 0.47]	25.6%	7.0%
16	14	133	39	341	0.9	92	[0.52; 1.64]	4.5%	6.4%
17	8	61	139	382	0.3	36	[0.19; 0.70]	7.8%	6.1%
18	0	4	3	3		1	[0.01; 1.52]	0.8%	1.8%
19	4	9	32	77	1.0)7	[0.49; 2.33]	1.4%	5.8%
20	5	38	17	29	-+- 0.2	22	[0.09; 0.54]	3.9%	5.4%
21	9	84	11	35	0.3	34	[0.16; 0.75]	3.2%	5.7%
22	0	4	4	8	0.2	21	[0.01; 3.09]	0.7%	1.7%
23	0	11	8	40	0.2	21	[0.01; 3.33]	0.8%	1.6%
24	17	54	13	20	+ 0.4	18	[0.29; 0.81]	3.9%	6.6%
25	0	3	0	38				0.0%	0.0%
Common-effect model		5469		3632	<u>ه</u> 0.3	86	[0.30; 0.42]	87.0%	
Random-effects model					O.3	34 j	[0.23; 0.51]		75.7%
Heterogeneity: $I^2 = 74\%$, τ^2	= 0.4048,	<i>p</i> < 0	.01						
group - COVID-19									
26	0	76	12	42	O ()2	10 00 [.] 0 371	3.3%	1.6%
27	Ő	13	2	2		14	[0.00; 0.56]	0.8%	1.6%
28	Õ	17	2	3)4	[0.00; 0.67]	0.8%	1.6%
29	5	47	7	36		55	[0.00, 0.07] [0.19, 1.58]	1.6%	4.8%
30	Ő	4	3	33) 6 [0.06.17.40]	0.2%	1.6%
31	0	50	0	76	1.0	, o	0.00, 17.40]	0.2%	0.0%
32	0	41	0	37	á l			0.0%	0.0%
Common-effect model	Ŭ	248	0	229	- 01	8	0 09. 0 371	6.7%	
Bandom-effects model		240		220		4	0.03 0.681	0.170	11 2%
Heterogeneity: $I^2 = 58\%$, τ^2	= 1.7162,	p = 0	.05						
o	,								
Common-effect model		6573		4163	• 0.3	33	[0.28; 0.39]	100.0%	
Random-effects model					♦ 0.2	29	[0.19; 0.43]		100.0%
	0 5565	-	~ .						
Heterogeneity: $I^{2} = 73\%$, τ^{2} Test for subgroup difference	= 0.5506, es (commo	p < 0 on effe	.01 ct): χ ₂ ² = 6.	.68, df :	$0.01 \ 0.1 \ 1 \ 10 \ 100$ = 2 (p = 0.04)				

Test for subgroup differences (random effects): $\chi_2^2 = 1.32$, df = 2 (p = 0.52)

Figure S5. Forest plot of the meta-analysis in Chu et al.² The meta-analysis investigated the effect of exposure proximity on the infection of COVID-19, SARS, or MERS.

