Fever therapy in febrile adults: systematic review with meta-analyses and trial sequential analyses

Supplementary materials

Authors

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Appendix

Supplementary methods

CENTRAL, BIOSIS, CINAHL, MEDLINE, Embase, LILACS, Scopus and Web of Science Core Collection were searched to identify relevant trials.[1] Databases were searched from their inception to July 2nd 2021.

Randomized clinical trials with adults irrespective of age, sex and comorbidities diagnosed with fever (as defined by trialists) or hyperthermia (as defined by trialists) were included. Trials had to compare fever therapy with no fever therapy (with or without placebo/ sham). Fever therapy was defined as any treatment or combination of treatments given with the intention to reduce core body temperature, e.g., physical cooling and antipyretic drugs.[1] Any co-intervention was allowed if the co-intervention was planned to be delivered similarly in the compared groups.

Primary outcomes

- All-cause mortality
- Serious adverse events, defined as any untoward medical occurrence that resulted in death, was life-threatening, required hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or jeopardized the patient.[2] Expecting the reporting of serious adverse events to be heterogeneous and not strictly according to the 'International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use - Good Clinical Practice' (ICH-GCP) recommendations in many trials, serious adverse events were included if the trialists either: (1) used the term ‘serious adverse event’ but did not refer to ICH-GCP, or (2) reported the proportion of participants with an event we considered fulfilling the ICH-GCP definition. Serious adverse events were considered as any untoward medical occurrence that at any dose:
    - results in death,
    - is life-threatening,
    - requires inpatient hospitalization or prolongation of existing hospitalization,
    - results in persistent or significant disability or incapacity or
    - is a congenital anomaly/birth defect

If several such events were reported, then the highest proportion reported in each trial was chosen.

Secondary outcomes

- Quality of life measured on any valid continuous scale
- Non-serious adverse event defined as those leading to discontinuation of the intervention or defined as 'adverse events' by the trialists. Each adverse event was, if possible, analysed separately.

Exploratory outcomes

- Resolution of fever (as defined by the trialists).
- Temperature change (measured by body temperature).
- Number of serious adverse events (analysed as count data).
- Number of non-serious adverse events (analysed as count data).

Two authors (JH + AC) independently reviewed and extracted the data for each trial using a data extraction sheet. Following independent data extraction, the authors conducted a meeting to discuss any discrepancies, disagreements were resolved by a third reviewer (JCJ) or by consensus. All trial authors were contacted in attempt to obtain information if there was missing or unclear data.

Assessing the risk of bias two authors (JH + AC) independently reviewed the trials using the instructions given in the *Cochrane Handbook for Systematic Reviews of Interventions* evaluating the methodology in respect of: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other risks of bias.[3] The second version of the Cochrane risk-of-bias tool for randomized trials (RoB2) was used to assess risk of bias.[4] Each domain was assessed according to a three-step nominal scale: low risk of bias, some concerns, and high risk of bias. The overall risk of bias for a trial was classified as low risk of bias if all domains were assessed to be low risk of bias, of some concern if one or more domain were assessed as of some concern but no domain assessed as high risk of bias, and high risk of bias if any domain was assessed to be at high risk of bias. Trials at high risk of bias tend to overestimate beneficial effects and underestimate harmful effects.[5-11]

For dichotomous outcomes, risk ratios (RR) with 95% confidence intervals were calculated in the meta-analyses. Additionally, trial sequential analysis adjusted confidence intervals (CIs) were calculated using the trial sequential analysis program.[12,13] Fisher's exact test was used to calculate the risk ratio for single trial results.

We planned to handle missing data following the eight-step procedure suggested by Jakobsen *et al.* Providing that missing data constituted ≥ 5% of the overall data, the impact of missing data was evaluated through a "best-worst-case" scenario and a "worst-best-case" scenario. In the "best-worst-case" scenario it is assumed that all participants lost to follow-up in the experimental group had a beneficial outcome and those lost to follow-up in the control group had a harmful outcome and in the "worst-best-case" scenario it is assumed that all participants lost to follow-up in the experimental group had a harmful outcome and all those lost to follow-up in the control group had a beneficial outcome. These sensitivity analyses reveal the range of uncertainty due to missing data.[14]

Heterogeneity was primarily assessed through visual inspection of forest plots assessing the dispersion of trials across the combined effect estimate and secondarily through the I^2 statistic.[3] The threshold for interpretation of the I^2 statistic used the overlapping scale:

- 0 to 40%: might not be important;
- 30 to 60%: may represent moderate heterogeneity;
- 50 to 90%: may represent substantial heterogeneity;
- 75 to 100%: considerable heterogeneity

Heterogeneity was further investigated through relevant subgroup analyses. Funnel plots were used to visually assess reporting bias in meta-analyses including ≥ 10 trials.[15,16]

Data synthesis

Meta-analyses were performed following the *Cochrane Handbook of Systematic Reviews of Interventions*, Keus *et al* and Jakobsen *et al*. Stata version 16 (StataCorp LLC, College Station, TX, USA) was used to analyse the data.[3,14,17,18] Meta-analyses were performed using both fixed-effects (Mantel-Haenszel) and random-effects (DerSimonian-Laird) model to assign weight to the trials.[19,20] The model providing the most conservative result (highest p-

value) was chosen as the primary result, the less conservative result was considered a sensitivity analysis.[18] In the presence of statistical heterogeneity, a random-effects model is considered superior to a fixed-effect model but if one or two trial accounts for approximately 80 % or more of the total weight then a fixed-effect model is considered superior as a random-effects model could provide erroneous results.[3] The most correct and precise result is provided in the absence of heterogeneity where the two models converge and show identical results.

Multiple outcomes have major implications on the interpretation of confidence intervals and p-values due to an increased risk of false declaration of the effectiveness of an assessed intervention (type I error). To adjust the thresholds for statistical significance according to the number of outcome comparisons, a conservative approach was used dividing the pre-defined p-value threshold with the value halfway between one (no adjustment) and the number of primary outcome comparisons (Bonferroni adjustment).[18] A multiplicity adjusted p-value of $\leq$ 0.02 was set as threshold of statistical significance due to four primary and secondary outcomes being assessed.[18] The eight-step procedure suggested by Jakobsen et al was used to assess the clinical significance of the results.[18]

Trial sequential analyses were performed using software version 0.9.5.10 Beta (CTU, Copenhagen, Denmark) in attempt to reduce the risks of type I & II errors.[13,21-30] The trial sequential analysis manual was followed to estimate diversity-adjusted required information size (DARIS) and cumulative Z-curve's breach of the trial sequential monitoring boundaries.[13] The required information size was based on the cumulative portion of participants with events relative to all participants in the group, a relative risk reduction or increase of 25% as suggested by GRADE authors as default threshold, an alpha of 2% (p = 0.02) for all outcomes, a beta of 10% (90% power) and the diversity of the trials in the meta-analysis [18,27,31]. We investigated and defined the lowest effect estimate that could be confirmed or rejected using trial sequential analyses.

Subgroup analyses were performed, using Stata version 16 (StataCorp LLC, College Station, TX, USA).[14] Subgroup analyses were performed to investigate heterogeneity between trials and to be hypothesis-generating for further studies. Multiple analyses increase the risk of type I errors and further interpretation of the subgroup analyses results should be done with caution. We planned the following subgroup analyses:

- Comparison of different types of fever therapies
- Critically ill compared to non-critically ill participants
- Participants with infectious fever compared to non-infectious fever
- Comparison of different follow-up time points
- Comparison of different control interventions
- Comparison of different funding resources (industry funded or unknown finding/ non-industry funding)

We performed a post hoc subgroup analysis comparing trials with a statistically significant temperature difference between the compared groups to trials with a non-significant temperature difference.

The approach proposed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) working group was used for rating the certainty of the evidence.[32-34] Five domains were assessed: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The evidence was rated to be either of high certainty, moderate certainty, low certainty, or very low certainty.[32-34]

Supplementary results

Quality of life

There was only one trial presenting data on quality of life. Using the EQ-5D-5L descriptive system comprising of the five dimensions of health (mobility, self-care, usual activities, pain and discomfort, and anxiety and depression) at 24, 48 and 72 hours the trial authors concluded that there was no significant difference in quality of life between paracetamol and placebo group and that further studies are needed to reveal a potential difference.[35]

Non-serious adverse events

Four trials (6 comparisons) with a total of 767 participants reported on non-serious adverse events. The included trials assessed the effects of three different fever therapy interventions: ibuprofen versus placebo [36,37] (2 trials), acetaminophen versus placebo [38] (1 trial), and sulindac versus placebo [39] (1 trial). 455/767 participants were hospitalised, and 453/767 were non-critically ill (Table S1). One trial included both critically ill and non-critically ill participants (314/767) (Table S1). 392/767 had infectious fever and 61/767 had non-infectious

fever (Table S1). For 120/767 participants the origin of fever was unknown (Table S1). A total of 137 trial participants out of 329 (41.6%) had a non-serious adverse event in the fever therapy group compared with 57 of 244 (23.4%) in the control group.

Meta-analysis of non-serious adverse events did not show evidence of a difference (RR 0.92; 95% CI 0.67 to 1.25; I^2=66.50%; p=0.58, 4 trials; very low certainty evidence) (Figure S20, Table 3). Quantitative measures of heterogeneity (I^2=66.50 %) combined with visual inspection of the forest plot revealed signs of significant heterogeneity (Figure S20). Trial sequential analysis showed that we could neither confirm nor reject that fever therapy reduced the relative risk of non-serious adverse events by 25% (Figure S21). This outcome result was assessed as high risk of bias and the certainty of the evidence was assessed as very low (Table 3). The certainty of the evidence was downgraded three levels due to considerable risk of bias in the included trials; imprecision due to trial sequential analysis showing no crossing of trial sequential analysis monitoring boundaries, low number of participants and inconsistency due to large heterogeneity. The assessment time-points varied between trials with an interval of 1 day after randomization to 28 days after randomization.[36,38]

Subgroup analysis comparing different fever therapies showed evidence of a subgroup difference (p≤0.01) (Figure S23). When trials assessing ibuprofen were analysed separately, meta-analysis showed RR 0.76; 95% CI 0.64 to 0.91; I^2=0%, 2 trials (Figure S23). When trials assessing acetaminophen were analysed separately, Fisher's exact test showed RR 4.76; 95% CI 0.24 to 96.16; 1 trial (Figure S23). When trials assessing sulindac were analysed separately, Fisher's exact test showed RR 2.18; 95% CI 1.28 to 3.70; 1 trial (Figure S23).

Subgroup analysis comparing different fever origins showed evidence of a subgroup difference (p≤0.01) (Figure S25). When trials assessing infectious fever were analysed separately, meta-analysis showed RR 2.23; 95% CI 1.32 to 3.75; I^2=0%, 2 trials (Figure S25). When trials assessing non-infectious fever were analysed separately, Fisher's exact test showed RR 0.81; 95% CI 0.55 to 1.18; 1 trial (Figure S25). When trials assessing fever of unknown origin were analysed separately, Fisher's exact test showed RR 0.75; 95% CI 0.62 to 0.91; 1 trial (Figure S25).

Subgroup analysis comparing different follow-up times showed evidence of a subgroup difference (p≤0.01) (Figure S24). When trials with 1-day follow-up were analysed separately,

Fisher's exact test showed RR 4.76; 95% CI 0.24 to 96.16; 1 trial (Figure S26). When trials with 7-days follow-up were analysed separately, Fisher's exact test showed RR 2.18; 95% CI 1.28 to 3.70; 1 trial (Figure S26). When trials with 28-days follow-up were analysed separately, Fisher's exact test showed RR 0.75; 95% CI 0.61 to 0.91; 1 trial (Figure S26). When trials with in-hospital follow-up were analysed separately, Fisher's exact test showed RR 0.81; 95% CI 0.55 to 1.18; 1 trial (Figure S26).

None of the other subgroup analyses showed evidence of a difference (Figure S24, S27).

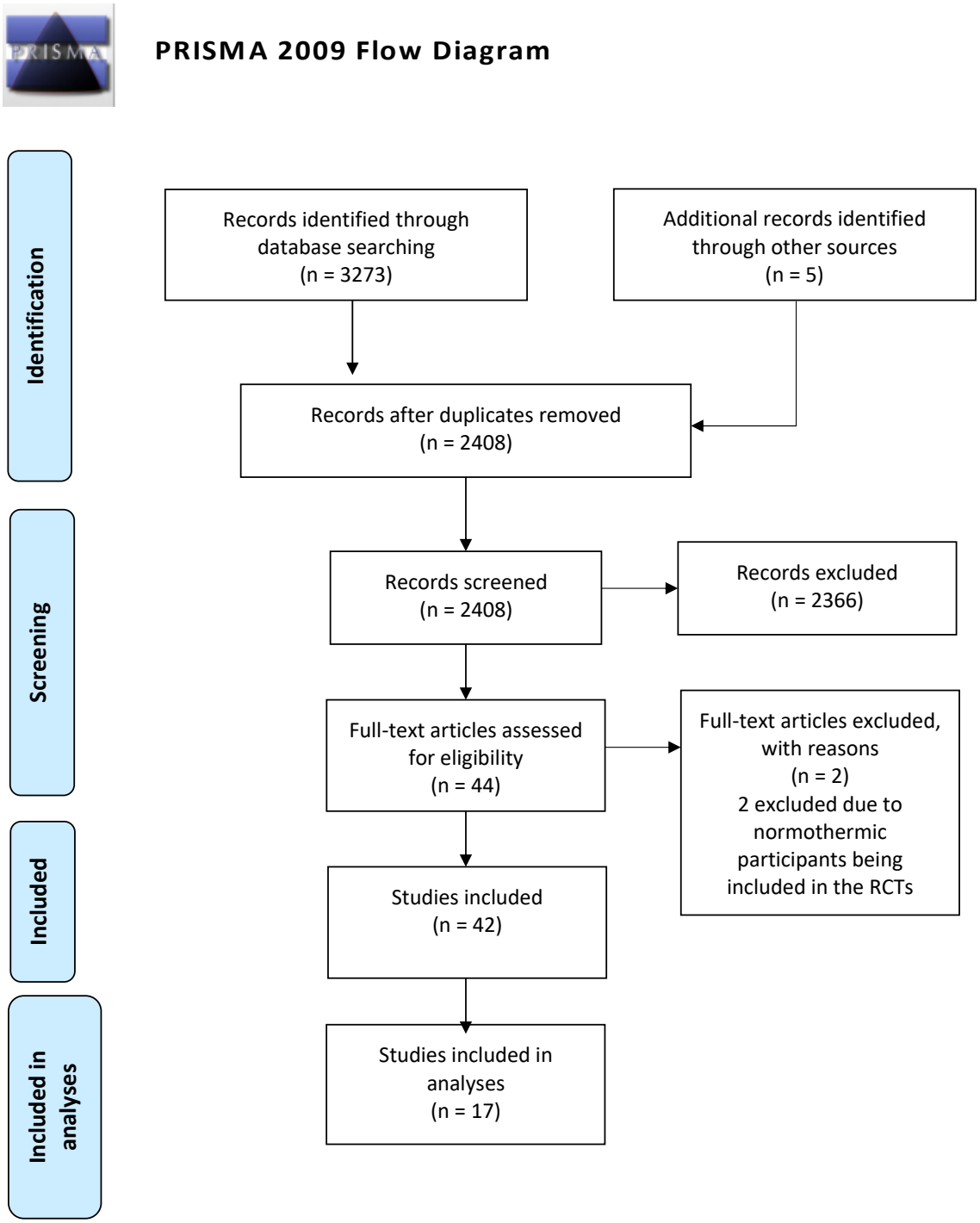
Exploratory outcomes

There was only one trial (two comparisons) presenting data on time until resolution of fever. The trial authors concluded that there was no significant difference in the time until resolution of fever in the three compared groups.[40]

Due to temperature change (fever reduction) data being presented in multiple ways not analysable in a meta-analysis, the available data are presented descriptively. The mean (±SD) maximal reported temperature reduction caused by antipyretics was 1.28ºC (±0.45) and the mean (±SD) maximal reported temperature reduction caused by physical cooling was 1.07 ºC (±0.62). Forty-six out of seventy-five comparisons showed a significantly lower temperature in the fever therapy group compared with the group without fever therapy (Table S1). The twenty-nine comparisons not presenting a significantly lower temperature in the fever therapy group consisted of 551 participants accounting for 10.7% of all participants.

