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Supplement of

Management and outcomes of culture-negative periprosthetic joint infection: a systematic review and meta-analysis

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Search Strategy:

Search Strategies

OVID

Database(s): Ovid MEDLINE(R) 1946 to Present and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) Daily, EBM Reviews - Cochrane Central Register of Controlled Trials June 2025, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to July 2, 2025, Embase 1974 to 2025 July 03
Search Strategy:

#	Searches
1	(Prosthesis-Related Infections/ or prosthesis infection/) and (joint* or hip* or knee* or shoulder* or elbow*).ti,ab.
2	(pji or (periprosthe* adj1 infect*) or (infected adj2 joint adj1 arthroplast*) or (prosthe* adj2 infect*) or (arthroplast* adj2 infect*) or (joint* adj1 infect*) or infected-prosthetic-arthroplast* or joint-replacement-infection* or infected-total-joint-arthroplast* or peri-implant-infection* or prosthesis-related infection* or infected-joint-replacement*).ti.
3	1 or 2
4	exp High-Throughput Nucleotide Sequencing/
5	exp *Microbiological Techniques/ or *microbiological examination/
6	(mi or di).fs.
7	"next-generation-sequencing".ti.
8	(diagnos* or test* or lab or laboratory or sonication or "sonicate-fluid" or "polymerase-chain-reaction" or "16S-RNA" or metagenomic* or "synovial-fluid-culture").ti,ab.
9	or/4-8
10	(negativ* or identify* or unidentified or inconclusive or steril* or accurate or accuracy).ti,ab.
11	Prosthesis-Related Infections/di or exp prosthesis infection/di
12	10 or 11
13	9 and 12
14	("culture-negative" or CN-PJI).ti,ab,hw,kf,kw. or (sterile adj2 culture*).ti,ab. or (culture* adj2 unidentified).ti,ab. or (staph* adj2 negative).ti,ab.
15	13 or 14
16	3 and 15
17	from 16 keep 1-6000
18	remove duplicates from 17
19	16 not 17
20	remove duplicates from 19
21	18 or 20

SCOPUS

1 TITLE(pji) OR TITLE-ABS-KEY (periprosthe* W/1 infect*) OR TITLE-ABS-KEY (infect* W/2 joint*) OR TITLE-ABS-KEY (prosthe* W/2 infect*) OR TITLE-ABS-KEY (arthroplast* W/2 infect*) OR TITLE-ABS-KEY (joint* W/1 infect*) OR TITLE-ABS-KEY (infected-prosthetic-arthroplast* OR joint-replacement-infection* OR infected-total-joint-arthroplast* OR peri-implant-infection* OR prosthesis-related infection* OR infected-joint-replacement*)

2 (TITLE-ABS-KEY ("culture-negative" or CN-PJI) OR TITLE-ABS-KEY (sterile W/2 culture*) or TITLE-ABS-KEY (culture* W/2 unidentified) or TITLE-ABS-KEY (staph* W/2 negative)) OR (TITLE (negativ* OR identify* OR unidentified OR inconclusive OR steril* OR accurate OR accuracy))

3 1 and 2

4 INDEX (embase) OR INDEX (medline) OR PMID (0* OR 1* OR 2* OR 3* OR 4* OR 5* OR 6* OR 7* OR 8* OR 9*)

5 3 NOT 4

Extracted Variables:

Extracted variables included study design and setting, sample size, affected joint, type and duration of antimicrobial therapy, surgical intervention (DAIR, one-stage exchange, two-stage exchange, resection arthroplasty, or arthrodesis), and clinical outcomes, including treatment success and failure and mortality.

Eligibility criteria

The inclusion criteria were as follows: (a) studies including adult participants (≥18 years); (b) studies including patients with CN-PJI, either as the full study population or as a mixed cohort if outcomes for the CN group were reported separately; (c) studies reporting medical and/or surgical treatment strategies for CN-PJI with clinical outcomes; (d) English-language publications; and (e) studies including at least five patients with CN-PJI. CN-PJI was defined according to each original study. Exclusion criteria were: (a) pediatric studies; (b) reviews, systematic reviews, meta-analyses, study protocols, or preprints; and (c) non-human studies. The primary objective of this review was to summarize the reported outcomes of different treatment strategies for CN-PJI.

Reference lists of all included studies:

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Table S1. Quality Assessment of cohort studies using Newcastle–Ottawa Scale (NOS)

