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

[a]424 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.
[b]Some 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 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	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	$m = 0$	$\lfloor n/4 \rfloor$	$\lfloor n/3 \rfloor$	$\lfloor n/2 \rfloor$	$m = 0$	$\lfloor n/4 \rfloor$	$\lfloor n/3 \rfloor$	$\lfloor n/2 \rfloor$	$m = 0$	$\lfloor n/4 \rfloor$	$\lfloor n/3 \rfloor$	$\lfloor n/2 \rfloor$
$n = 15$												
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

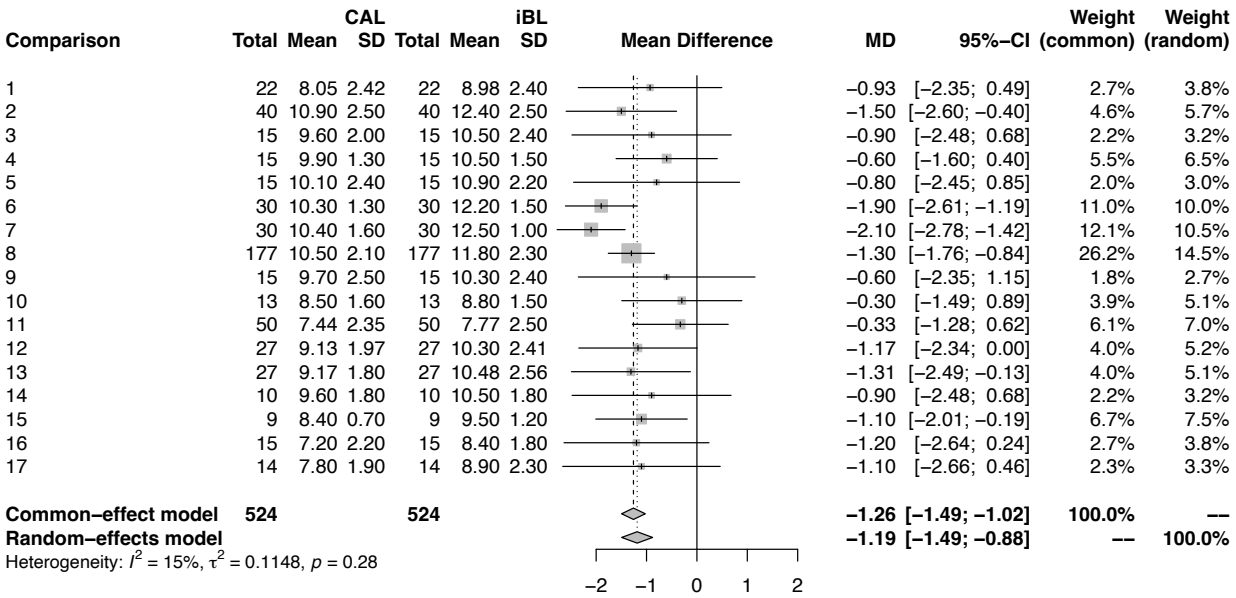

Figure S1. Forest plot of the meta-analysis comparing clinical attachment level (CAL) and intraoperative bone level (iBL) of periodontal infrabony defects.

