Electronic supplementary material

Supplement to

The clinical effect of cerebral near-infrared spectroscopy monitoring (NIRS) in children and adults: a systematic review with meta-analysis and Trial Sequential Analysis

Hansen et. al

Appendix A: PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	5
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6-7
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	9
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	9 (and appendix)
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9-10 (and appendix)
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	10-11
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	10-11

Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	11
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	11
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11-14
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11-14 (and appendix)
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	14-20 (and appendix)
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	14-20. Data extraction for individ. studies in appendix
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	14-20
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	14-20 (and appendix)
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	14-20 (and appendix
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	20-22
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	20-22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	23
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	3

Appendix B: Search strategy

PubMed (November 2020)
((((((((((((cerebral oxygen) OR (cerebral oximetry)) OR (cerebral saturation)) OR (cerebral oxymeter)) OR (cerebral tissue oxygen)) OR (near-infrared spectroscopy)) OR (cerebral oxygenation)) OR (brain oxygen)) OR (cerebral NIRS)) OR (near-infrared refracted spectroscopy)) OR (cerebral near infrared spectroscopy)) OR (near infrared spectroscopy)) AND ((((((randomized controlled trial) OR (randomised controlled trial)) OR (randomized clinical trial)) OR (randomised clinical trial)) OR (randomized)) OR (randomised))) AND ((((((randomized controlled trial) OR (randomised controlled trial)) OR (randomized clinical trial)) OR (randomised clinical trial)) OR (randomized)) OR (randomised))
MEDLINE (Ovid) (March 2021)
1. exp Spectroscopy, Near-Infrared/ 2. (((near adj infrared) or nir) and (spectroscop* or spectromet*)).ti,ab. 3. 1 or 2 4. exp Cerebrovascular Circulation/ 5. exp Oximetry/ 6. ((cerebr* and (nir* or oxygen* or saturation* or oximetr* or perfusion*)) or (oxygen and (brain or saturation*))).ti,ab. 7. 4 or 5 or 6 8. 3 or 7 9. (randomized controlled trial or controlled clinical trial).pt. or clinical trials as topic.sh. or trial.ti. 10. (random* or blind*).ti,ab. 11. 8 and (9 or 10) 12. 11 not (exp animals/ not humans.sh.)

Appendix C: Characteristics of trials, data extraction and risk of bias assessment

Please go to

LINK FIGSHARE: https://figshare.com/s/a9ef63687962c4e686a8

For full access to extracted data, risk of bias assessment and characteristics of included and excluded trials.