	Selection				**Comparability**	**Outcome**			
Author, Year	*1) Representativeness of the Exposed Cohort	*2) Selection of the Non-Exposed Cohort	*3) Ascertainment of Exposure	*4) Demonstration That Outcome of Interest Was Not Present at Start of Study	**1) Comparability of Cohorts on the Basis of the Design or Analysis	*1) Assessment of Outcome	*2)Was Follow-Up Long Enough for Outcomes to Occur	*3) Adequacy of Follow Up of Cohorts	Total score
Berbari, 2007	*	-	*	-	-	*	*	-	5
Browning, 2022	*	*	*	**	**	*	*	-	8
Choi, 2013	*	*	*	-	-	*	*	-	6
Garabano,2022	*	-	*	-	-	*	*	*	6
Ibrahim,2018	*	*	*	*	*	*	*	*	8
Ji, 2020	*	*	*	*	*	*	*	*	8
Kang, 2018	*	*	*	*	*	*	*	*	8
Kim, 2021	*	*	*	*	*	*	*	-	7
Kim, 2015	*	*	*	-	-	*	*	*	7
Kim, 2015	*	*	*	-	-	*	*	*	7
Li, 2017	*	*	*	-	-	*	*	*	7
Lin, 2025	*	*	*	-	-	*	*	*	7
Lu, 2024	*	*	*	*	*	*	*	*	8
Malekzadeh, 2010	*	*	*	**	**	*	*	*	9
Paz, 2021	*	*	*	-	-	*	*	-	6
Ronan, 2024	*	*	*	*	*	*	*	*	8
Santoso, 2018	*	*	*	*	*	*	*	-	7
Soundarrajan,2023	*	*	*	**	**	*	*	*	9
Tan, 2018	*	-	*	-	-	*	*	-	5

Tirumala, 2021	*	*	*	*	*	*	*	*	8
Vajapey, 2021	*	*	*	-	-	*	-	-	5
Van Den Kieboom, 2021	*	*	*	-	-	*	*	-	6
Van Sloten, 2022	*	*	*	-	-	*	*	*	7
Wang, 2018	*	*	*	*	*	*	*	-	7
Watanabe, 2021	*	*	*	-	-	*	*	-	6
Xu, 2022	*	*	*	-	-	*	*	*	7
Zanna, 2023	*	-	*	-	-	*	*	*	6

Table S2. Meta-regression results evaluating publication year and follow-up duration (months) as moderators of pooled outcome estimates (success, failure), reporting residual heterogeneity (τ^2, I^2, H^2) and the moderator test (QM p-value).

Outcome	**Moderator**	**k**	**Residual τ^2**	**Residual I^2 (%)**	**Residual H^2**	**P value for moderator (QM)**
Treatment success	Follow-up duration (months)	23	0.4160	73.90	3.83	0.6265
Treatment success	Publication year	23	0.3810	73.16	3.73	0.4275
Treatment failure	Follow-up duration (months)	21	0.3643	71.58	3.52	0.9939
Treatment failure	Publication year	21	0.3582	72.57	3.65	0.5257