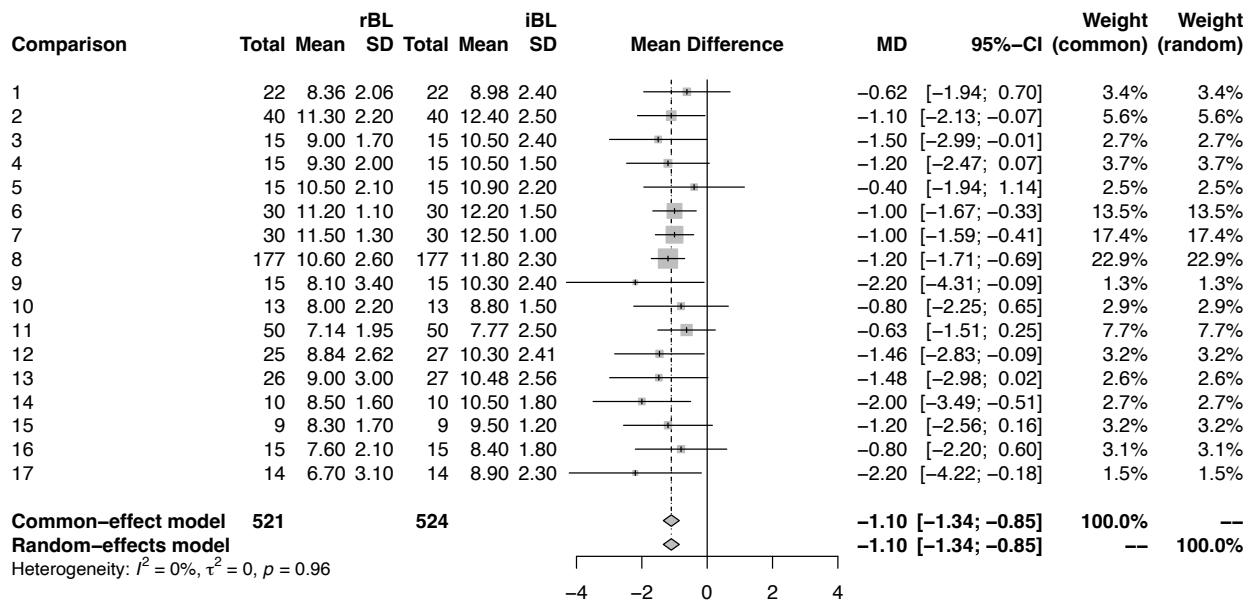

Figure S2. Forest plot of the meta-analysis comparing radiographic bone level (rBL) and intraoperative bone level (iBL) of periodontal infrabony defects.

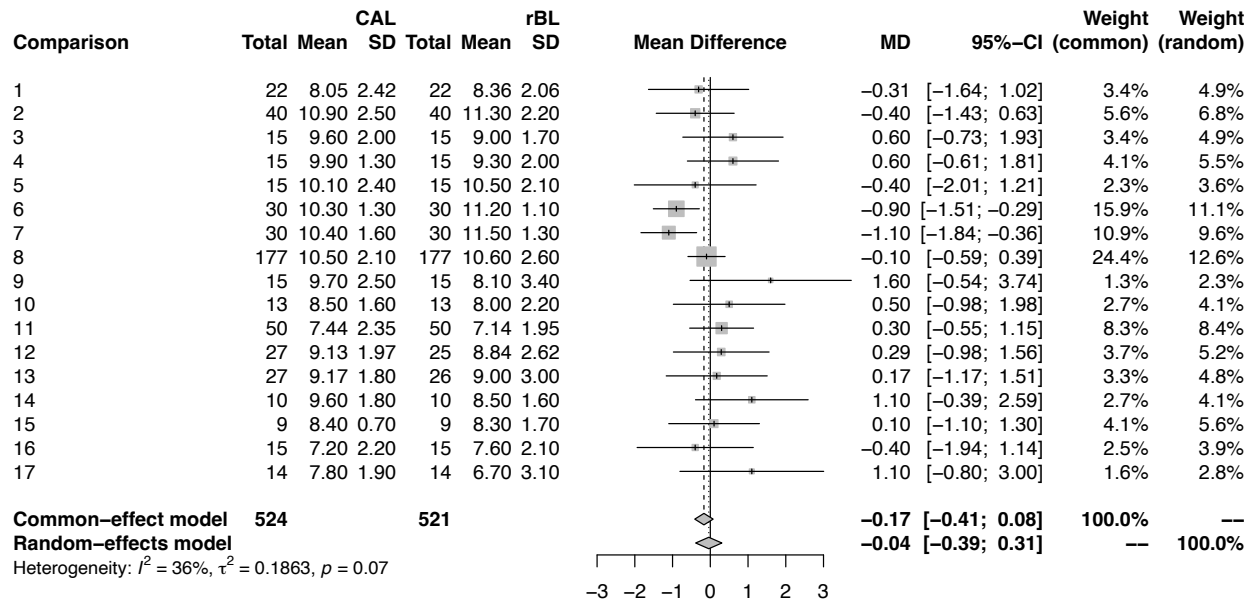

Figure S3. Forest plot of the meta-analysis comparing clinical attachment level (CAL) and radiographic bone level (rBL) of periodontal infrabony defects.

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.