Figures

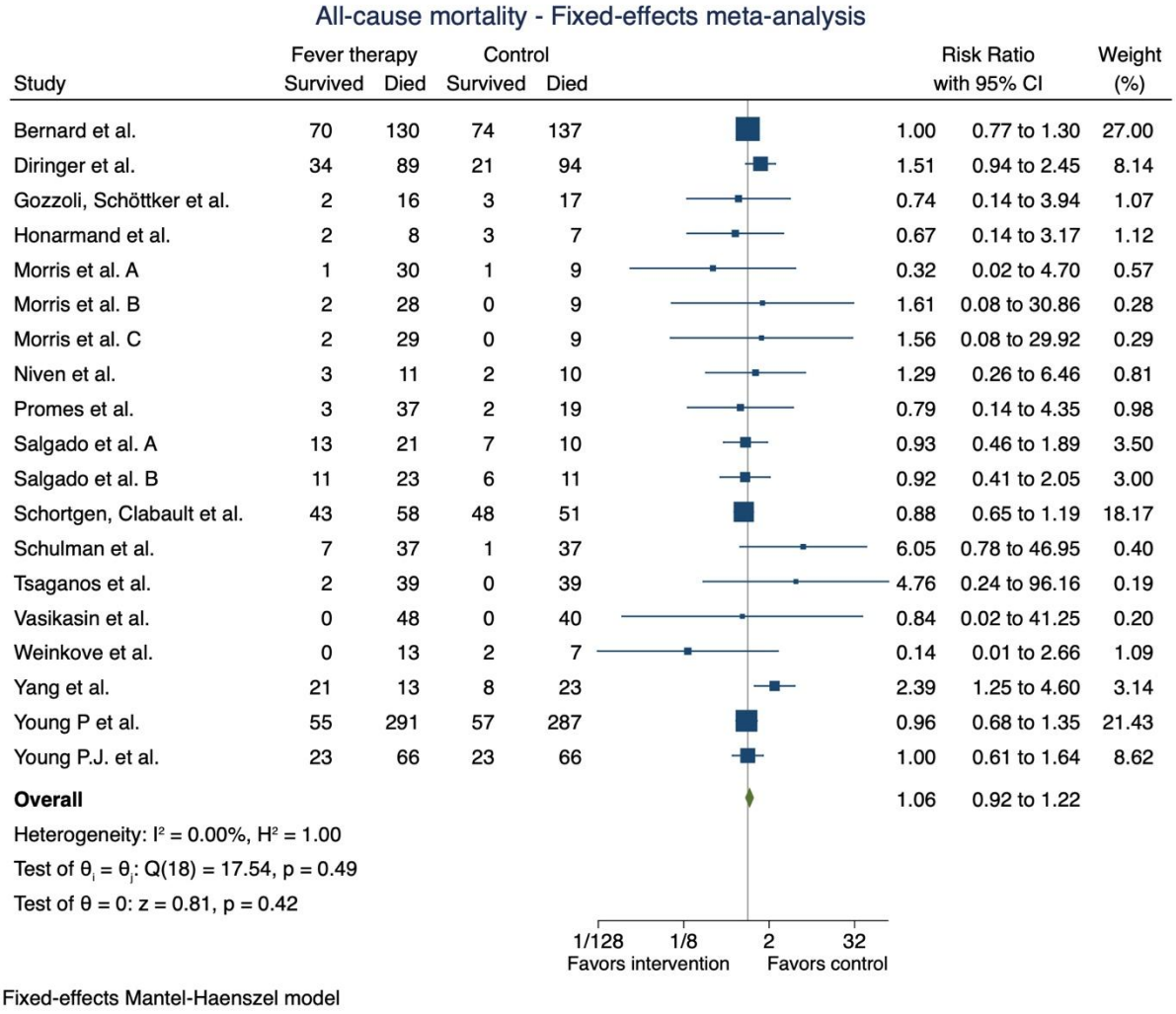
Figure S1: PRISMA Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

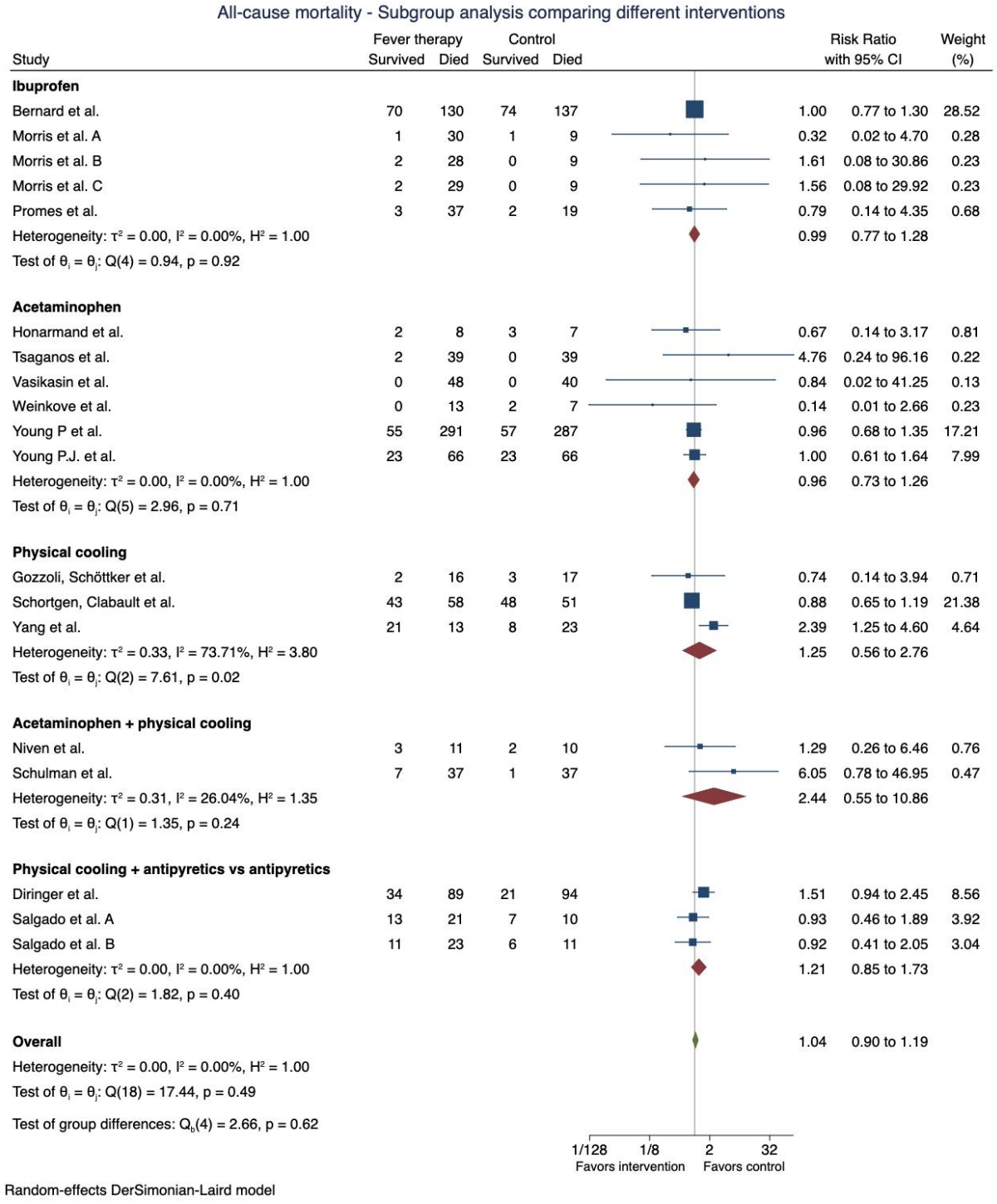
For more information, visit www.prisma-statement.org.

Figure S2: Fixed-effects meta-analysis of fever therapy versus control interventions on all-cause mortality



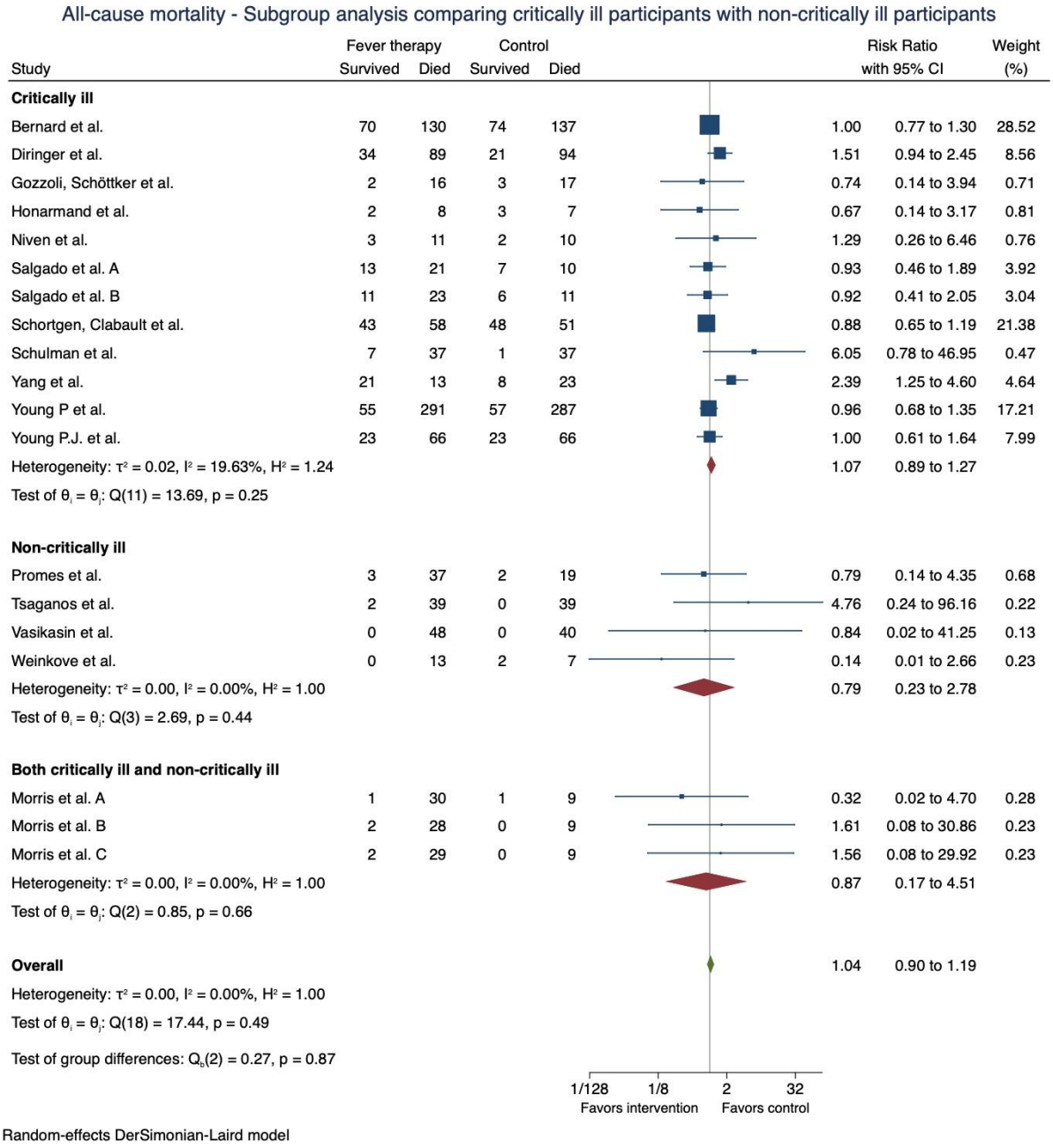
Fixed-effects meta-analysis showed no evidence of a difference between fever therapy and control interventions on all-cause mortality (RR 1.06; 95% CI 0.92 to 1.22; $p = 0.42$; $I^2 = 0$ %; 16 trials).
RR: Risk ratio
CI: Confidence interval
I^2: Measure of heterogeneity

Figure S3: Subgroup analysis of all-cause mortality comparing different intervention types



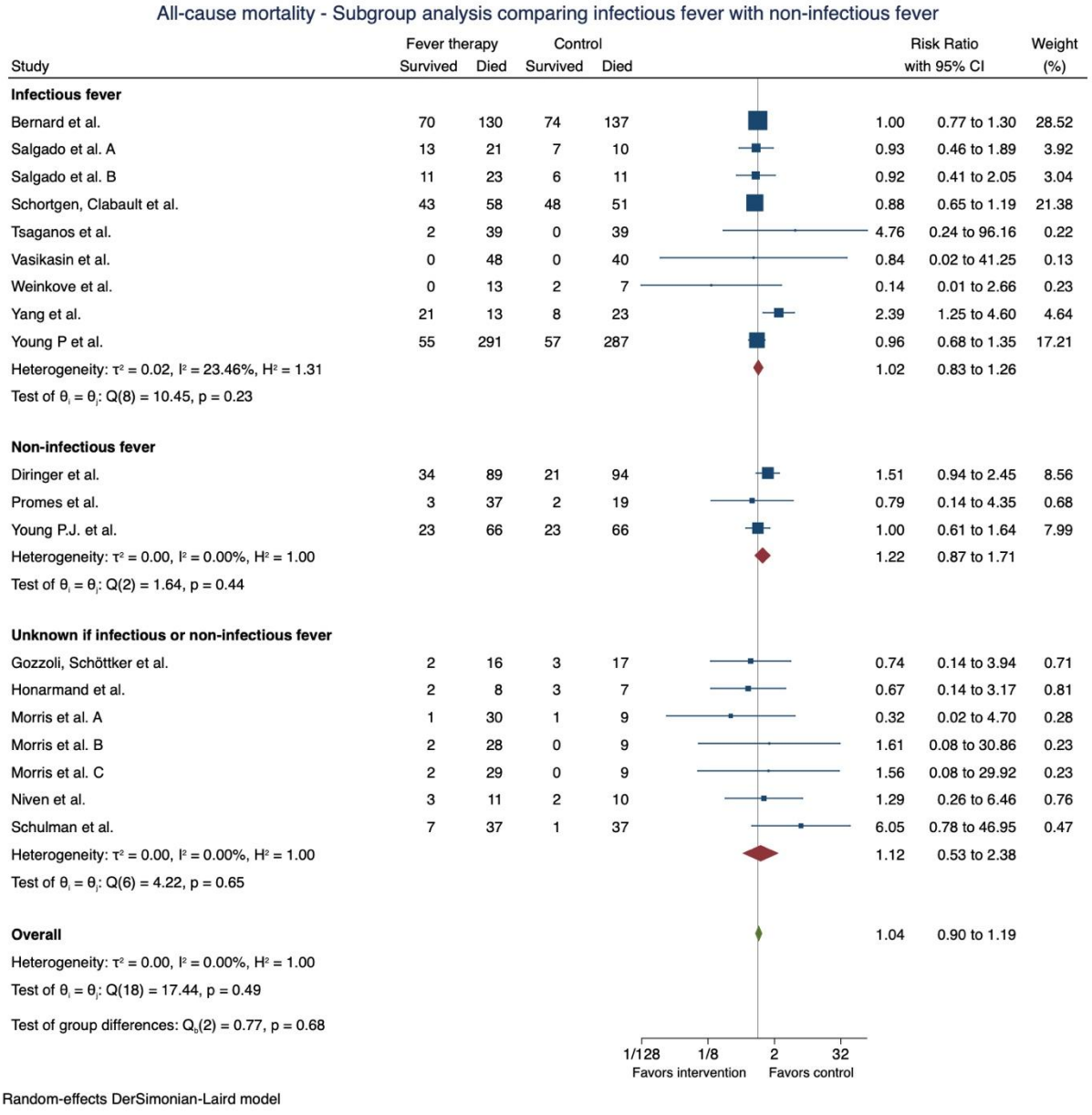
Subgroup analysis comparing different intervention types showed no evidence of a subgroup difference (p = 0.62).
RR: Risk ratio
CI: Confidence interval
I^2: Measure of heterogeneity

Figure S4: Subgroup analysis of all-cause mortality comparing critically ill versus non-critically ill