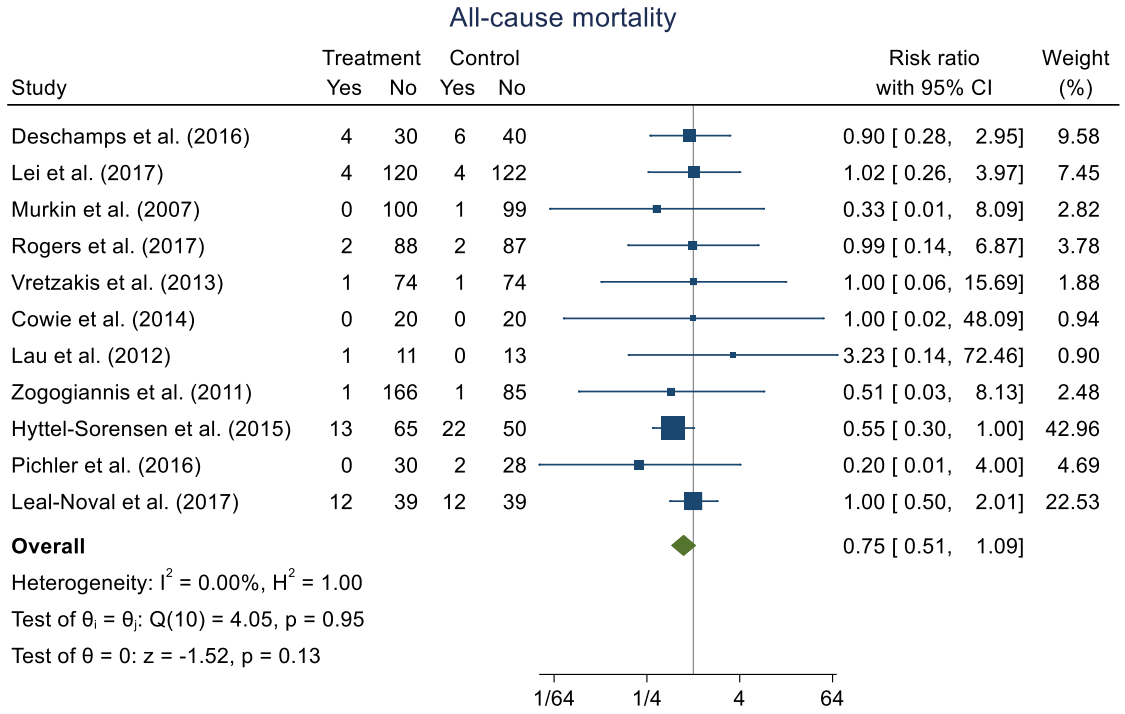
Appendix D: Statistical analyses

Content declaration

All-cause mortality

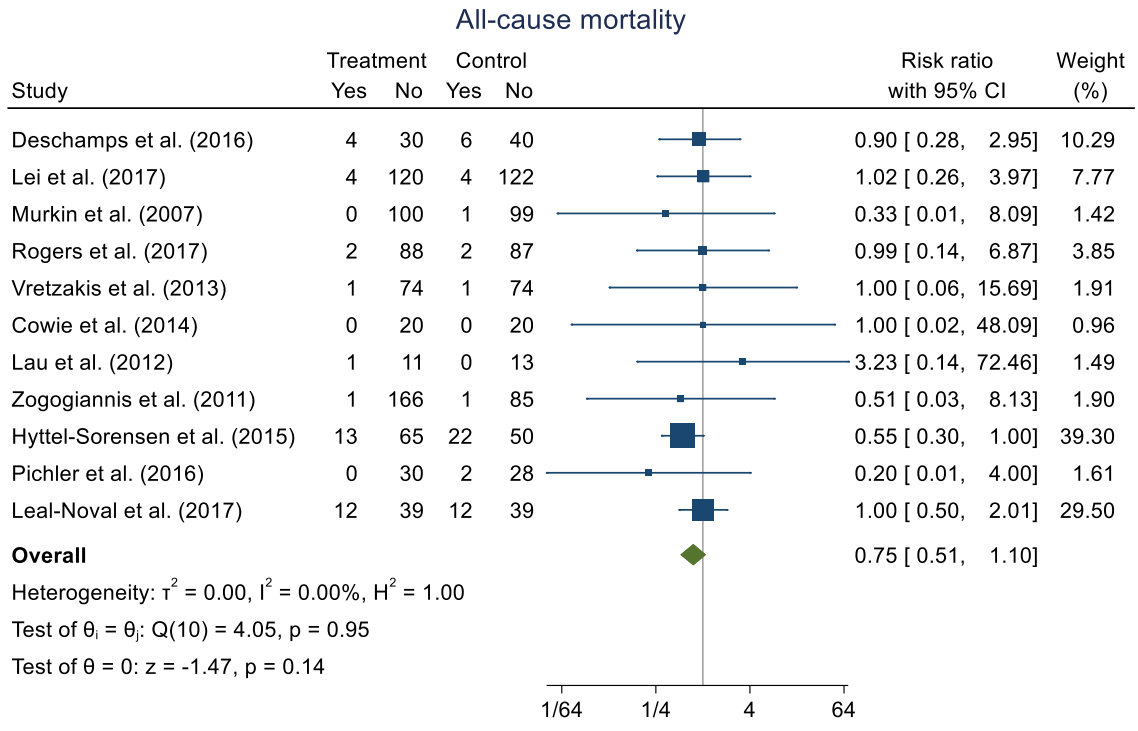
Primary analysis