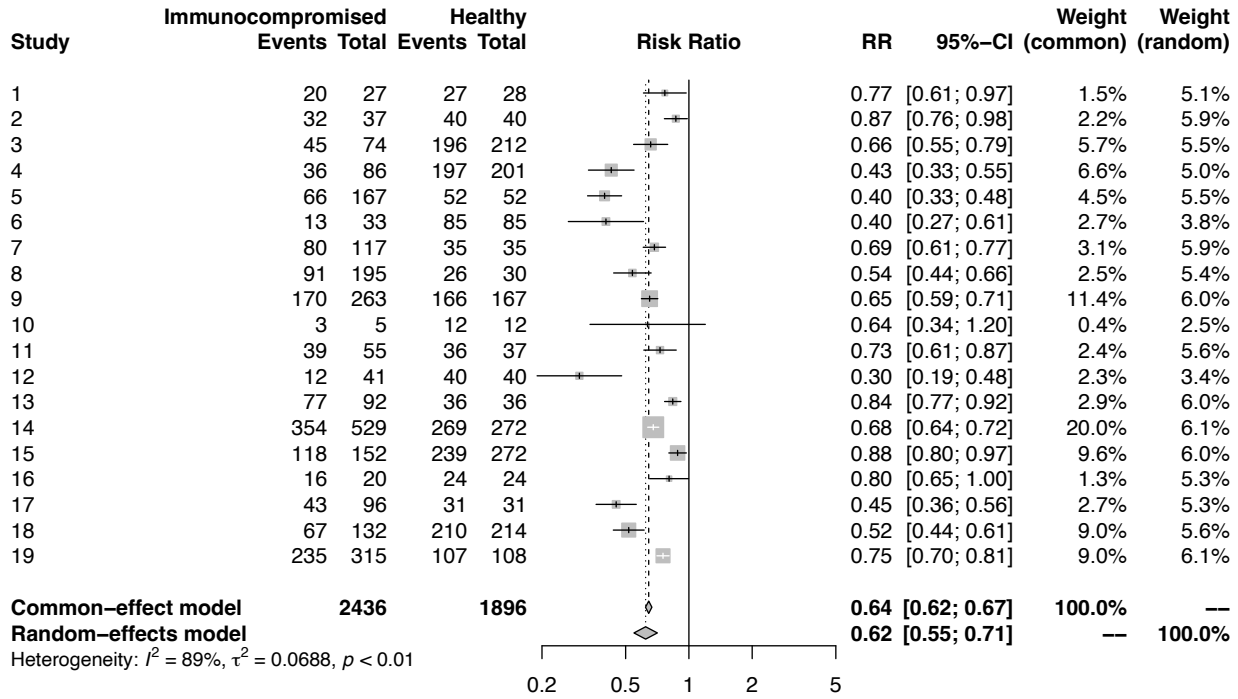

Figure S4. Forest plot of the meta-analysis in Lee et al.[1] The meta-analysis investigated the efficacy of COVID-19 vaccines in immunocompromised patients after the second dose.