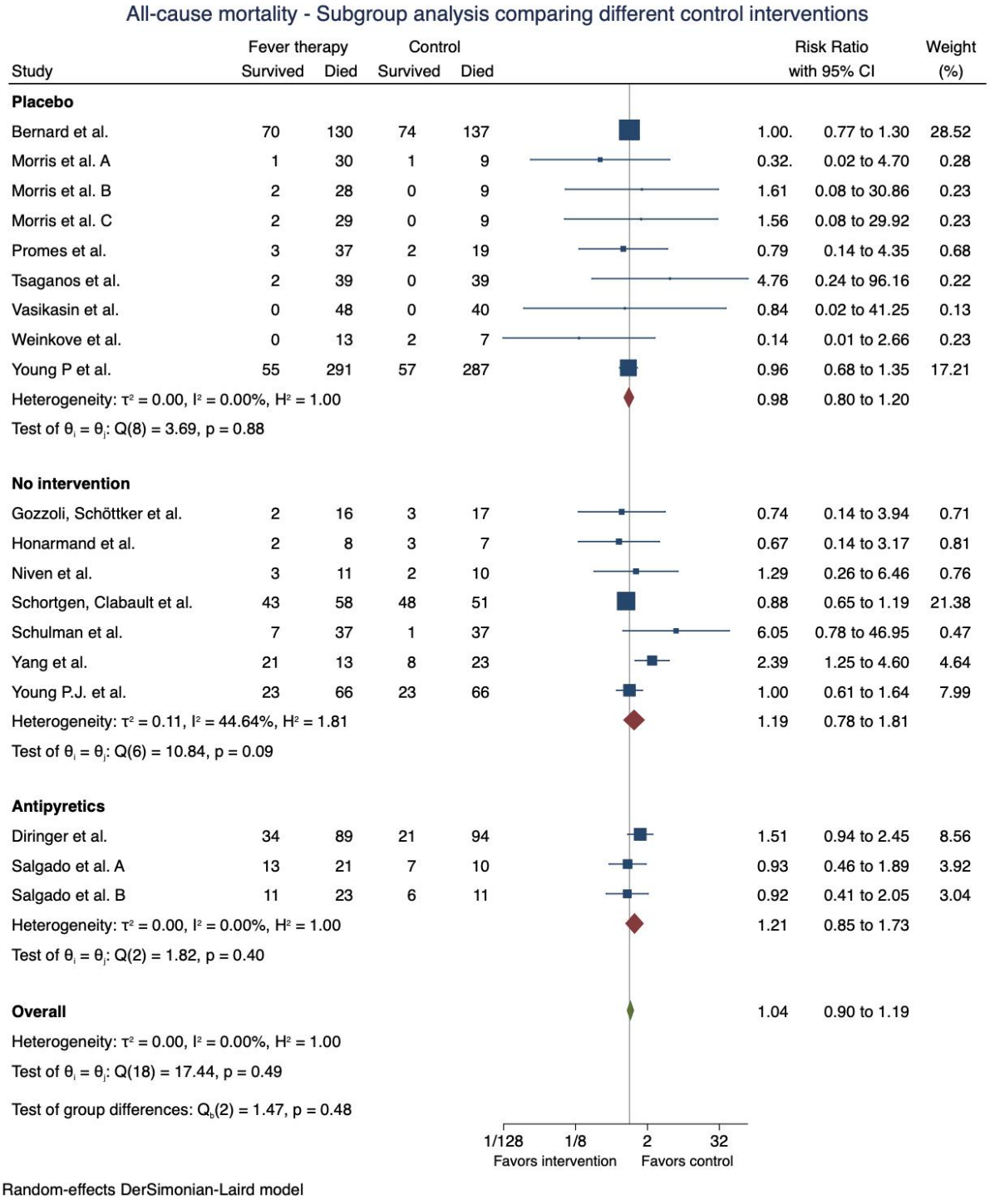
Subgroup analysis comparing critically ill participants with non-critically ill participants showed no evidence of a subgroup difference (p = 0.87).
RR: Risk ratio
CI: Confidence interval
I^2: Measure of heterogeneity

Figure S5: Subgroup analysis of all-cause mortality comparing infectious fever with non-infectious fever



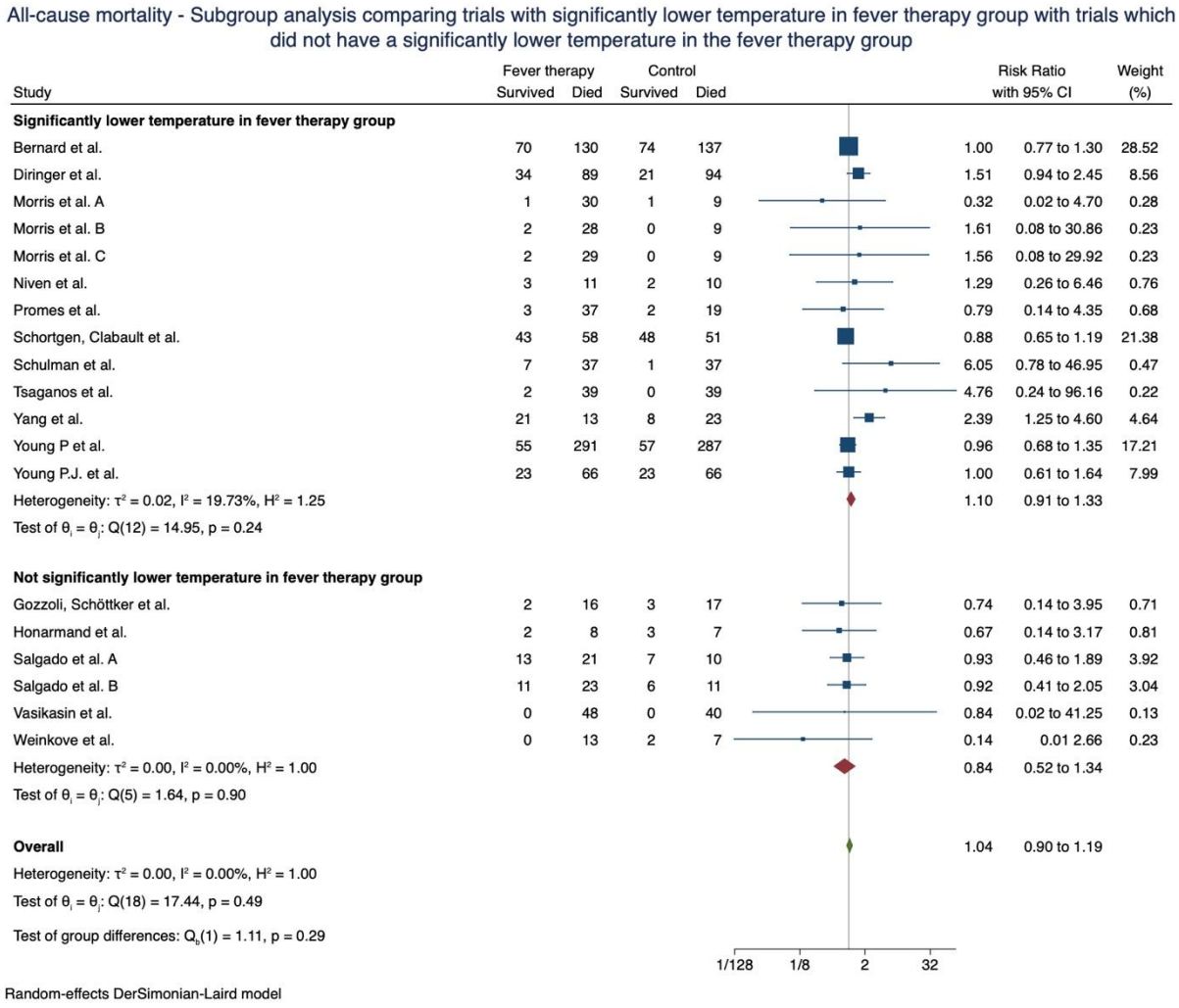
Subgroup analysis comparing infectious fever with non-infectious fever showed no evidence of a subgroup difference (p = 0.68).
RR: Risk ratio
CI: Confidence interval
I^2: Measure of heterogeneity

Figure S6: Subgroup analysis of all-cause mortality comparing different control interventions



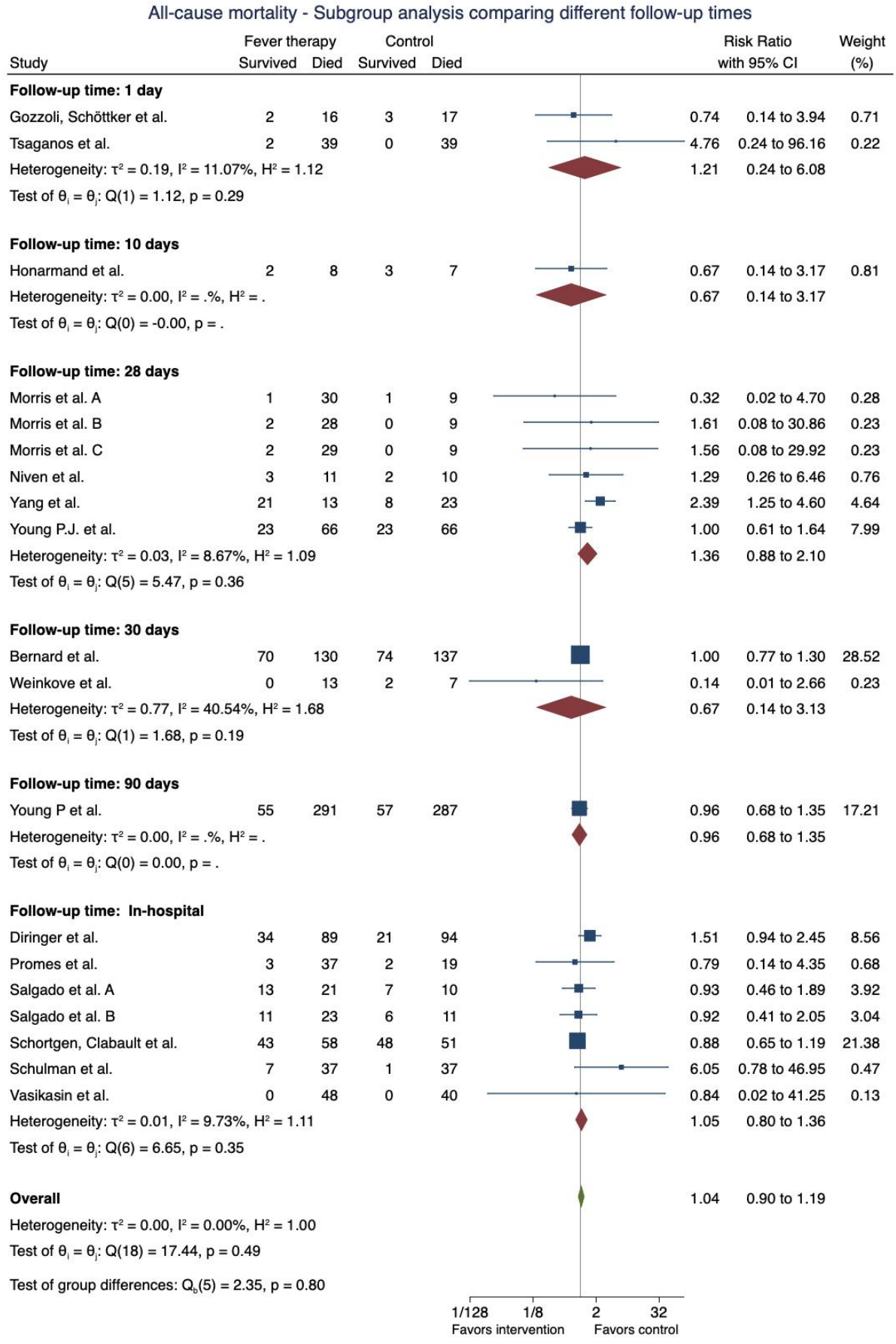
Subgroup analysis comparing different control interventions (placebo, standard care and antipyretics) showed no evidence of a subgroup difference (p = 0.48).
RR: Risk ratio
CI: Confidence interval
I^2: Measure of heterogeneity

Figure S7: Subgroup analysis of all-cause mortality comparing trials with significantly lower temperature in fever the fever therapy group with trials with non-significantly lower temperature in the fever therapy group



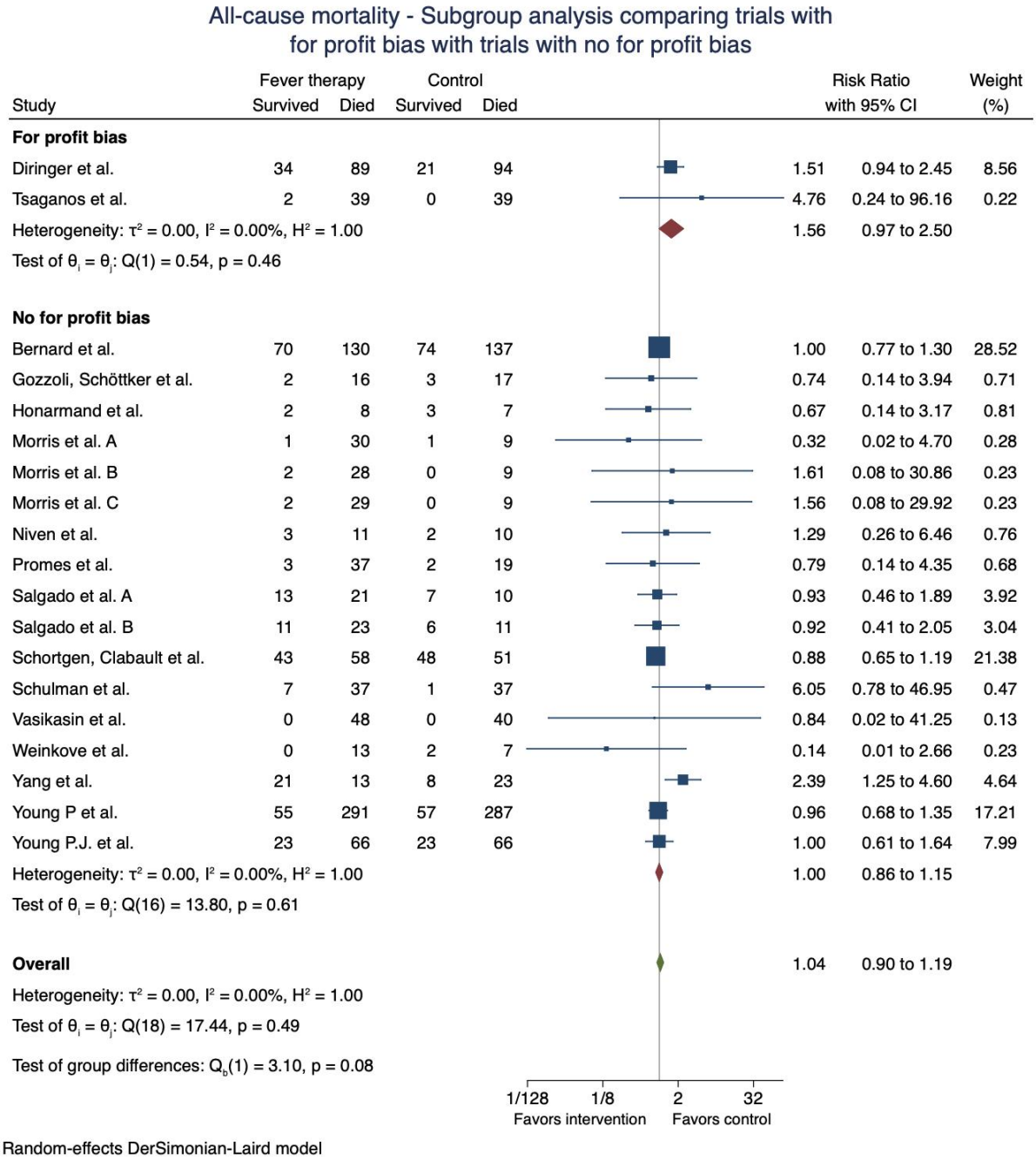
Subgroup analysis comparing trials with significantly lower temperature in fever the fever therapy group with trials with non-significantly lower temperature in the fever therapy group showed no evidence of a subgroup difference (p = 0.29).
RR: Risk ratio
CI: Confidence interval
I^2: Measure of heterogeneity

Figure S8: Subgroup analysis of all-cause mortality comparing different follow-up times