Supplementary Figures

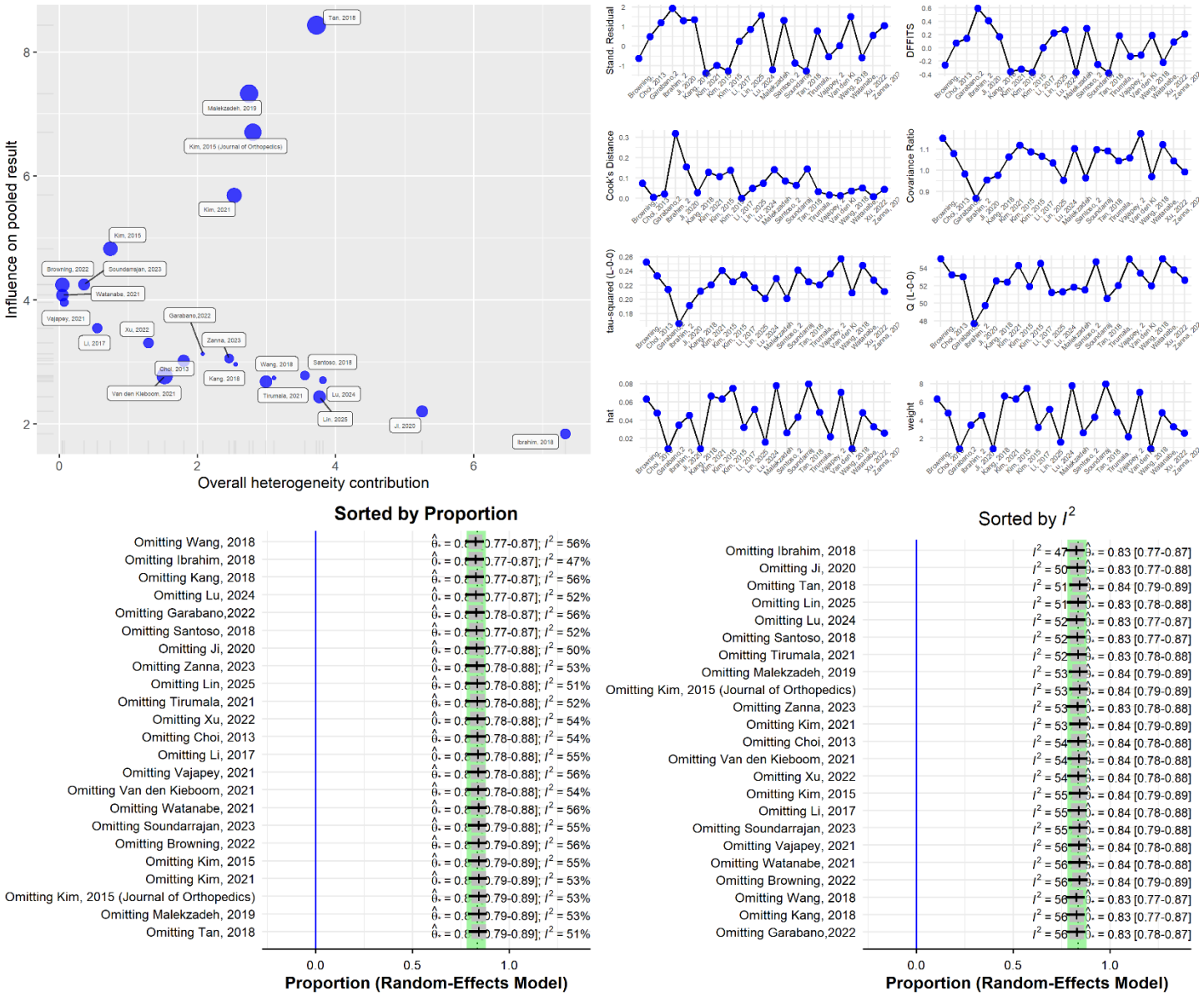

Fig. S1. Influence analysis and leave-one-out sensitivity analysis for overall treatment success.

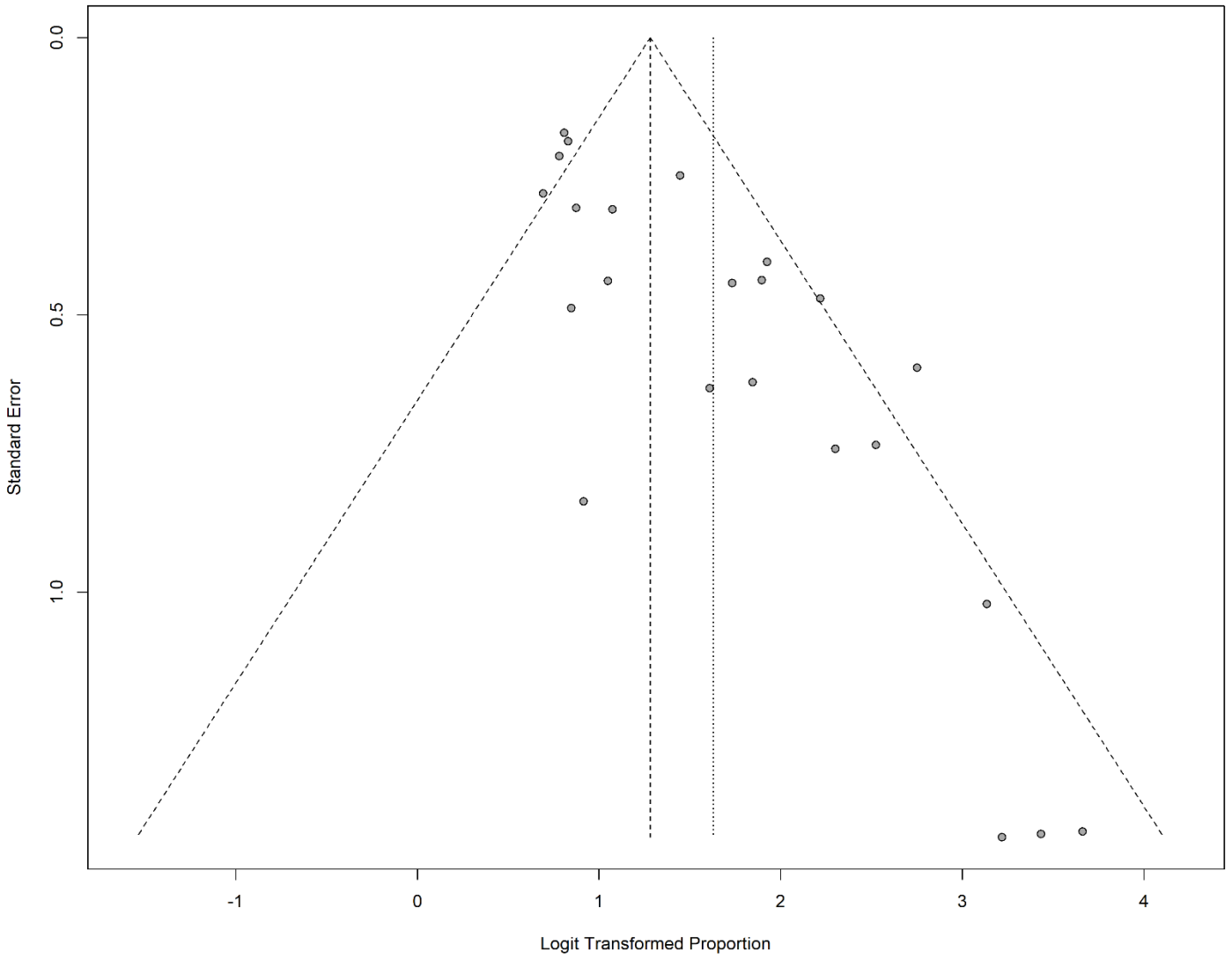

Fig. S2. Funnel plot for overall treatment success. Visual inspection of the funnel plot suggests asymmetry, with a relative paucity of smaller studies on the left side of the plot and several small studies reporting higher success rates on the right, raising concern for small-study effects or publication bias. This was supported by Egger's test ($p < 0.0001$).