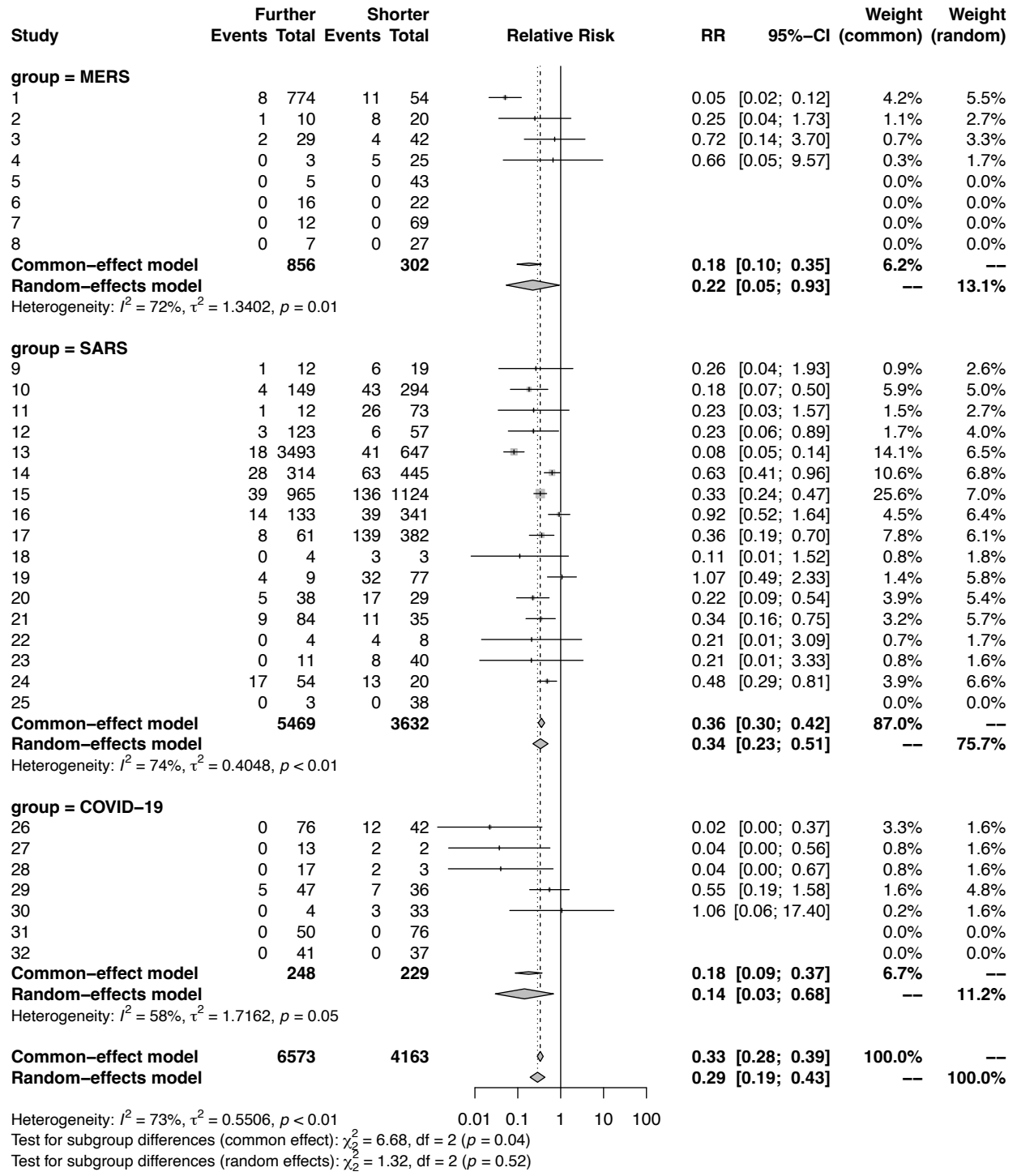

Figure S5. Forest plot of the meta-analysis in Chu et al.[2] The meta-analysis investigated the effect of exposure proximity on the infection of COVID-19, SARS, or MERS.