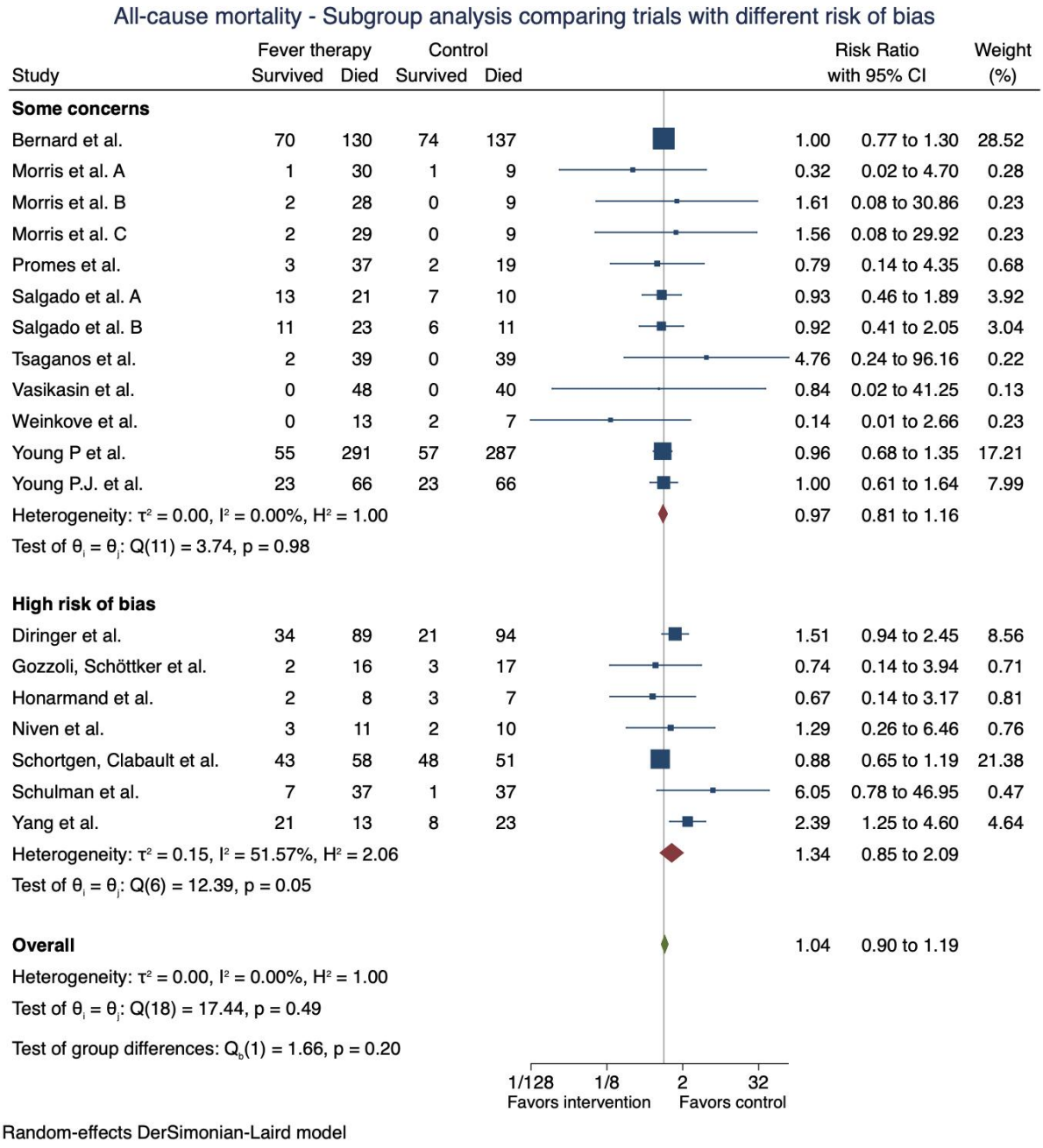
Subgroup analysis comparing different follow-up times showed no evidence of a subgroup difference ($p = 0.80$).
RR: Risk ratio
CI: Confidence interval
I^2: Measure of heterogeneity

Figure S9: Subgroup analysis of all-cause mortality comparing trials with for profit bias with trials without for-profit bias



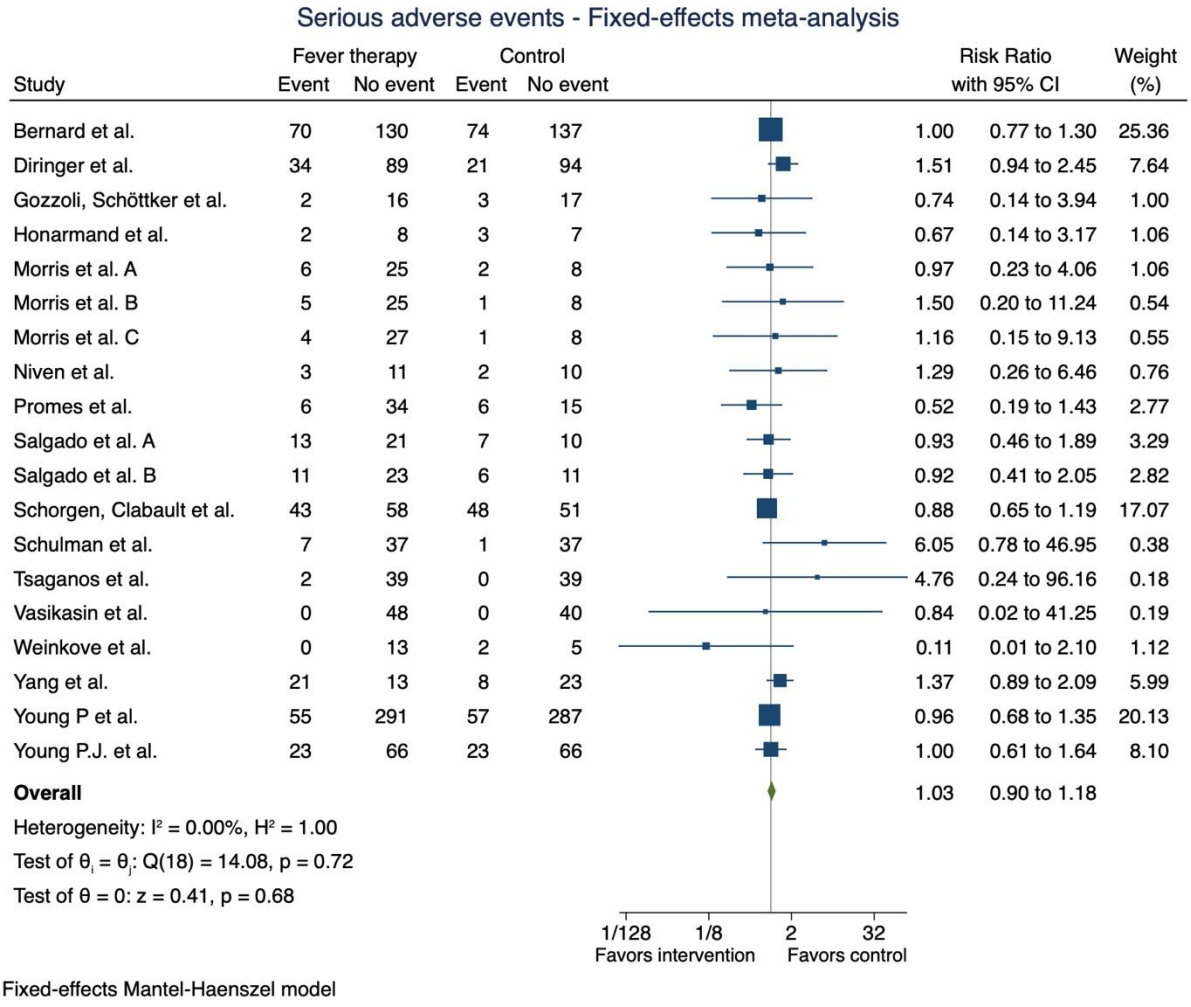
Subgroup analysis comparing trials with for profit biased with trials with no for profit bias showed no evidence of a subgroup difference (p = 0.08).
RR: Risk ratio
CI: Confidence interval
I^2: Measure of heterogeneity

Figure S10: Subgroup analysis of all-cause mortality comparing trials with different levels of risk of bias



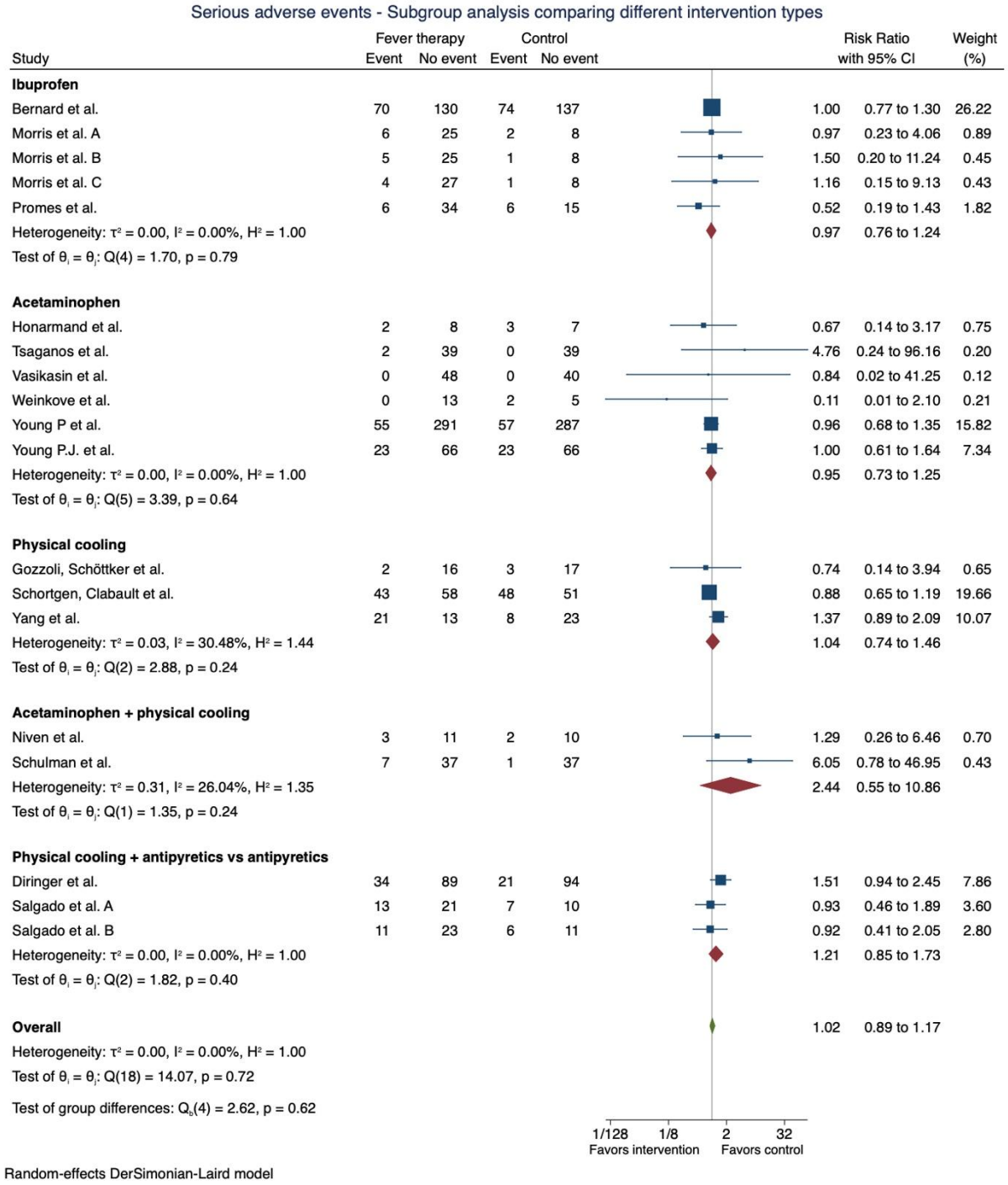
Subgroup analysis comparing trials with different risk of bias showed no evidence of a subgroup difference (p = 0.20).
RR: Risk ratio
CI: Confidence interval
I^2: Measure of heterogeneity

Figure S11: Fixed-effects meta-analysis of fever therapy versus control interventions on serious adverse events



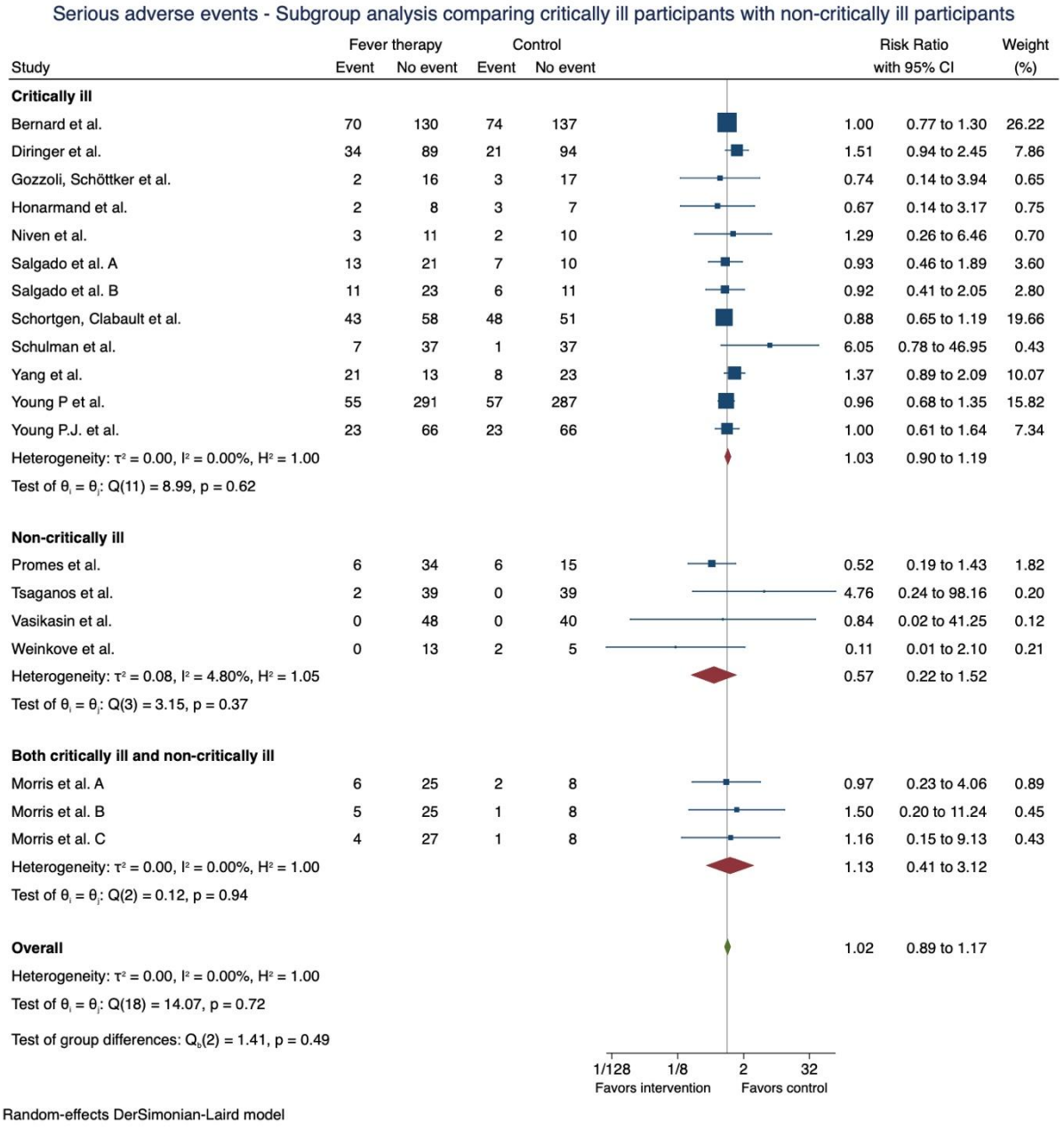
Fixed-effects meta-analysis showed no evidence of a difference between fever control interventions and control interventions on serious adverse events (RR 1.03; 95% CI 0.90 to 1.18; $p = 0.68$; $I^2 = 0$ %; 16 trials).
RR: Risk ratio
CI: Confidence interval
I^2: Measure of heterogeneity

Figure S12: Subgroup analysis of serious adverse events comparing different intervention types