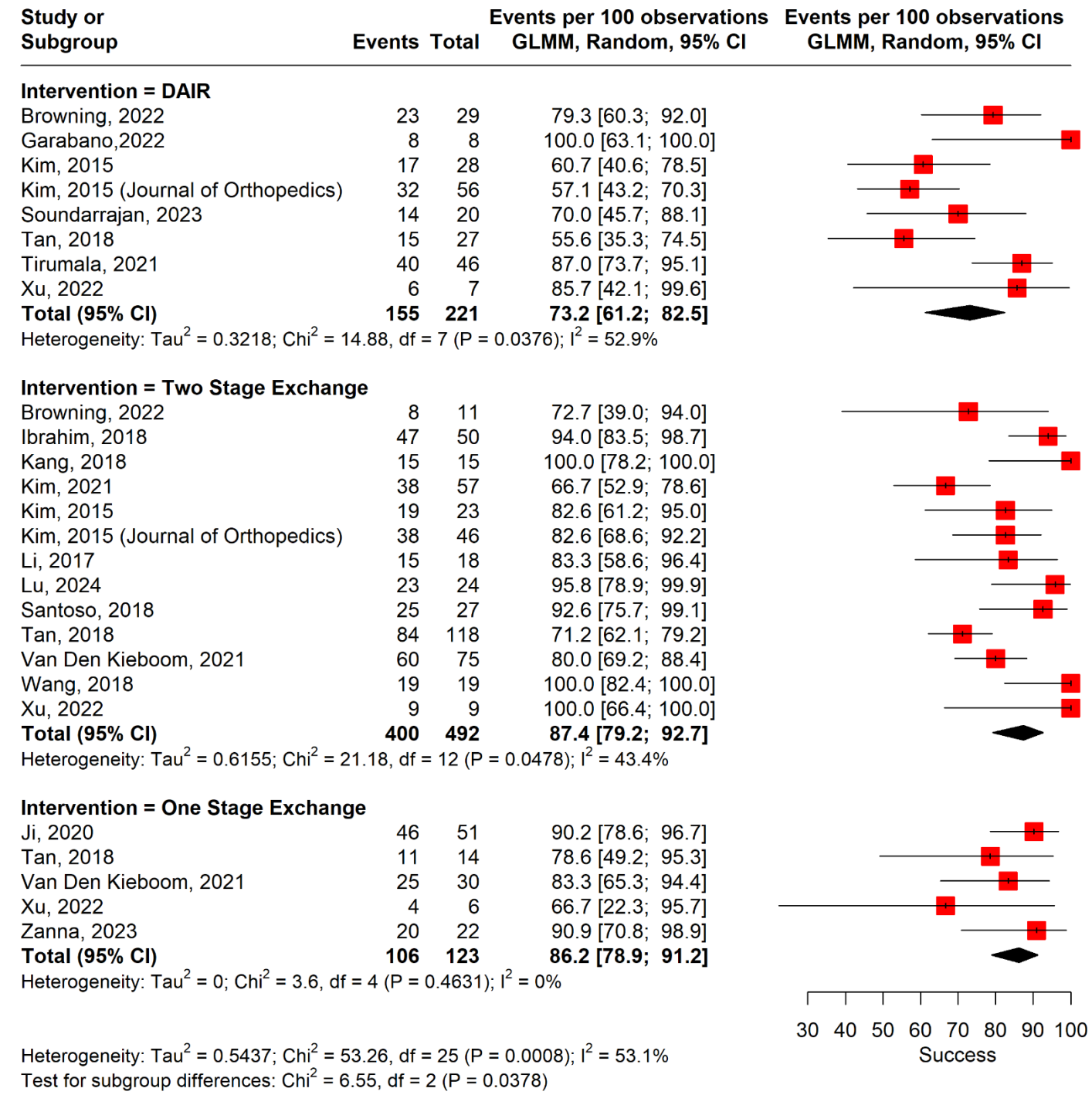

Fig. S3. Subgroup meta-analysis of treatment success according to surgical strategy. In the random-effects subgroup analysis, pooled treatment success was 73.2% (95% CI, 61.2%–82.5%; I^2 = 52.9%) for DAIR, 87.4% (95% CI, 79.2%–92.7%; I^2 = 43.4%) for two-stage exchange, and 86.2% (95% CI, 78.9%–91.2%; I^2 = 0%) for one-stage exchange. The difference between treatment-strategy subgroups was statistically significant (p = 0.0378)