Figure S1 – fixed effect



Fixed-effects Mantel–Haenszel model

Figure S2 – random effects

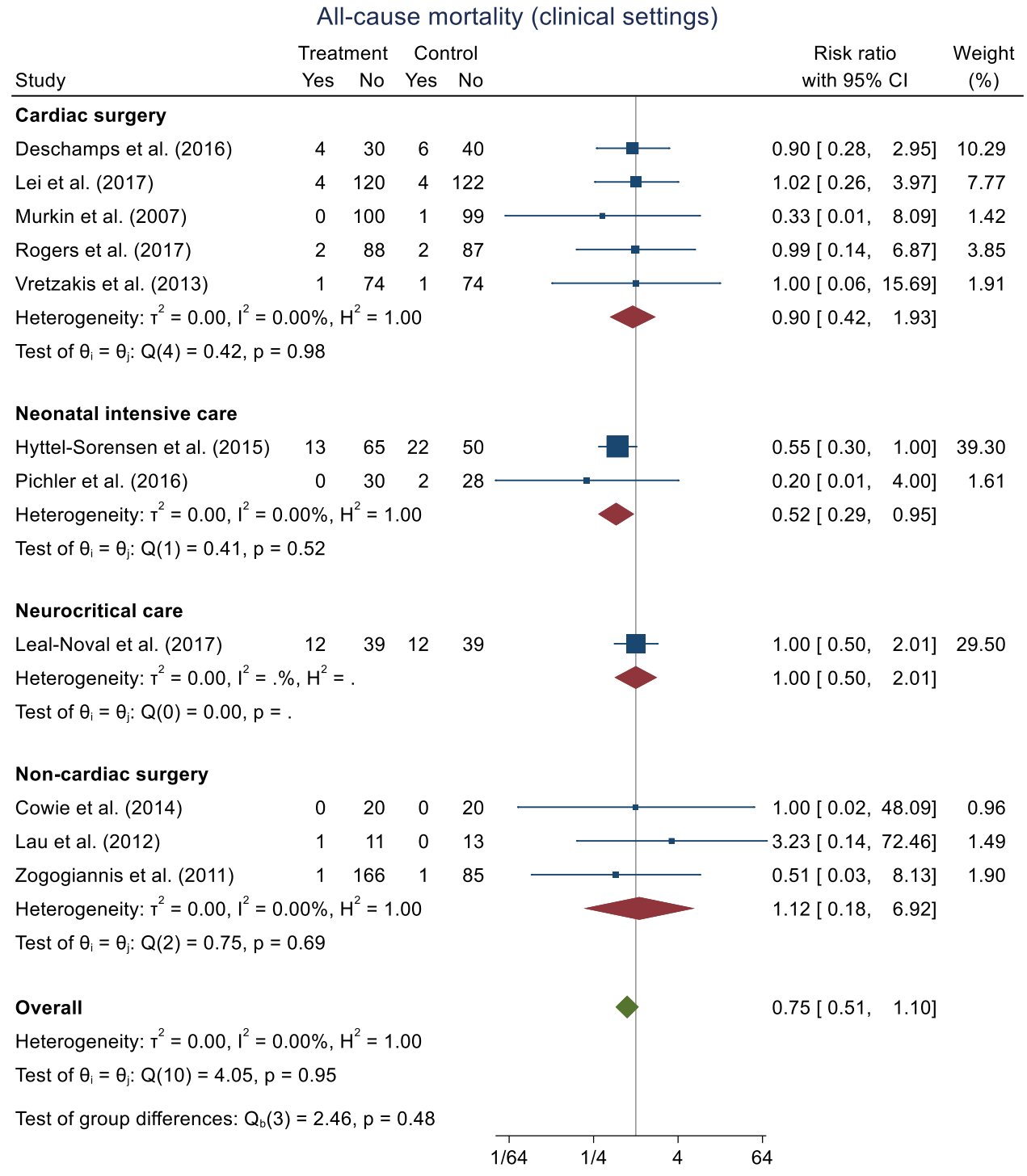


Random-effects DerSimonian–Laird model