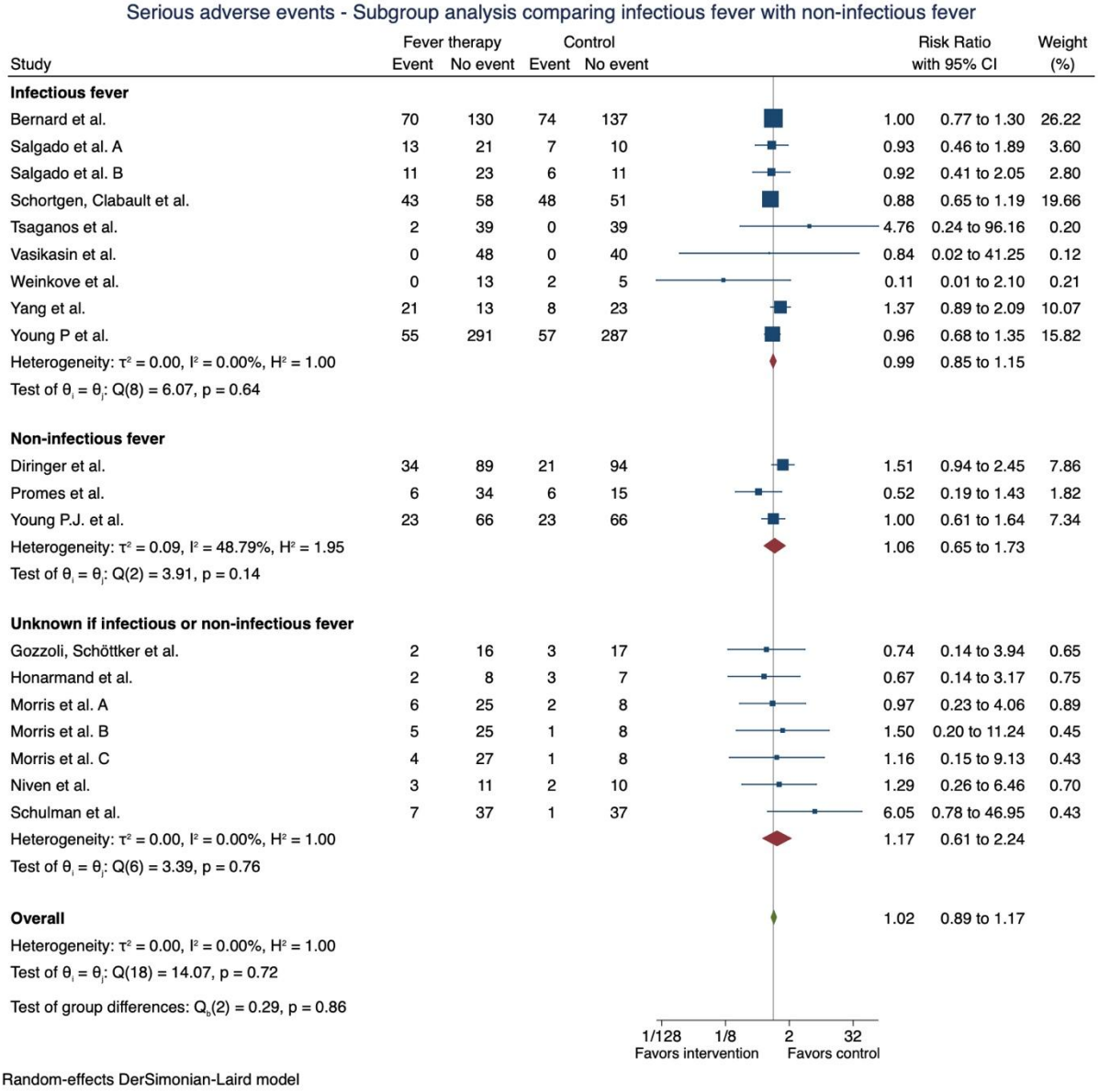
Subgroup analysis comparing different intervention types showed no evidence of a subgroup difference (p = 0.62).
RR: Risk ratio
CI: Confidence interval
I^2: Measure of heterogeneity

Figure S13: Subgroup analysis of serious adverse events comparing critically ill versus non-critically ill



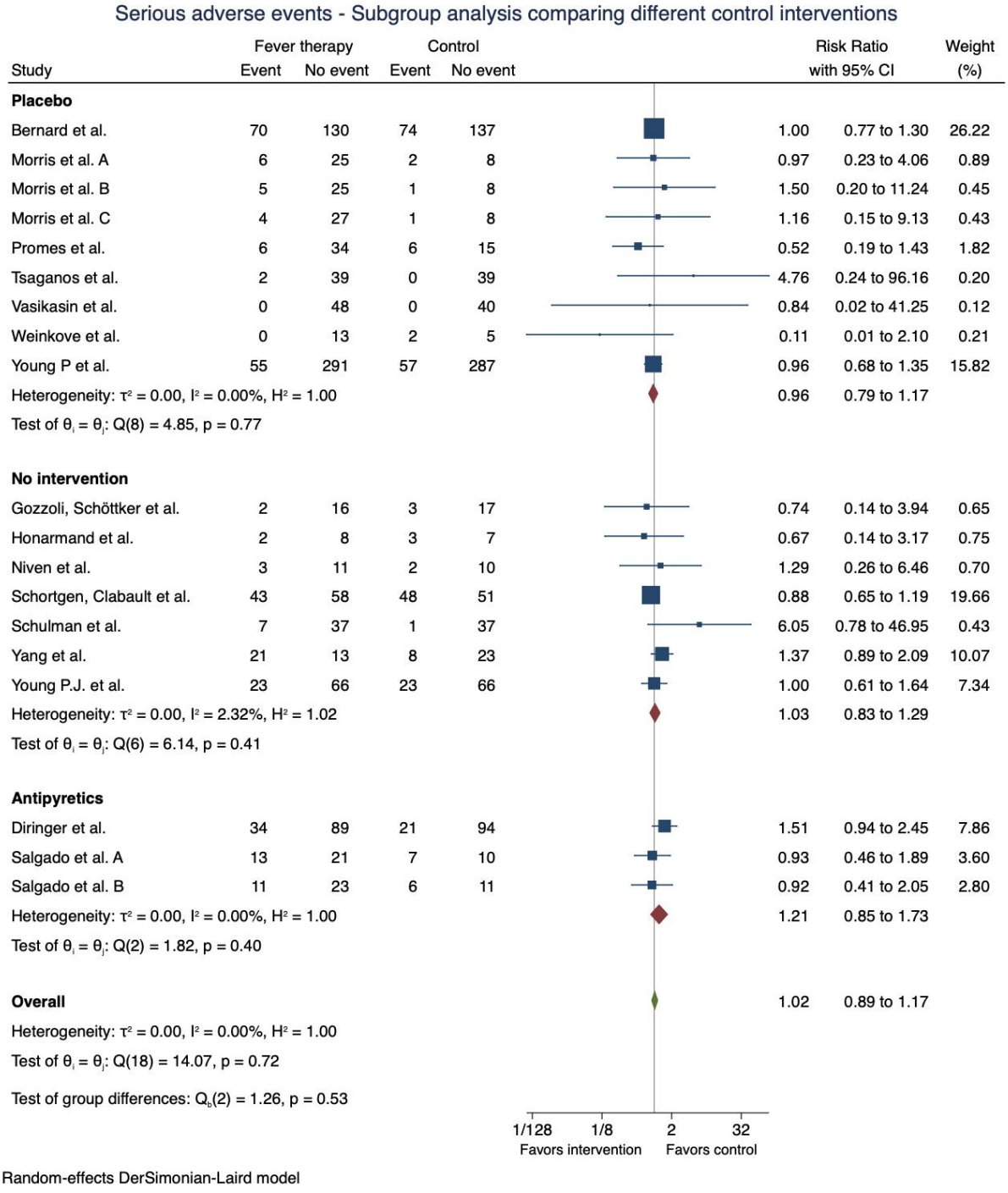
Subgroup analysis comparing critically ill with non-critically ill showed no evidence of a subgroup difference (p = 0.49).
RR: Risk ratio
CI: Confidence interval
I^2: Measure of heterogeneity

Figure S14: Subgroup analysis of serious adverse events comparing infectious fever with non-infectious fever



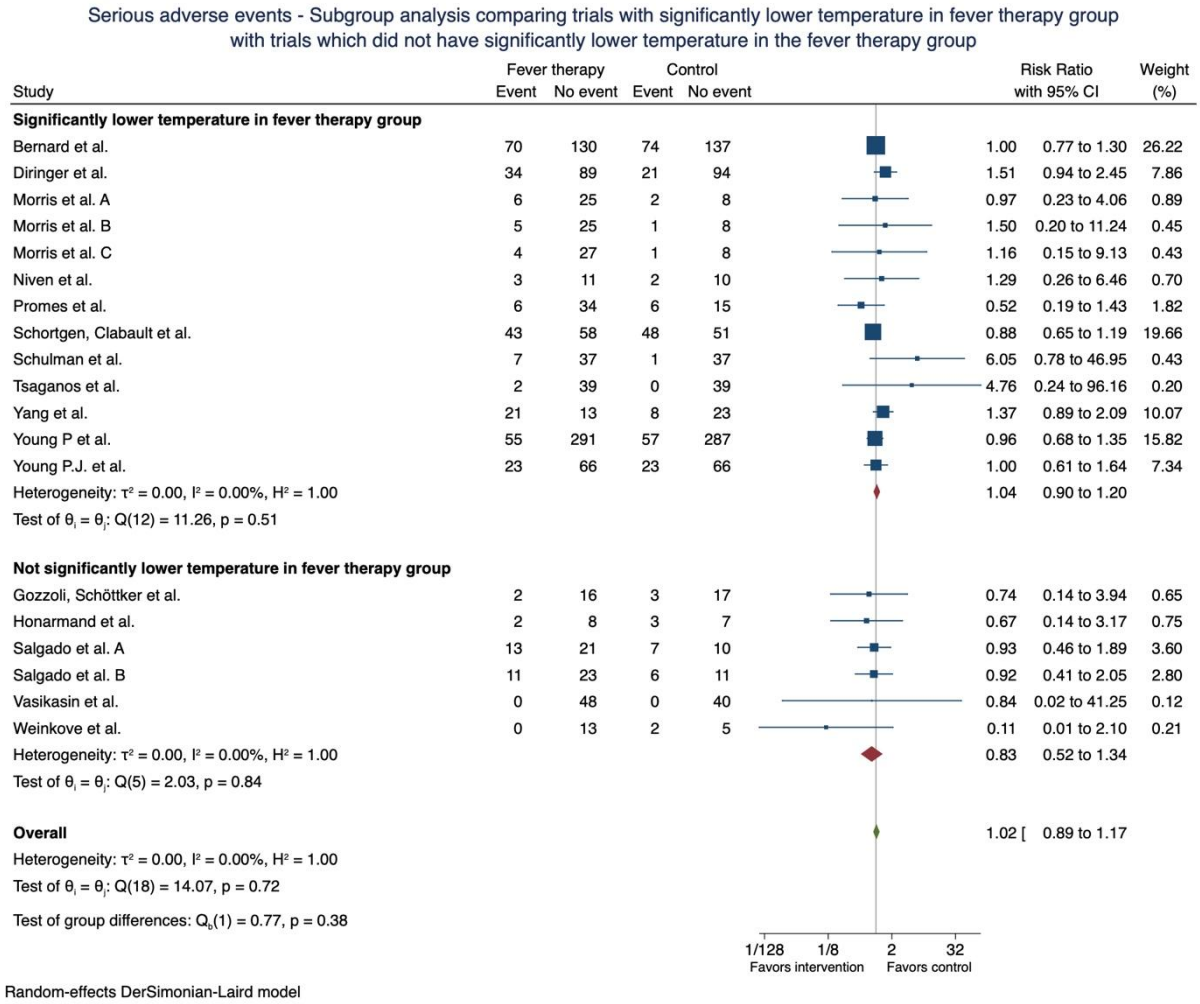
Subgroup analysis comparing infectious fever with non-infectious fever showed no evidence of a subgroup difference (p = 0.86).
RR: Risk ratio
CI: Confidence interval
I^2: Measure of heterogeneity

Figure S15: Subgroup analysis of serious adverse events comparing different control interventions



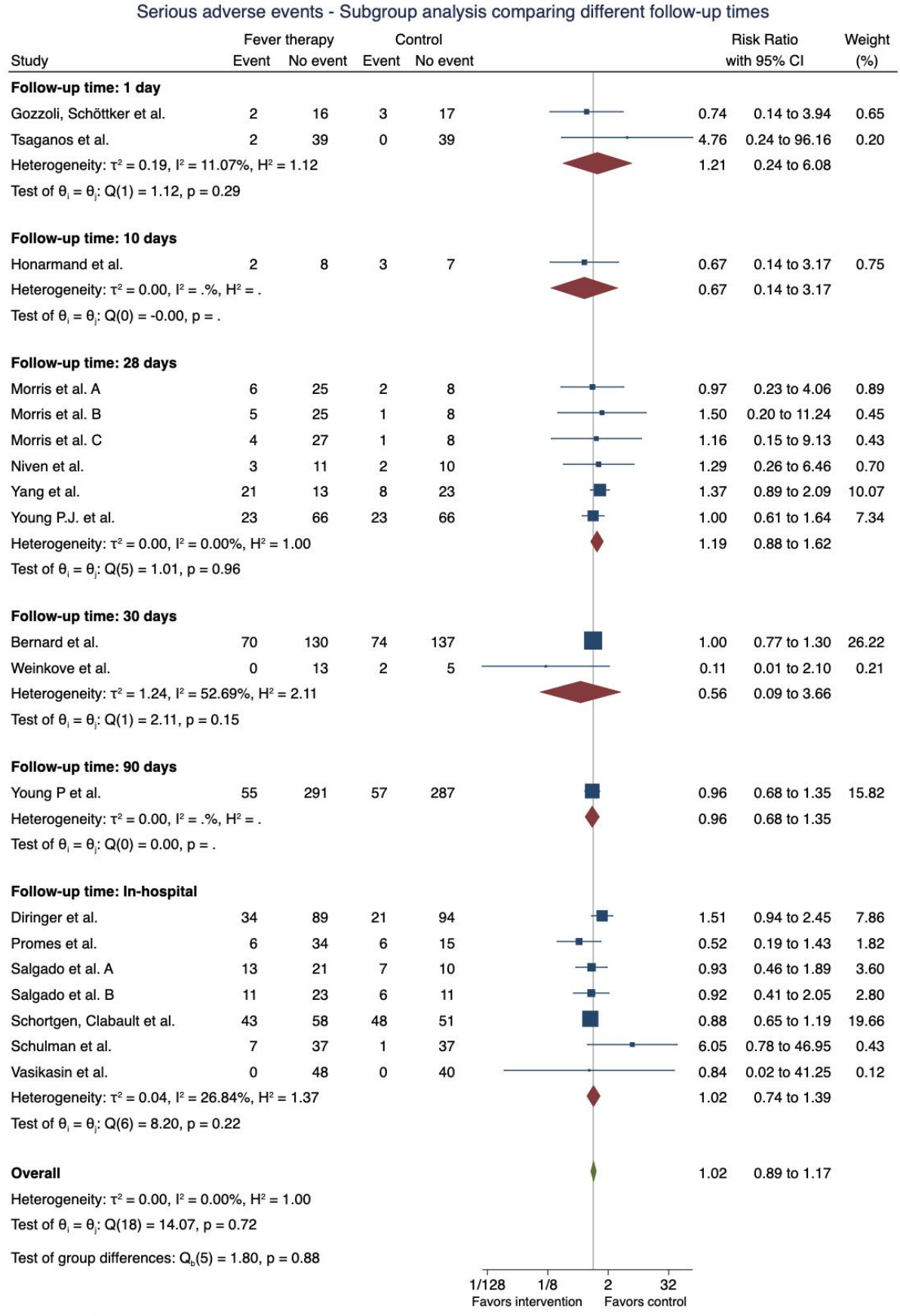
Subgroup analysis comparing different interventions showed no evidence of a subgroup difference (p = 0.53).
RR: Risk ratio
CI: Confidence interval
I^2: Measure of heterogeneity

Figure S16: Subgroup analysis of serious adverse events comparing trials with significantly lower temperature in fever the fever therapy group with trials with non-significantly lower temperature in the fever therapy group