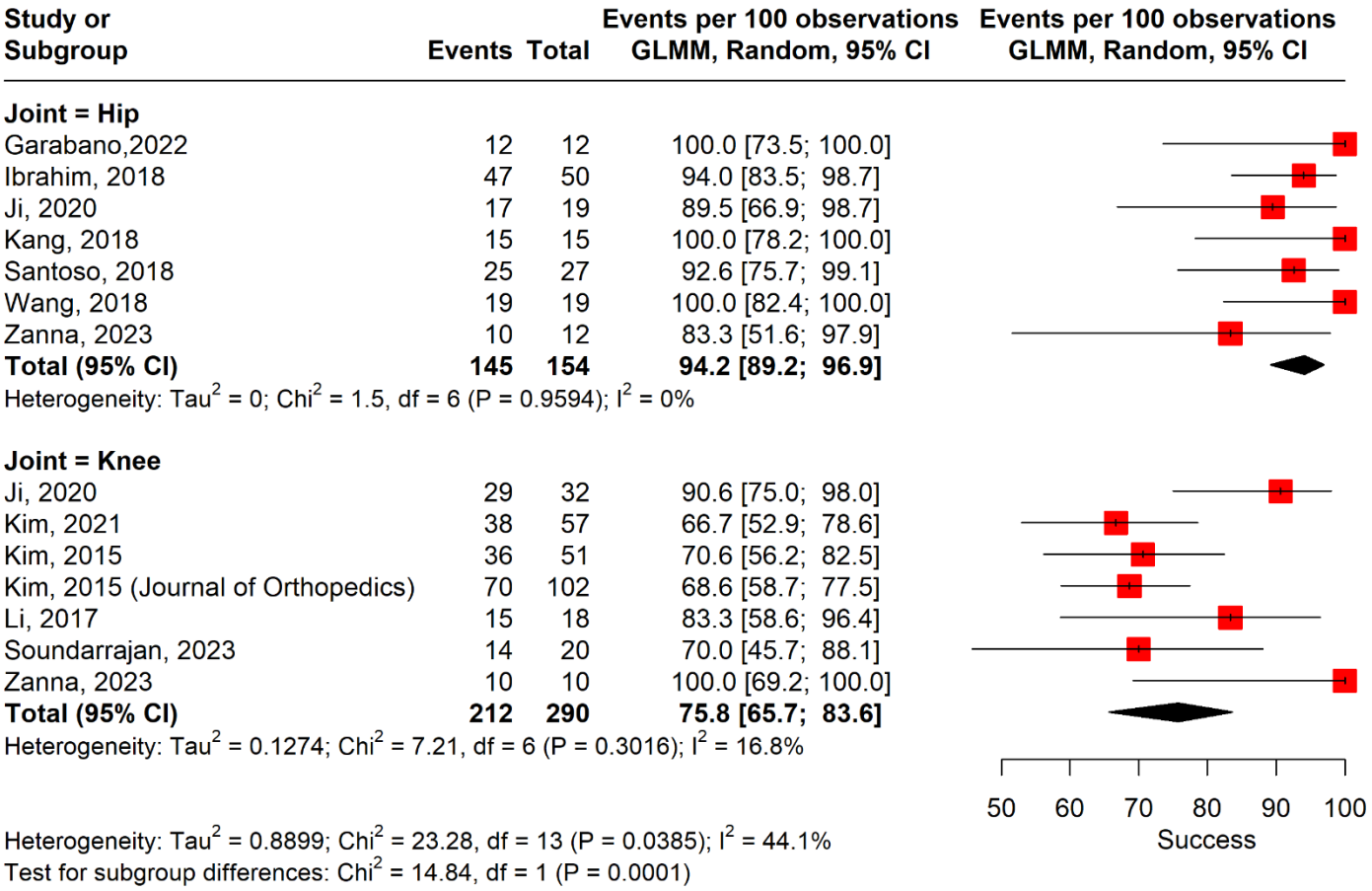

Fig. S4. Subgroup meta-analysis of treatment success according to joint type. In the random-effects subgroup analysis, pooled treatment success was significantly higher for hip PJI than for knee PJI, with success rates of 94.2% (95% CI, 89.2%–96.9%; $I^2 = 0\%$) and 75.8% (95% CI, 65.7%–83.6%; $I^2 = 16.8\%$), respectively. The difference between subgroups was statistically significant ($p = 0.0001$).