		Males		Females				Weight	Weight
Study	Events	Total	Events	Total	Odds Ratio	OR	95%-Cl	(common)	(random)
	50	0500		0.400	1.110		[0 00: 1 0.4]	0.10/	0.00/
1	00	3598	2024	3489		1.24	[0.83; 1.84]	0.1%	0.9%
2	653	20003	3234	21601		1.91	[1.62, 2.01]	2.7%	1.7%
4	314	4672	237	6372		1.05	[1.40, 1.02]	0.3%	1.5%
5	94	2998	67	3380		1.60	[1.17; 2.20]	0.1%	1.1%
6	4515	84841	3627	91911		1.37	[1.31; 1.43]	4.5%	1.7%
7	503	8545	350	6446		1.09	[0.95; 1.25]	0.5%	1.5%
8	17877	102628	11815	119267		1.92	[1.87; 1.97]	12.2%	1.7%
9	3240	16755	2616	28733	- 2	2.39	[2.26; 2.53]	2.1%	1.7%
10	128	4151	107	4201		1.22	[0.94; 1.58]	0.1%	1.3%
11	649	12975	681	17813	-	1.32	[1.19; 1.48]	0.7%	1.6%
12	142	4664	127	6561		1.59	[1.25; 2.03]	0.1%	1.3%
13	049	12020	8928	141983		1.81	[1.76; 1.87]	9.3%	1.7%
14	175	13654	110	12318	<u> </u>	1.00	[1.50, 1.64]	0.0%	1.0 %
16	2274	14140	1851	20300		1.00	[1 79 2 04]	1.7%	1.0%
17	134	3248	151	3380	_ (0.92	[0.73; 1.17]	0.2%	1.3%
18	185	4336	132	4442		1.46	[1.16; 1.83]	0.2%	1.3%
19	699	7559	487	10724	- 2	2.14	[1.90; 2.41]	0.5%	1.6%
20	367	8083	276	8413		1.40	[1.20; 1.64]	0.3%	1.5%
21	121	1585	51	1297		2.02	[1.44; 2.83]	0.1%	1.1%
22	30	783	31	958		1.19	[0.71; 1.99]	0.0%	0.7%
23	571	7930	315	6665		1.56	[1.36; 1.80]	0.4%	1.5%
24	18684	66186	13134	//540		1.93	[1.88; 1.98]	11.8%	1.7%
20	011	44720	1755	12070		1.91	[1.77, 2.00]	1.3%	1.0%
20	495	13540	200	10564		1 26	[1.00, 1.00]	0.5%	1.5%
28	2139	15964	1082	12736		1.67	[1.54: 1.80]	1.4%	1.6%
29	5760	44473	2837	33550		1.61	[1.54; 1.69]	3.8%	1.7%
30	43	1654	13	1386		2.82	[1.51; 5.26]	0.0%	0.6%
31	62	2041	48	1960		1.25	[0.85; 1.83]	0.1%	1.0%
32	942	13496	554	11042		1.42	[1.27; 1.58]	0.8%	1.6%
33	332	8576	142	7147		1.99	[1.63; 2.42]	0.2%	1.4%
34	294	7091	202	6784		1.41	[1.17; 1.69]	0.3%	1.4%
35	10050	1/4/	243	2750		1.80	[1.50; 2.17]	0.2%	1.4%
37	10002	7583	100	6503		1.00	[1.30, 1.37]	12.4%	1.7%
38	2560	48821	2042	51690		1.25	[1.02, 1.43] $[1.27 \cdot 1.43]$	2.5%	1.4 /8
39	2406	29153	2578	36420	-	1.18	[1.11: 1.25]	2.8%	1.7%
40	2954	39658	3189	49077		1.16	[1.10; 1.22]	3.6%	1.7%
41	2718	25150	2411	28360	=	1.30	[1.23; 1.38]	2.7%	1.7%
42	1926	43450	1521	42252	-	1.24	[1.16; 1.33]	2.0%	1.7%
43	574	8794	470	9941		1.41	[1.24; 1.60]	0.6%	1.6%
44	1363	14602	1143	20077		1.71	[1.57; 1.85]	1.2%	1.6%
45	1054	21283	1038	23141		1.11	[1.02; 1.21]	1.3%	1.6%
40	573	10419	240	1/425	T. I.	1.03	[0.92; 1.16]	0.7%	1.0%
47	218	4067	201	5330		1.13	[0.96, 1.31]	0.4%	1.3%
49	319	6800	270	9600		1.70	[1.44: 2.01]	0.3%	1.5%
50	341	4915	352	7232		1.46	[1.25: 1.70]	0.4%	1.5%
51	1092	16445	1004	14864	+ (0.98	[0.90; 1.07]	1.3%	1.6%
52	954	15230	904	17040		1.19	[1.09; 1.31]	1.1%	1.6%
53	312	8657	238	8317		1.27	[1.07; 1.51]	0.3%	1.5%
54	492	11051	465	11433	++	1.10	[0.97; 1.25]	0.6%	1.6%
55 56	1372	25611	1074	26262		1.33	[1.22; 1.44]	1.4%	1.6%
50 57	181	4328	228	4008		1.00	[0.69; 1.02]	0.3%	1.4%
58	1858	18662	1962	22702	-	1.00	[1.09.1.25]	2.2%	1.3 %
59	326	6439	367	8196		1.14	[0.98: 1.33]	0.4%	1.5%
60	92	2006	80	1617	_	0.92	[0.68; 1.26]	0.1%	1.1%
61	31	458	24	513		1.48	[0.85; 2.56]	0.0%	0.7%
62	171	2986	158	3338		1.22	[0.98; 1.53]	0.2%	1.3%
63	486	8679	398	9756		1.39	[1.22; 1.60]	0.5%	1.5%
64	789	12088	628	12759		1.35	[1.21; 1.50]	0.8%	1.6%
C0	169	4117	187	5091		1.12	[0.91; 1.39]	0.2%	1.4%
00 67	08 720	1/2/	5/ 171	1929		1.60	[1.13; 2.25]	U.1% ດາກ/	1.0%
68	237	2007	7	-142		1.31	[0.51:3.84]	0.2%	0.3%
69	107	5358	101	4180	(0.82	[0.63; 1.08]	0.2%	1.2%
70	39	1249	43	1513	[_]	1.10	[0.71; 1.71]	0.1%	0.8%
		-	-			-		- /-	
Common-effect model		1319094		1416420		1.57	[1.56; 1.59]	100.0%	
Handom-effects model	2 0 0					1.39	[1.31; 1.47]		100.0%
Heterogeneity: $I^- = 97\%$, τ^-	= 0.0500,	p = 0		0	.2 0.5 1 2 5				

Figure S6. Forest plot of the meta-analysis in Peckham et al.³ The meta-analysis investigated the effect of the risk factor of the male sex on mortality in patients with COVID-19.



 \Box 0.1 \Box 0.05 \Box 0.01 \Box 0 < p < 0.01

Figure S7. Contour-enhanced funnel plots for the three supplementary metaanalyses on COVID-19. The filled points represent published data; the unfilled points represent imputed missing studies by the trim-and-fill method.

Table S4. Results of the three supplementary meta-analyses on COVID-19. The compared tests include the two-sided Egger's test (Reg: two-sided), the two-sided modified regression test (Reg-het: two-sided), Begg's rank test (Rank: two-sided), the trim-and-fill method (T & F), the proposed one-sided Egger's test (Reg: one-sided), and the proposed one-sided modified regression test (Reg-het: one-sided).

	Lee et al. ¹	Chu et al. ²	Peckham et al. ³
I ² (%)	94	74	97
Reg: two-sided (<i>p</i> -value)	0.034	0.266	0.001
Reg-het: two-sided (<i>p</i> -value)	0.045	0.211	0.779
Rank: two-sided (<i>p</i> -value)	0.080	0.156	0.249
T&F			
Imputation side	Right	Right	Right
No. of imputed studies	6	4	1
<i>p</i> -value	0.004	0.031	0.500
Reg: one-sided (<i>p</i> -value)	0.017	0.133	0.001
Reg-het: one-sided (p-value)	0.023	0.106	0.389

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