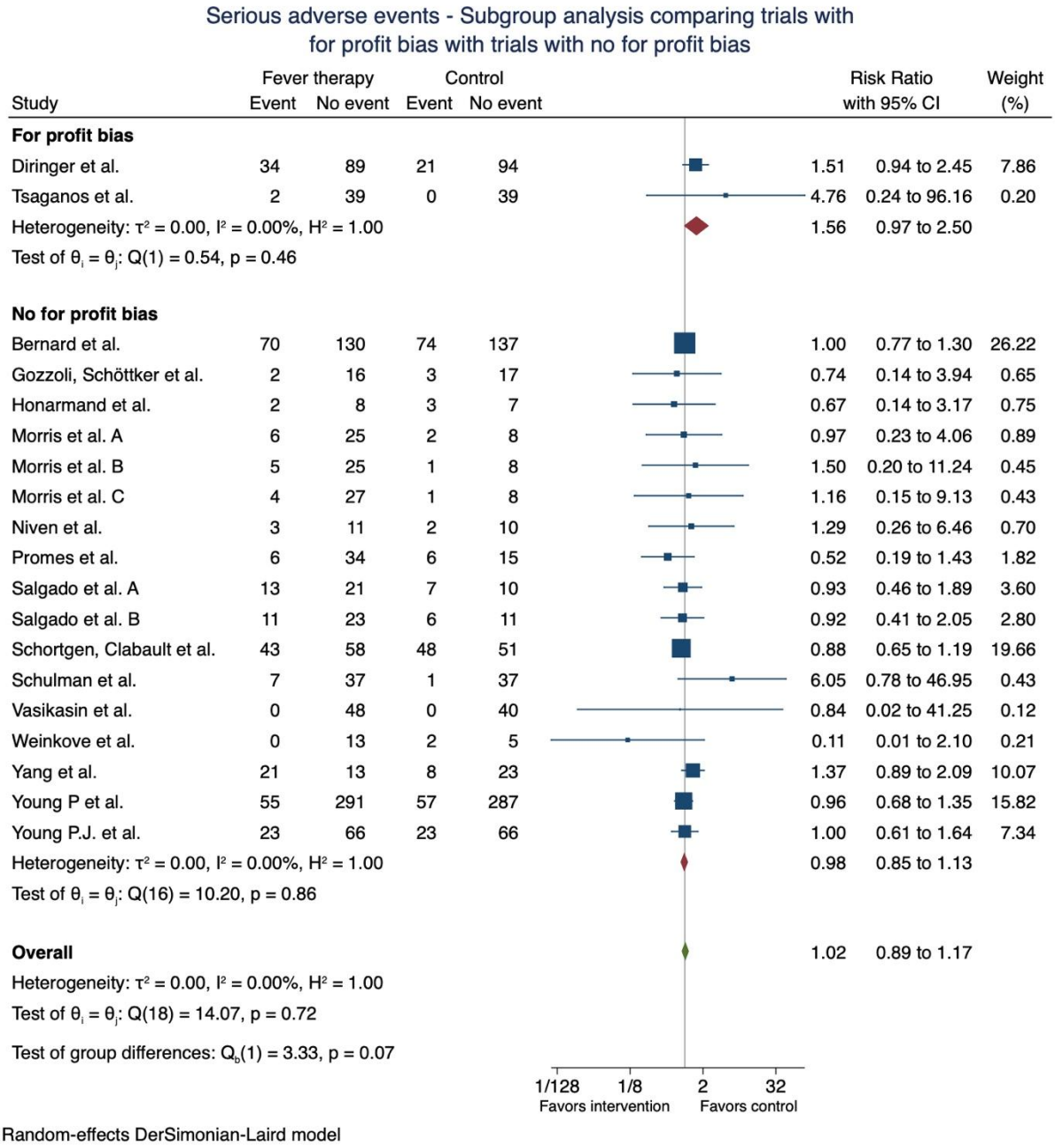
Subgroup analysis comparing trials with significantly lower temperature in fever the fever therapy group with trials with non-significantly lower temperature in the fever therapy group showed no evidence of a subgroup difference (p = 0.38).
RR: Risk ratio
CI: Confidence interval
I^2: Measure of heterogeneity

Figure S17: Subgroup analysis of serious adverse events comparing different follow-up times



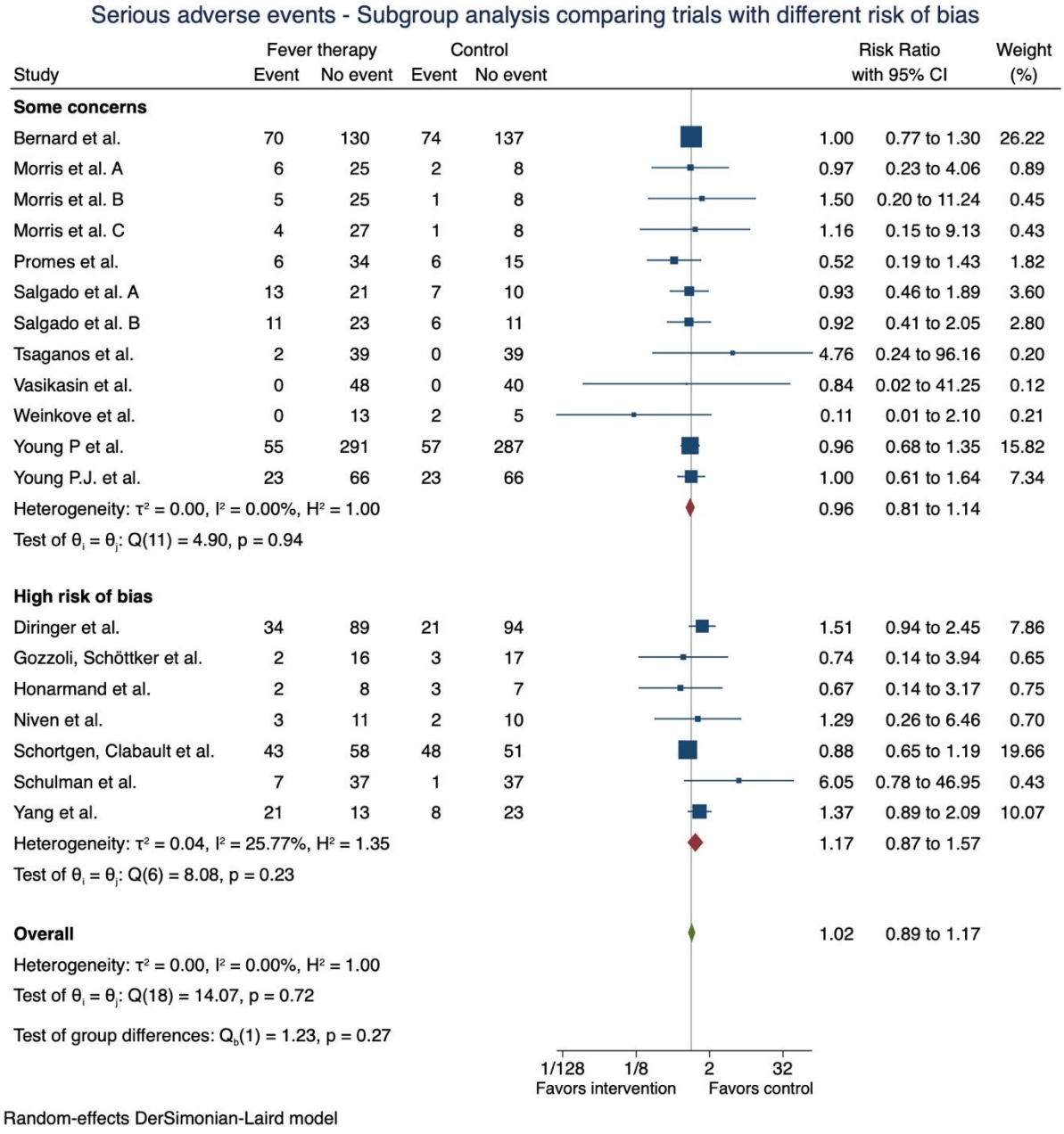
Subgroup analysis comparing different follow-up times showed no evidence of a subgroup difference ($p = 0.88$).
RR: Risk ratio
CI: Confidence interval
I^2: Measure of heterogeneity

Figure S18: Subgroup analysis of serious adverse events comparing trials with for profit bias with trials without for-profit bias



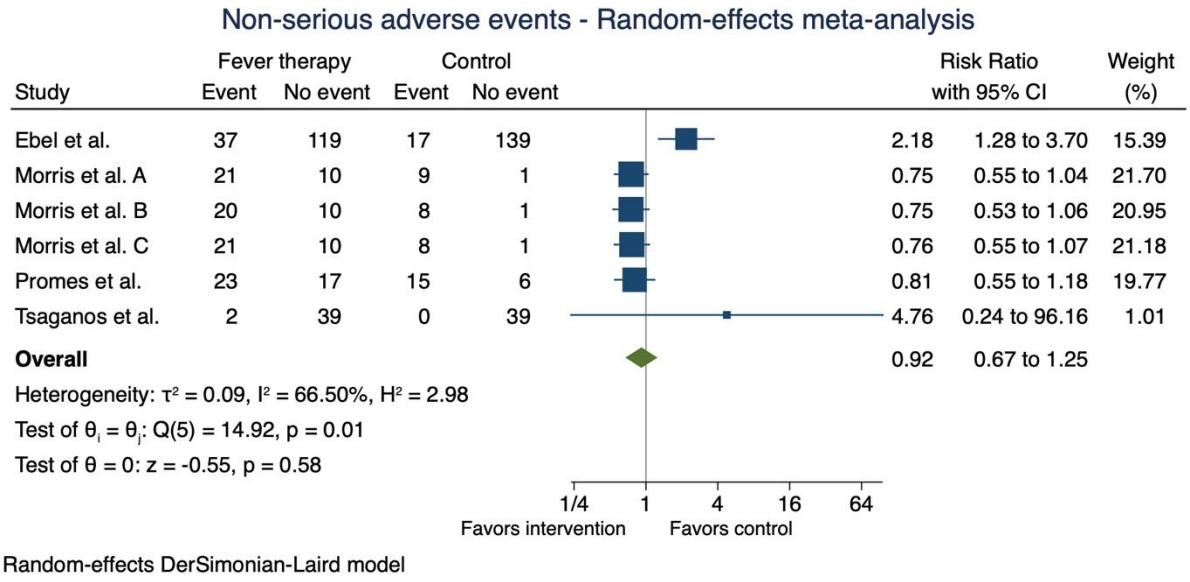
Subgroup analysis comparing trials with for profit bias with trials without for profit showed no evidence of a subgroup difference (p = 0.07).
RR: Risk ratio
CI: Confidence interval
I^2: Measure of heterogeneity

Figure S19: Subgroup analysis of serious adverse events comparing trials with different levels of risk of bias



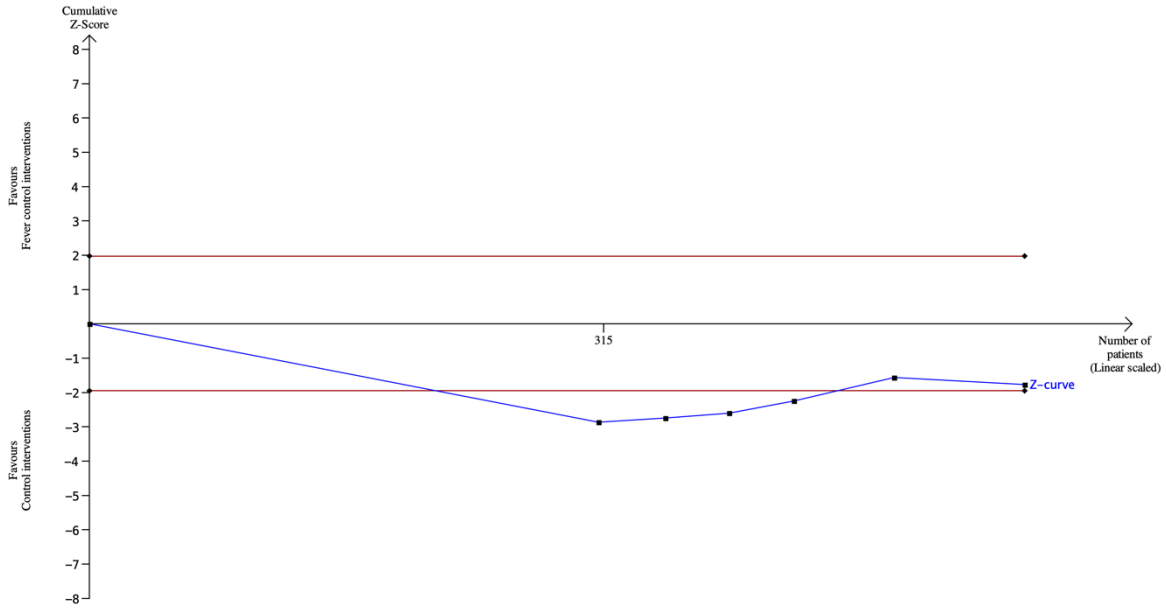
Subgroup analysis comparing trials with different risk of bias showed no evidence of a subgroup difference (p = 0.27).
RR: Risk ratio
CI: Confidence interval
I^2: Measure of heterogeneity

Figure S20: Random-effects meta-analysis of fever therapy versus control interventions on non-serious adverse events



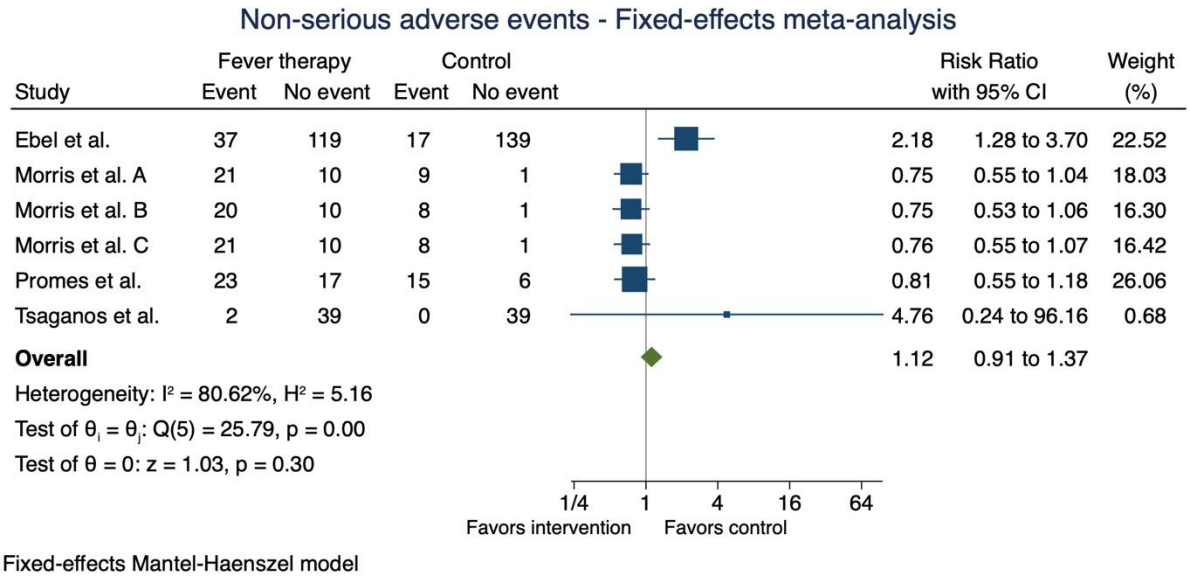
Random-effects meta-analysis showed no evidence of a difference between fever control interventions and control interventions on non-serious adverse events (RR 0.92; 95% CI 0.67 to 1.25; $p = 0.58$; $I^2 = 66.50$ %; four trials).
RR: Risk ratio
CI: Confidence interval
I^2: Measure of heterogeneity

Figure S21: Trial sequential analysis of fever therapy versus control interventions on non-serious adverse events