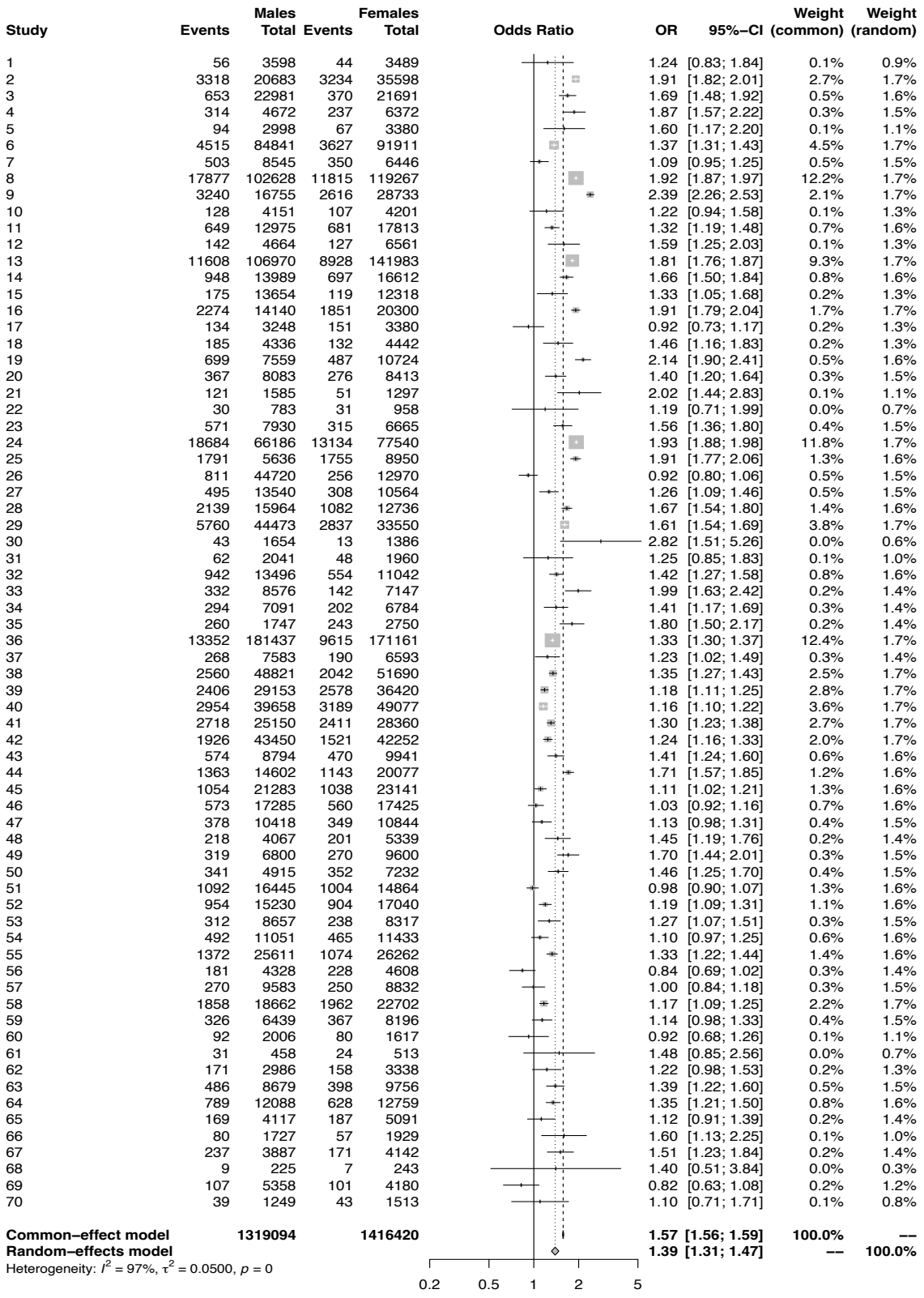

Figure S6. Forest plot of the meta-analysis in Peckham et al.[3] The meta-analysis investigated the effect of the risk factor of the male sex on mortality in patients with COVID-19.

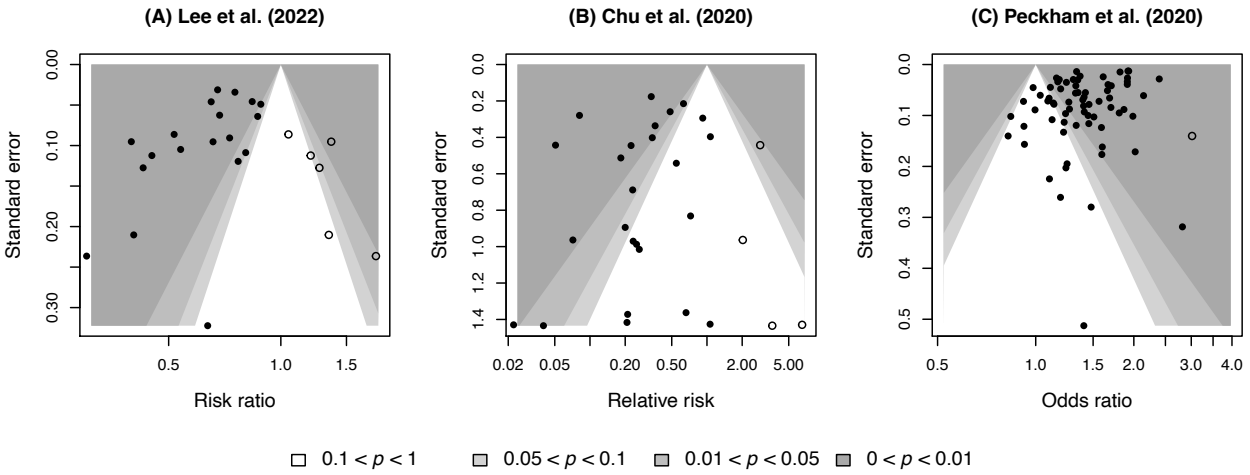

Figure S7. Contour-enhanced funnel plots for the three supplementary meta-analyses on COVID-19. The filled points represent published data; the unfilled points represent imputed missing studies by the trim-and-fill method.

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 (p-value)	0.034	0.266	0.001
Reg-het: two-sided (p-value)	0.045	0.211	0.779
Rank: two-sided (p-value)	0.080	0.156	0.249
T & F			
Imputation side	Right	Right	Right
No. of imputed studies	6	4	1
p-value	0.004	0.031	0.500
Reg: one-sided (p-value)	0.017	0.133	0.001
Reg-het: one-sided (p-value)	0.023	0.106	0.389

References

1. Lee ARYB, Wong SY, Chai LYA, et al. Efficacy of covid-19 vaccines in immunocompromised patients: systematic review and meta-analysis. *BMJ* 2022;376:e068632. doi: 10.1136/bmj-2021-068632
2. Chu DK, Akl EA, Duda S, et al. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis. *The Lancet* 2020;395(10242):1973-87. doi: 10.1016/S0140-6736(20)31142-9
3. Peckham H, de Gruijter NM, Raine C, et al. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. *Nature Communications* 2020;11(1):6317. doi: 10.1038/s41467-020-19741-6