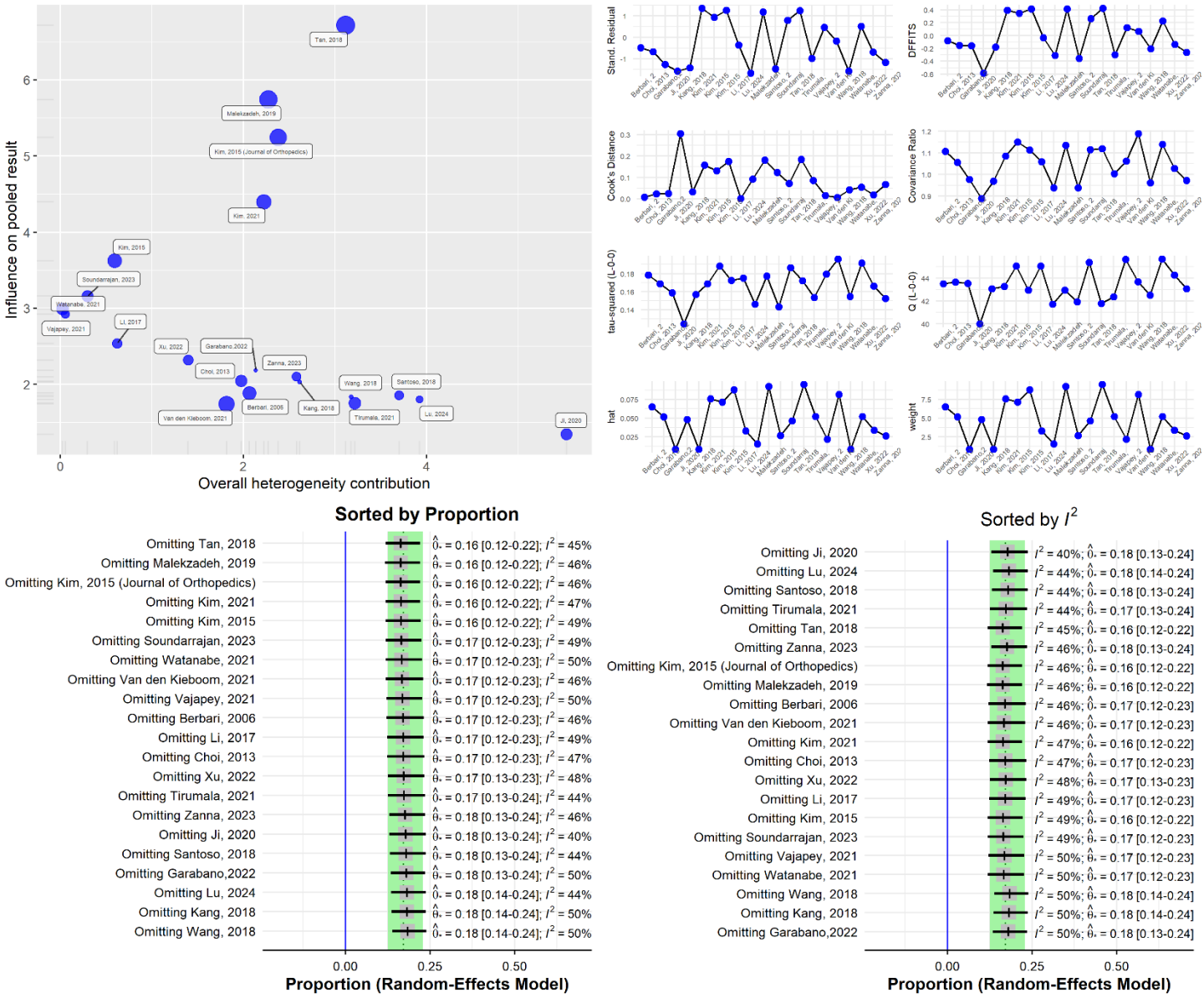

Fig. S5. Influence analysis and leave-one-out sensitivity analysis for treatment failure. Upper panels show study-level influence diagnostics, indicating that Tan, 2018; Malekzadeh, 2019; Kim, 2015 (Journal of Orthopedics); and Kim, 2021 were among the most influential contributors to the pooled treatment failure estimate and between-study heterogeneity.