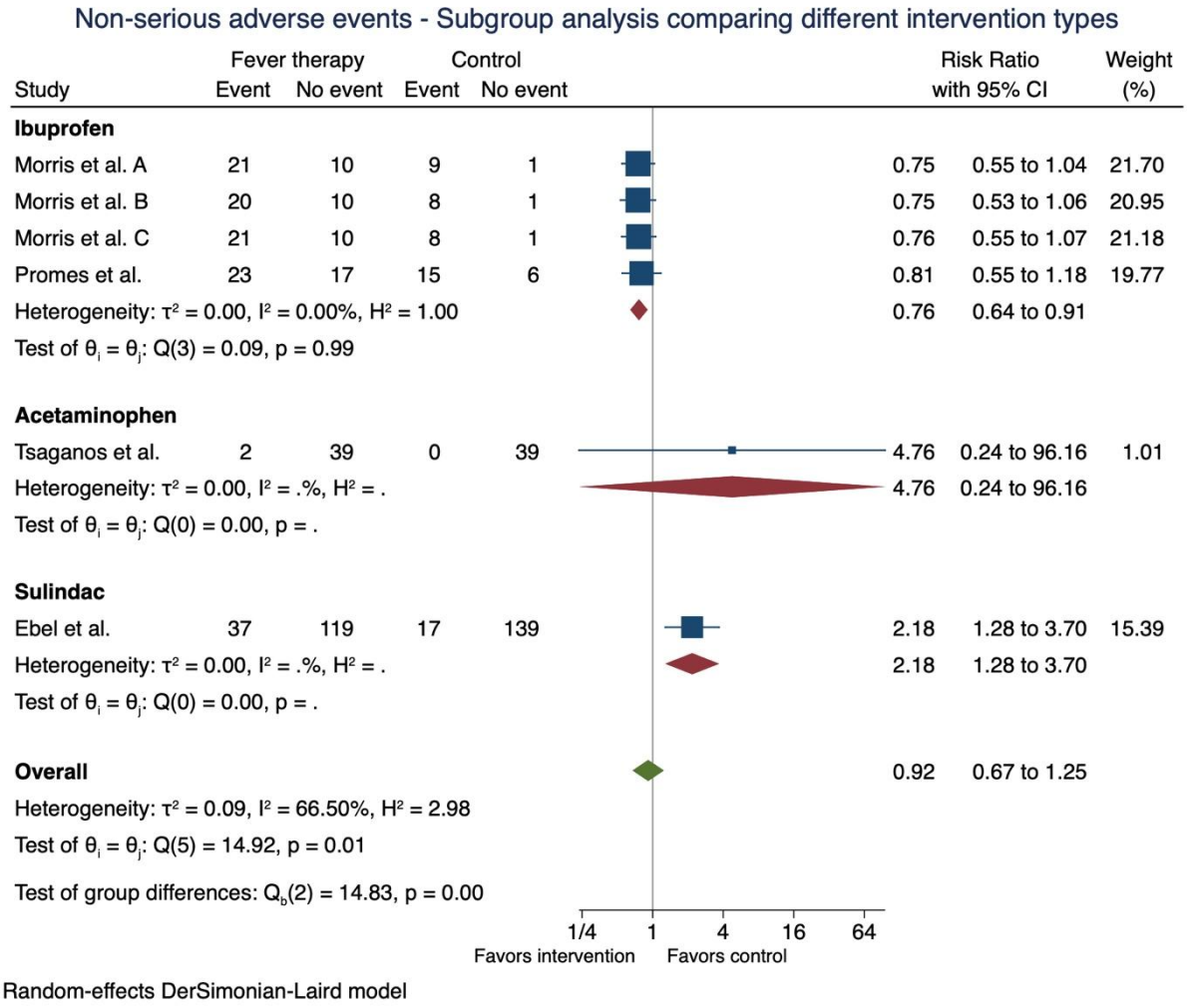
Two-sided trial sequential analysis graph of fever control interventions versus control interventions on non-serious adverse events in 4 trials. The diversity-adjusted required information size (DARIS) was calculated based on an all-cause mortality proportion in the control group (Pc) of 23.4 %, relative risk reduction (RRR) of 25 % in the experimental group, type I error (alpha) of 2 %, and type II error (beta) of 10 % (90% power). Diversity was 81 %. The required information size was calculated to be 13158 participants. The cumulative Z-curve (blue line) did not cross the trial sequential monitoring boundaries for neither benefit nor harm. The cumulative Z-curve did not cross the inner-wedge futility line (red outward sloping lines). The dark red lines show the conventional boundary (alpha 5%).

Figure S22: Fixed-effects meta-analysis of fever therapy versus control interventions on non-serious adverse events



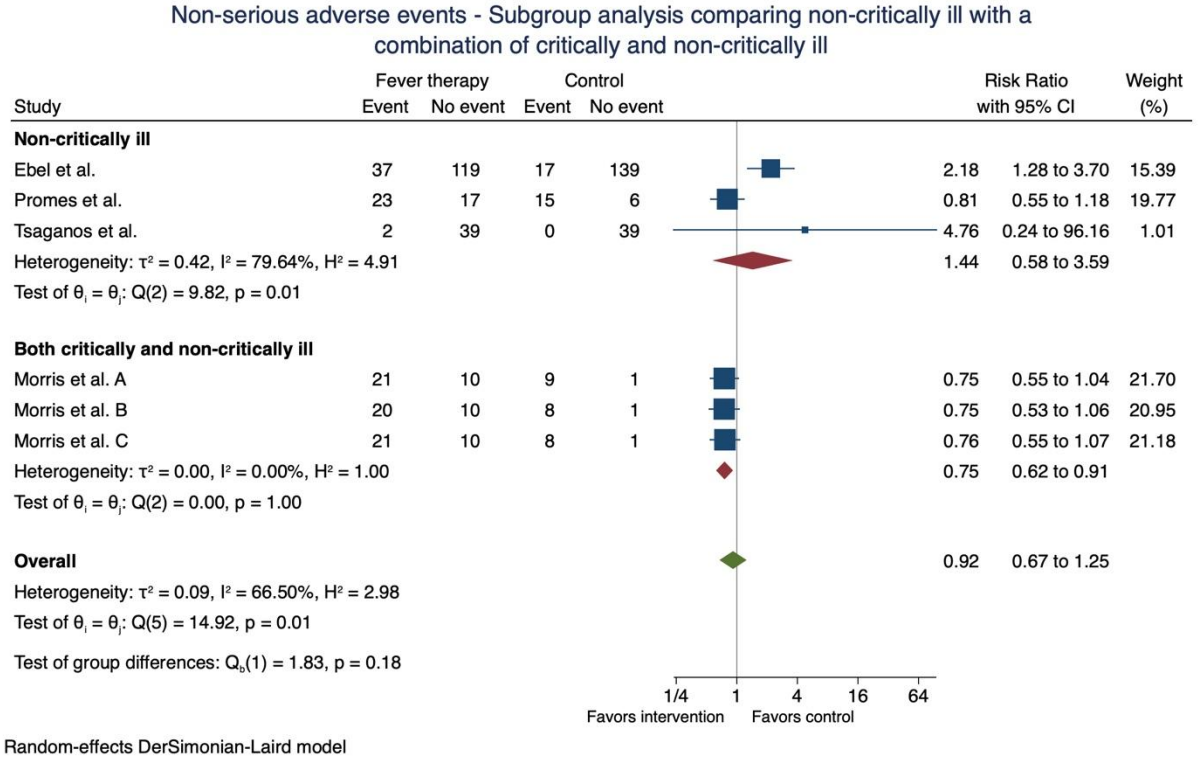
Fixed-effects meta-analysis showed no evidence of a difference between fever control interventions and control interventions on non-serious adverse events (RR 1.12; 95% CI 0.91 to 1.37; $p = 0.30$; $I^2 = 80.62$ %; four trials).
RR: Risk ratio
CI: Confidence interval
I^2: Measure of heterogeneity

Figure S23: Subgroup analysis of non-serious adverse events comparing different intervention types



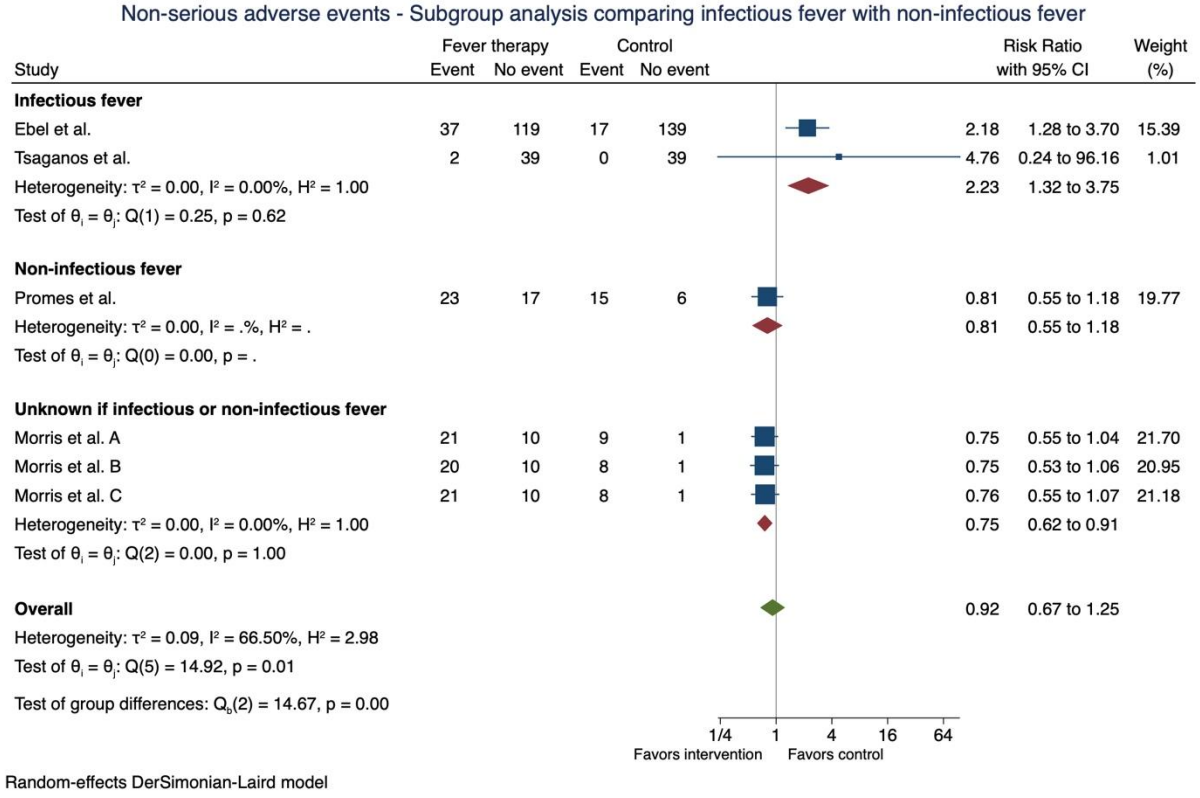
Subgroup analysis comparing different intervention types showed evidence of a subgroup difference (p = 0.00).
RR: Risk ratio
CI: Confidence interval
I^2: Measure of heterogeneity

Figure S24: Subgroup analysis of non-serious adverse events comparing critically ill versus non-critically ill



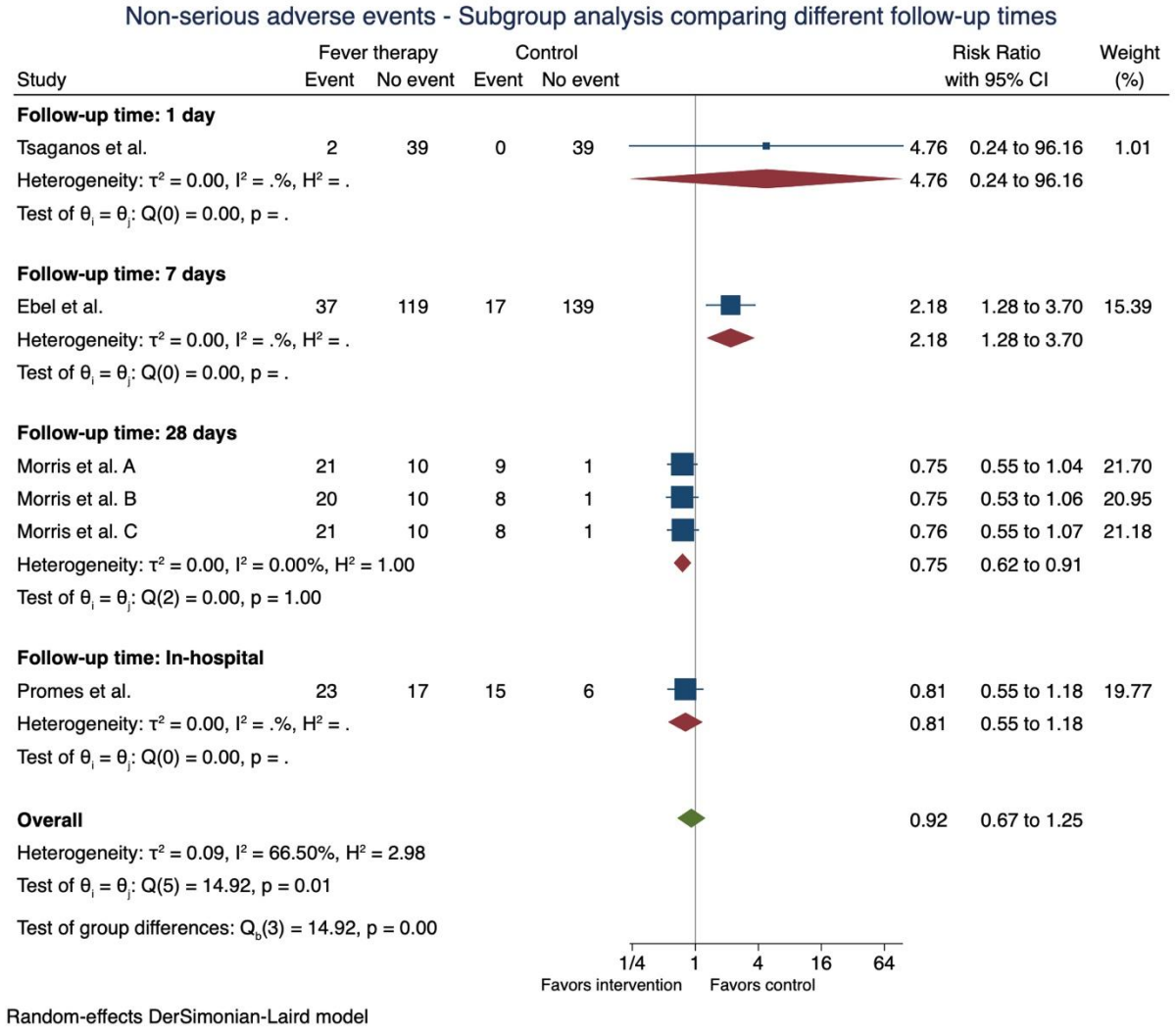
Subgroup analysis comparing critically ill with non-critically ill showed no evidence of a subgroup difference (p = 0.18).
RR: Risk ratio
CI: Confidence interval
I^2: Measure of heterogeneity

Figure S25: Subgroup analysis of non-serious adverse events comparing infectious fever with non-infectious fever