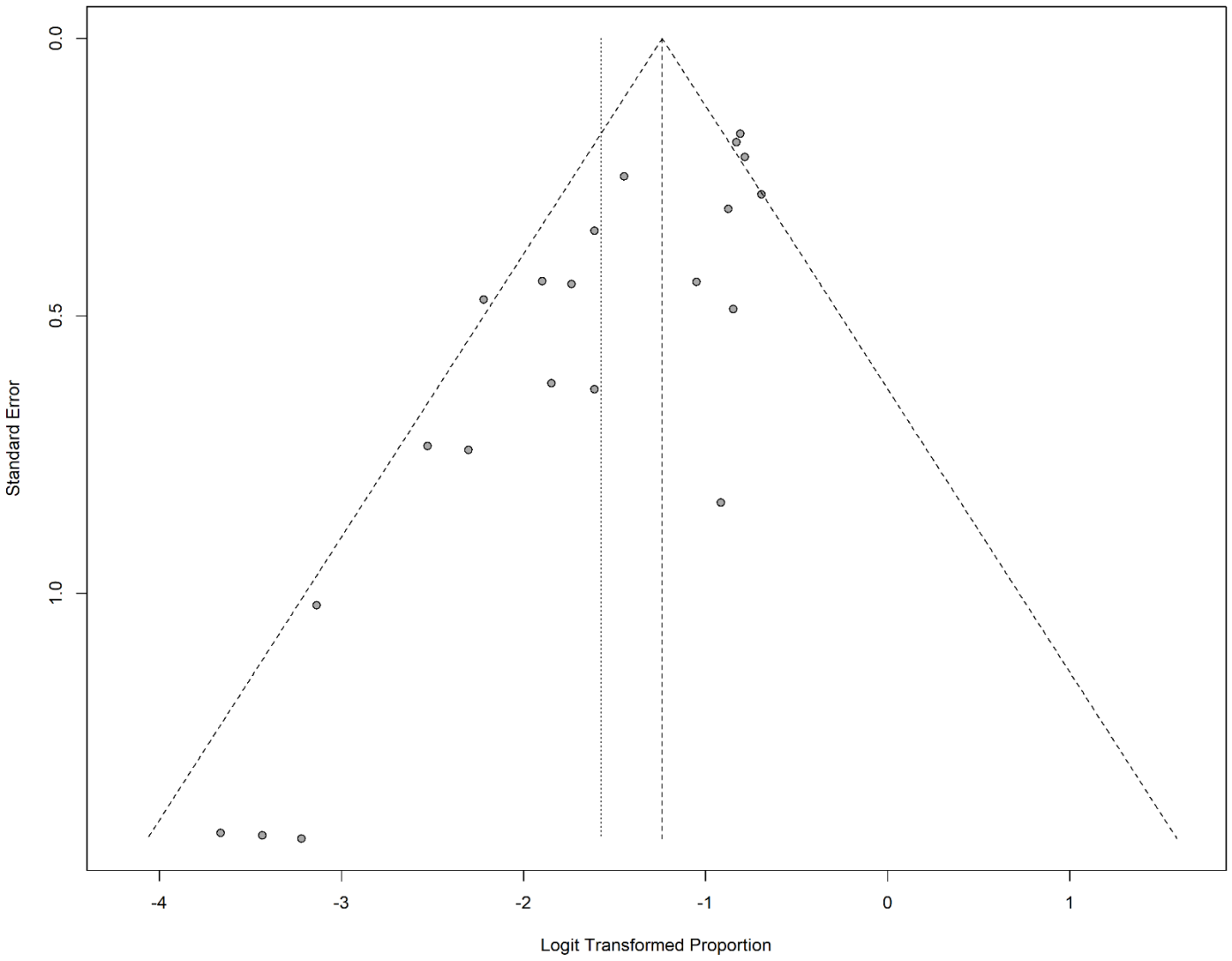

Fig. S6. Funnel plot for treatment failure. Visual inspection of the funnel plot suggests asymmetry, with a relative paucity of smaller studies on the right side of the plot and several small studies with lower reported failure rates on the left, raising concern for small-study effects or publication bias.

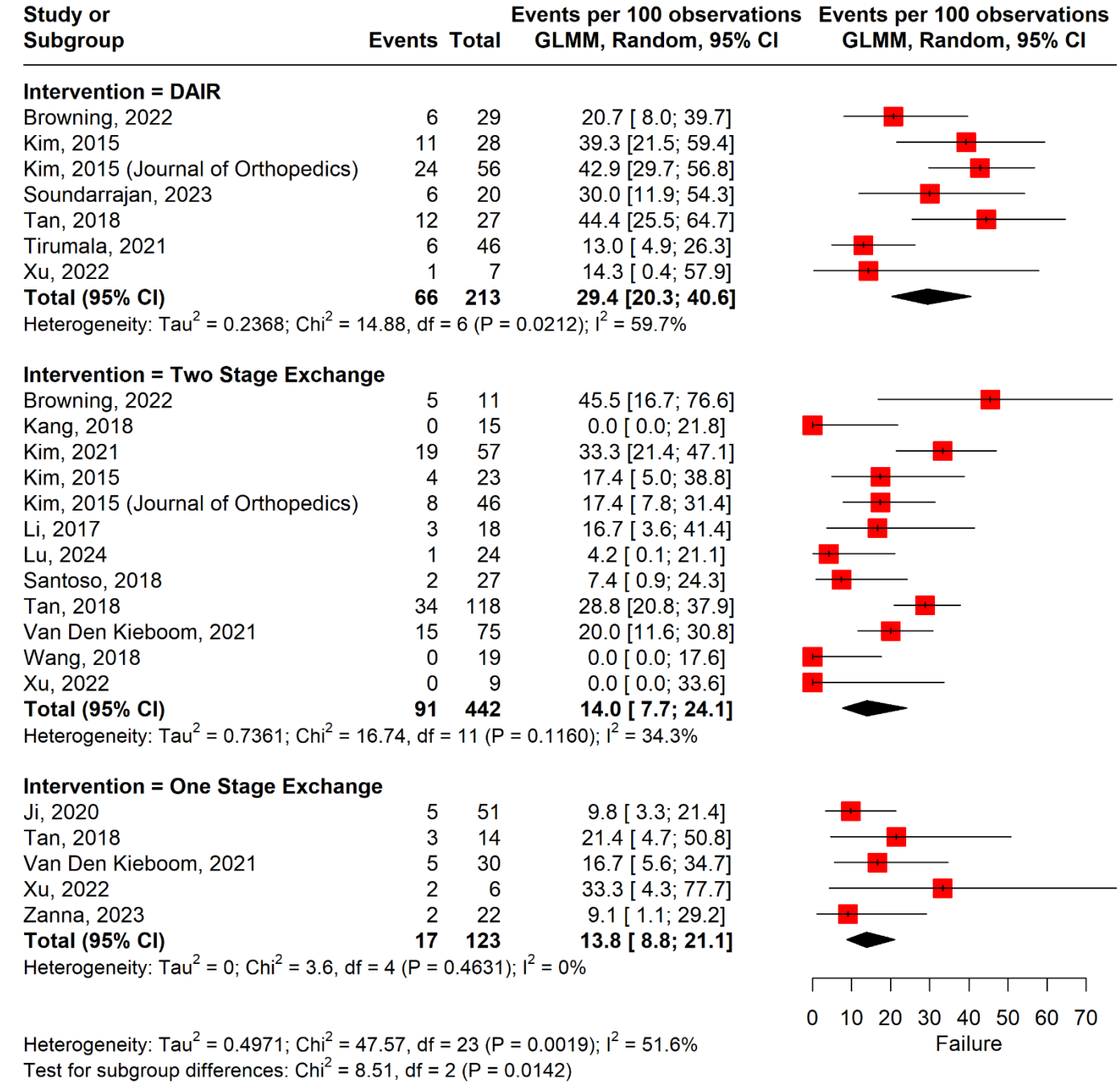

Fig. S7. Subgroup meta-analysis of treatment failure according to surgical strategy. In the random-effects subgroup analysis, pooled treatment failure was 29.4% (95% CI, 20.3%–40.6%; I^2 = 59.7%) for DAIR, 14.0% (95% CI, 7.7%–24.1%; I^2 = 34.3%) for two-stage exchange, and 13.8% (95% CI, 8.8%–21.1%; I^2 = 0%) for one-stage exchange. The difference between treatment-strategy subgroups was statistically significant (p = 0.0142).

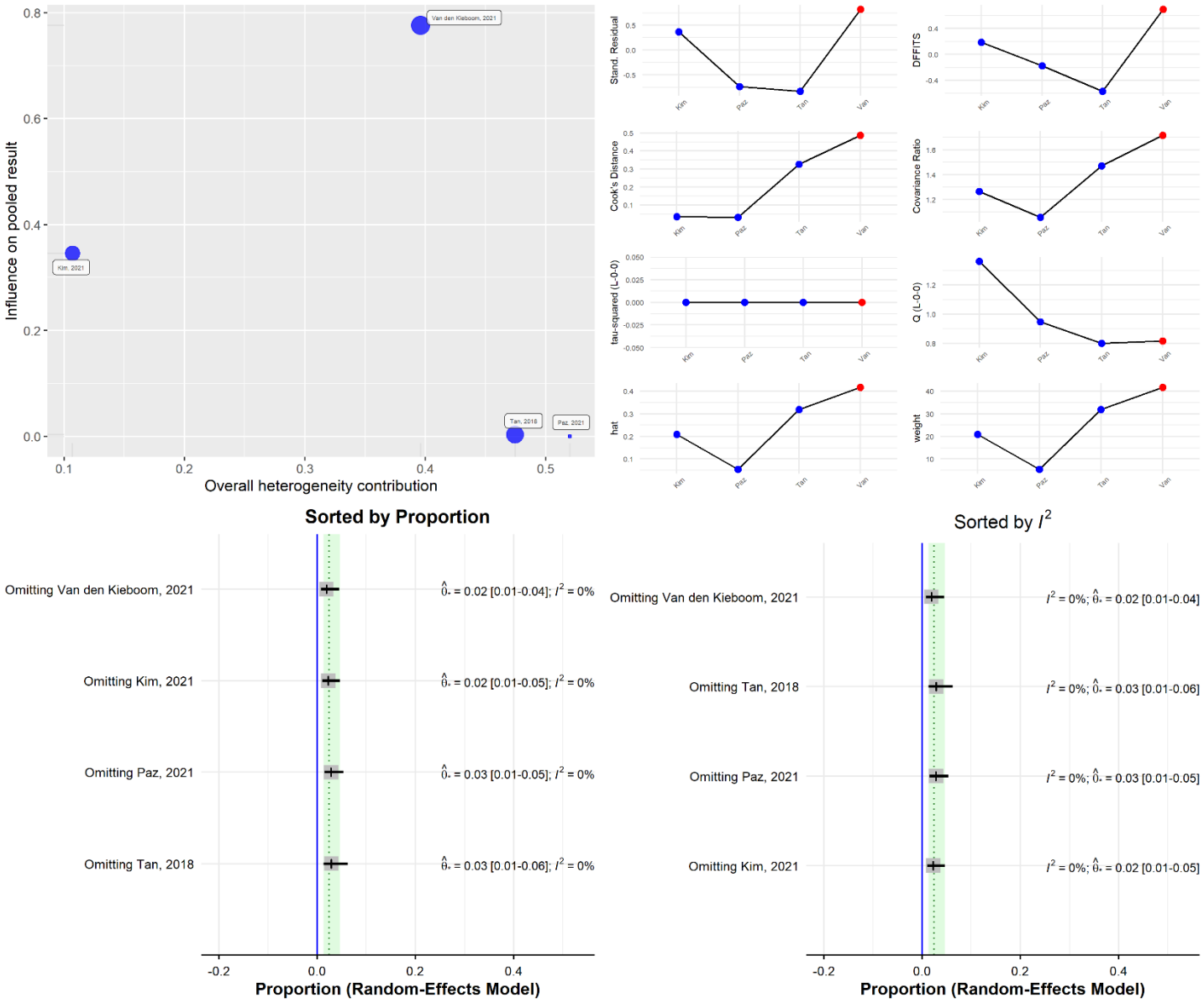

Fig. S8. Influence analysis and leave-one-out sensitivity analysis for mortality. Upper panels show study-level influence diagnostics, with Van den Kieboom, 2021 appearing to contribute most to the pooled mortality estimate and between-study heterogeneity. Lower panels show leave-one-out random-effects analyses, demonstrating that omission of any single study produced only minimal changes in the pooled mortality estimate and did not alter heterogeneity ($I^2 = 0\%$), supporting the stability of the findings.