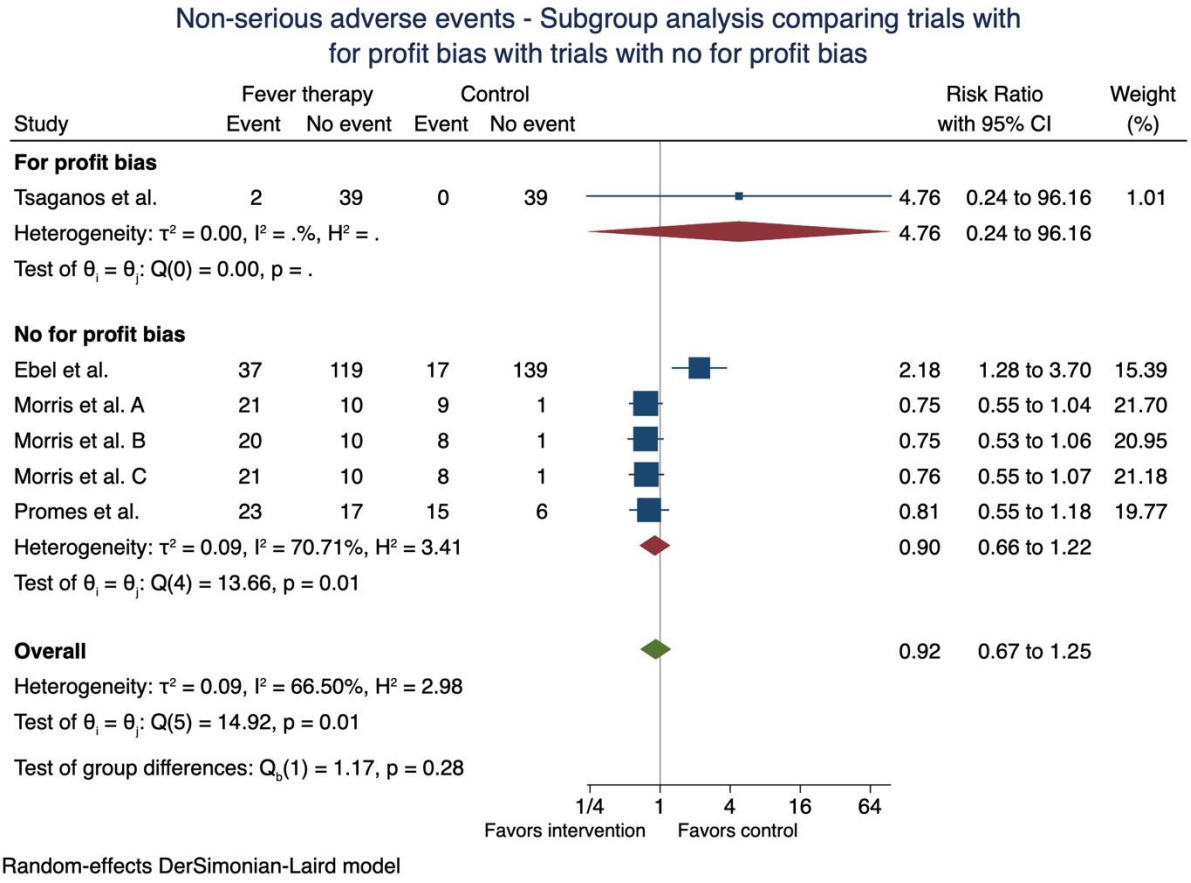
Subgroup analysis comparing infectious fever with non-infectious fever showed evidence of a subgroup difference (p = 0.00).
RR: Risk ratio
CI: Confidence interval
I^2: Measure of heterogeneity

Figure S26: Subgroup analysis of non-serious adverse events comparing different follow-up times



Subgroup analysis comparing different follow-up times showed evidence of a subgroup difference (p = 0.00).
RR: Risk ratio
CI: Confidence interval
I^2: Measure of heterogeneity

Figure S27: Subgroup analysis of non-serious adverse events comparing trials with for profit bias with trials without for-profit bias



Subgroup analysis comparing trials with for profit bias with trials without for profit showed no evidence of a subgroup difference (p = 0.28).
RR: Risk ratio
CI: Confidence interval
I^2: Measure of heterogeneity

Tables

Table S1: Characteristics of included trials

Trial ID	Intervention	Control	Number of participants	Critically ill (Yes/No/Both)	Infectious fever (Yes/No/Unknown)	All-cause mortality (Intervention / Control)	Serious adverse events (Intervention / Control)	Non-serious adverse events (Intervention / Control)	Quality of life	Temperature change p-value*
Azuma et al. A [41]	Zaltoprofen	Placebo	131	No	Yes	N/A	N/A	N/A	N/A	<0.001
Azuma et al. B [41]	Loxoprofen	Placebo	131	No	Yes	N/A	N/A	N/A	N/A	<0.001
Bachert et al. A [42]	Acetylsalicylic acid 500mg	Placebo	97	No	Yes	N/A	N/A	N/A	N/A	<0.001
Bachert et al. B [42]	Acetylsalicylic acid 1000mg	Placebo	97	No	Yes	N/A	N/A	N/A	N/A	<0.001
Bachert et al. C [42]	Acetaminophen 500mg	Placebo	99	No	Yes	N/A	N/A	N/A	N/A	<0.001
Bachert et al. D [42]	Acetaminophen 1000mg	Placebo	99	No	Yes	N/A	N/A	N/A	N/A	<0.001
Bernard et al. [43]	Ibuprofen	Placebo	455	Yes	Yes	70/200 / 74/211	70/200 / 74/211	N/A	N/A	<0.001
DeMartini et al. [44]	Physical cooling	No intervention	16	No	No	N/A	N/A	N/A	N/A	N/A
Diringer et al. [45]	IV-catheter based cooling + standard antipyretic treatment	Standard antipyretic treatment	238	Yes	No	34/123 / 21/115	34/123 / 21/115	N/A	N/A	<0.001
Ebel et al. [39]	Sulindac	Placebo	312	No	Yes	N/A	N/A	37/156 / 17/156	N/A	<0.001
Fankhauser et al. A [46]	Acetylsalicylic acid 1000mg	Placebo	32	No	Unknown	N/A	N/A	N/A	N/A	<0.001
Fankhauser et al. B [46]	Fluproquazone	Placebo	27	No	Unknown	N/A	N/A	N/A	N/A	<0.001
Focan et al. [47]	Suprofen	Placebo	61	Both	Unknown	N/A	N/A	N/A	N/A	<0.05
Gehanno et al. A [48]	6.25mg Diclofenac	Placebo	135	No	Yes	N/A	N/A	N/A	N/A	<=0.05
Gehanno et al. B [48]	12.5mg Diclofenac	Placebo	135	No	Yes	N/A	N/A	N/A	N/A	<0.01
Gehanno et al. C [48]	25mg Diclofenac	Placebo	139	No	Yes	N/A	N/A	N/A	N/A	<0.01
Gehanno et al. D [48]	1000mg Acetaminophen	Placebo	134	No	Yes	N/A	N/A	N/A	N/A	<=0.05
Gozzoli, Schöttker et al. [49]	External cooling	No antipyretic treatment	38	Yes	Unknown	2/18 / 3/20	2/18 / 3/20	N/A	N/A	>0.05

Grebe et al. A [50]	Diclofenac	Placebo	179	No	Yes	N/A	N/A	N/A	N/A	<0.001
Grebe et al. B [50]	Ibuprofen	Placebo	177	No	Yes	N/A	N/A	N/A	N/A	<0.001
Hagobian et al. [51]	Physical cooling	No intervention	6	No	No	N/A	N/A	N/A	N/A	N/A
Henker et al. A [52]	Antipyretics and physical cooling	Antipyretics	8	Yes	Unknown	N/A	N/A	N/A	N/A	>0.05
Henker et al. B [52]	Antipyretics and physical cooling	Cooling	9	Yes	Unknown	N/A	N/A	N/A	N/A	>0.05
Honarmand et al. [53]	Intravenous Acetaminophen	No antipyretic treatment	20	Yes	Unknown	2/10 / 3/10	2/10 / 3/10	N/A	N/A	>0.05
Hosokawa et al. [54]	Physical cooling	No intervention	14	No	No	N/A	N/A	N/A	N/A	N/A
Hosokawa et al. [55]	Physical cooling	No intervention	14	No	No	N/A	N/A	N/A	N/A	N/A
Kett et al. [56]	Acetaminophen IV	Placebo	60	Both	No	N/A	N/A	N/A	N/A	p=0.0376
Krudsood et al. [57]	IV ibuprofen	Placebo	60	No	Yes	N/A	N/A	N/A	N/A	p=0.0019
Lissoway et al. [58]	Physical cooling	No intervention	10	No	No	N/A	N/A	N/A	N/A	N/A
Lopez et al. [59]	Cooling vest	Passive cooling	10	No	No	N/A	N/A	N/A	N/A	>0.05
Luhring et al. [60]	Physical cooling	No intervention	16	No	No	N/A	N/A	N/A	N/A	N/A
Mayer et al. [12]	Acetaminophen + air blanket	Acetaminophen	220	Yes	No	N/A	N/A	N/A	N/A	>0.05
Morgan et al. A [40]	Hypothermia blanket + acetaminophen	Acetaminophen	11	Yes	No	N/A	N/A	N/A	N/A	>0.05
Morgan et al. B [40]	Tepid water sponging + acetaminophen	Acetaminophen	10	Yes	No	N/A	N/A	N/A	N/A	>0.05
Morris et al. A [36]	100 mg IV ibuprofen	Placebo	41	Both	Unknown	1/31 / 1/10	6/31 / 2/10	27/31 / 9/10	N/A	<0.05
Morris et al. B [36]	200mg IV ibuprofen	Placebo	39	Both	Unknown	2/30 / 0/9	5/30 / 1/9	25/30 / 8/9	N/A	<0.05
Morris et al. C [36]	400mg IV ibuprofen	Placebo	40	Both	Unknown	2/31 / 0/9	4/31 / 1/9	23/31 8/9	N/A	<0.001
Mullins et al. A [61]	Acetaminophen + ibuprofen	ibuprofen	38	Yes	No	N/A	N/A	N/A	N/A	>0.05
Mullins et al. B [61]	Acetaminophen + ibuprofen	Acetaminophen	41	Yes	No	N/A	N/A	N/A	N/A	0.03
Niven et al. [62]	Aggressive fever treatment	Permissive fever treatment	26	Yes	Unknown	3/14 / 2/12	3/14 / 2/12	N/A	N/A	0.02
Pernerstorfer et al. A [63]	Aspirin	Placebo	15	No	No	N/A	N/A	N/A	N/A	0.001

Pernerstorfer et al. B [63]	Acetaminophen	Placebo	15	No	No	N/A	N/A	N/A	N/A	0.001
Promes et al. [37]	ibuprofen	Placebo	61	No	No	3/40 / 2/21	6/40 / 6/21	23/40 / 15/21	N/A	<0.05
Salgado et al. A [64]	Ice-packs + antipyretics	Antipyretics	51	Yes	Unknown	13/34 / 7/17	13/34 / 7/17	N/A	N/A	>0.05
Salgado et al. B [64]	Warm compress + antipyretics	Antipyretics	51	Yes	Unknown	11/34 / 6/17	11/34 / 6/17	N/A	N/A	>0.05
Schell-Chaple et al. [65]	Acetaminophen	Placebo	40	Yes	Unknown	N/A	N/A	N/A	N/A	0.05
Schortgen, Clabault et al. [66]	External cooling	No external cooling	200	Yes	Yes	43/101 / 48/99	43/101 / 48/99	N/A	N/A	<0.01
Schulman et al. [67]	Aggressive antipyretic protocol	Permissive antipyretic protocol	82	Yes	Unknown	7/44 / 1/38	7/44 / 1/38	N/A	N/A	<0.0001
Schwartz et al. A [68]	Rofecoxib 12.5mg	Placebo	33	No	Unknown	N/A	N/A	N/A	N/A	<0.05
Schwartz et al. B [68]	Rofecoxib 25mg	Placebo	31	No	Unknown	N/A	N/A	N/A	N/A	<0.05
Schwartz et al. C [68]	Ibuprofen 400mg	Placebo	30	No	Unknown	N/A	N/A	N/A	N/A	<0.05
Tan et al. [69]	Physical cooling	No intervention	22	No	No	N/A	N/A	N/A	N/A	N/A
Tsaganos et al. [38]	Acetaminophen	Placebo	80	No	Yes	2/41 / 0/39	2/41 / 0/39	2/41 / 0/39	N/A	0.003
Vargas et al. A [70]	Keterolac 60mg IM	Placebo IM	40	No	No	N/A	N/A	N/A	N/A	<0.0001
Vargas et al. B [70]	Keterolac 30mg IM	Placebo IM	38	No	No	N/A	N/A	N/A	N/A	<0.0001
Vargas et al. C [70]	Keterolac 15mg IM	Placebo IM	38	No	No	N/A	N/A	N/A	N/A	0.0006
Vargas et al. D [70]	Acetaminophen 650mg PO	Placebo PO	38	No	No	N/A	N/A	N/A	N/A	<0.0001
Vasikasin et al. [71]	Acetaminophen	Placebo	86	No	Yes	0/48 / 0/40	0/48 / 0/40	N/A	N/A	>0.05
Weinkove et al. [35]	Acetaminophen	Placebo	22	No	Yes	0/13 / 2/9	0/13 / 2/9	N/A	Yes	>0.05
Yang et al. [72]	Aggressive antipyretic protocol	Permissive antipyretic protocol	65	Yes	Unknown	21/34 / 8/31	9/22 / 9/32	N/A	N/A	<0.0001
Young P et al. [73]	Acetaminophen	Placebo	690	Yes	Yes	55/346 / 57/344	55/346 / 57/344	N/A	N/A	<0.001
Young P.J. et al. [74]	Aggressive antipyretic protocol	Permissive antipyretic protocol	168	Yes	No	23/89 / 23/89	23/89 / 23/89	N/A	N/A	0.01

Table 2: Characteristics of included trials.

*p-value for trialist defined temperature difference between fever therapy group and control group. A p-value below or equal to 0.05 represents a significantly lower temperature in the fever therapy group.

Table S2: Summary of serious adverse events in the included trials

Trial	Comparison	Fever therapy group		Control group	
		Number and type of serious adverse event	**Proportion of participants with a serious adverse event**	**Number and type of serious adverse event**	**Proportion of participants with a serious adverse event**
Bernard et al.	Ibuprofen vs placebo	70 deaths	70/200	70 deaths	74/211
Diringer et al.	Physical cooling + antipyretics vs antipyretics	34 deaths	34/123	34 deaths	21/115
Gozzoli, Schöttker et al.	Physical cooling vs no intervention	2 deaths	2/18	3 deaths	3/20
Honarmand et al.	Acetaminophen vs no intervention	2 deaths	2/10	3 deaths	3/10
Morris et al. A	Ibuprofen vs placebo	Not stated	6/31	Not stated	2/10
Morris et al. B	Ibuprofen vs placebo	Not stated	5/30	Not stated	1/9
Morris et al. C	Ibuprofen vs placebo	Not stated	4/31	Not stated	1/9
Niven et al.	Acetaminophen + physical cooling vs no intervention	3 deaths	3/14	2 deaths	2/12
Promes et al.	Ibuprofen vs placebo	1 ARDS, 1 tachypnea, 1 septic shock, 1 septicemia, 1 invasive wound sepsis and 1 breathlessness	6/40	2 ARDs, 1 cardiac arrest, 1 cardiopulmonary arrest, 1 tachypnea and 1 hypotension	6/21
Salgado et al. A	Physical cooling + antipyretics vs antipyretics	13 deaths	13/34	7 deaths	7/17
Salgado et al. B	Physical cooling + antipyretics vs antipyretics	11 deaths	11/34	6 deaths	6/17
Schortgen, Clabault et al.	Physical cooling vs no intervention	43 deaths	43/101	48 deaths	48/99
Schulman et al.	Acetaminophen + physical cooling vs no intervention	7 deaths	7/44	1 death	1/38
Tsaganos et al.	Acetaminophen vs placebo	2 deaths	2/41	No serious adverse events	0/39
Vasikasin et al.	Acetaminophen vs placebo	No serious adverse events	0/48	No serious adverse events	0/40
Weinkove et al.	Acetaminophen vs	No serious adverse events	0/13	2 deaths	2/7
Yang et al.	Physical cooling vs no intervention	21 deaths	21/34	8 deaths	8/31
Young P et al.	Acetaminophen vs placebo	55 deaths	55/346	57 deaths	57/344
Young P.J. et al.	Acetaminophen vs no intervention	23 deaths	23/89	23 deaths	23/89

Table S3: Summary of findings table of fever therapy versus control interventions

Fever therapy compared with no fever therapy for adults with fever

Patients or population: Adults diagnosed with fever of any origin
Setting: Any setting
Intervention: Any type of fever therapy (antipyretics or physical cooling)
Comparison: No fever therapy (with or without placebo/sham)

Outcome	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control	Risk with intervention				
All-cause mortality *Follow-up mean: 25 days*	226 per 1,000	**235 per 1,000** (203 to 269)	**RR:** 1.04 (0.90 to 1.19)	2415 (16 RCT)	⊕⊕⊕⊕ HIGH	-
Serious adverse events *Follow-up mean: 25 days*	242 per 1,000	**247 per 1,000** (215 to 283)	**RR:** 1.02 (0.89 to 1.17)	2415 (16 RCT)	⊕⊕⊕⊕ HIGH	-
Non-serious adverse events *Follow-up mean: 18 days*	234 per 1,000	**215 per 1,000** (157 to 293)	**RR:** 0.92 (0.67 to 1.25)	767 (4 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	-

***The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).**

RR: Risk ratio CI: Confidence interval; GRADE: GRADE Working Group grades of evidence

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Downgraded 2 for risk of bias
b. Downgraded 2 for imprecision due to Trial Sequential Analysis showing no crossing of TSA-monitoring boundaries and insufficient number of participants
c. Downgraded 1 for inconsistency due to large heterogeneity

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