Subgroup analyses

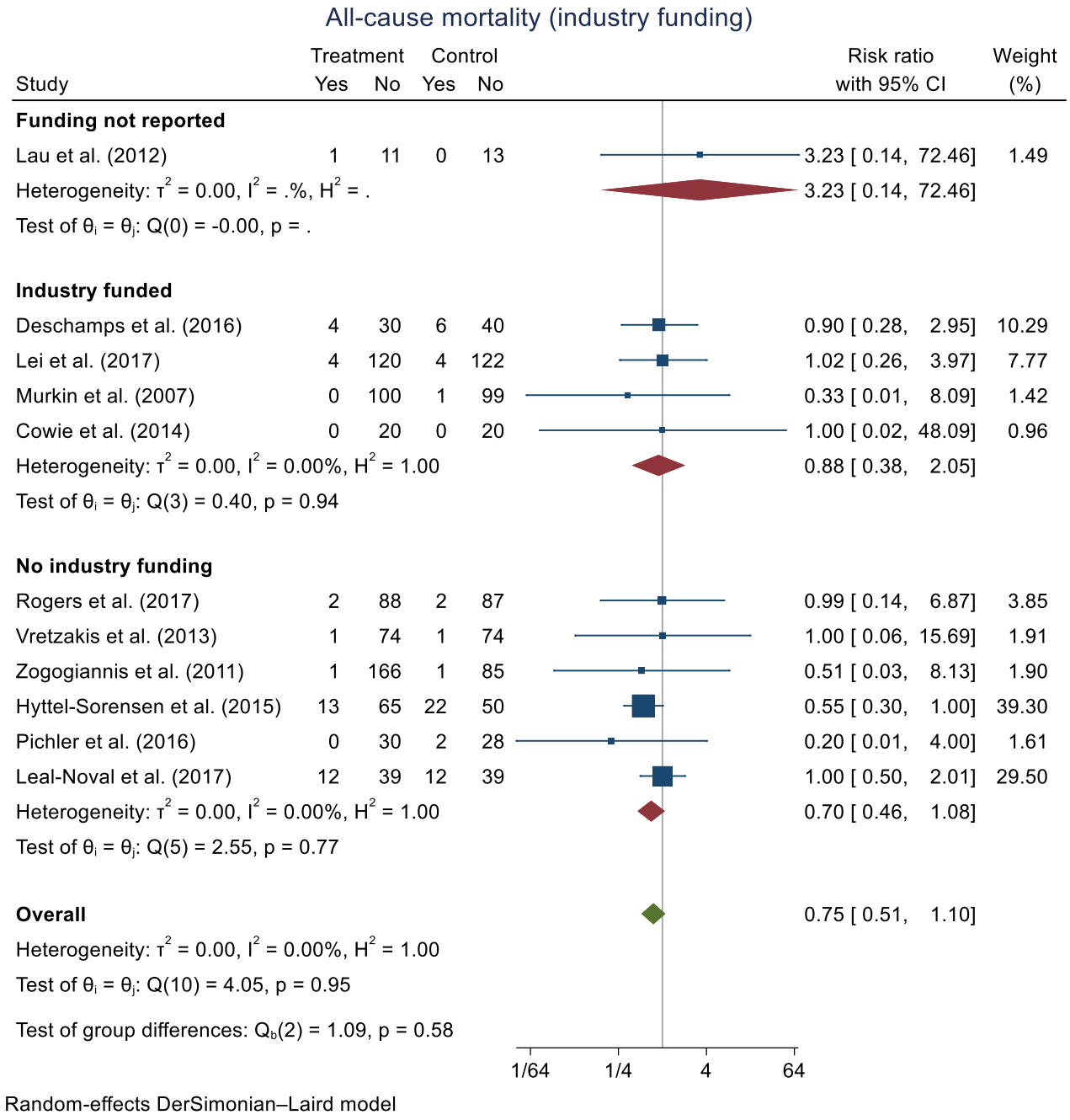
Clinical setting (cardiac surgery compared to neonatal intensive care compared to neurocritical care compared to non-cardiac surgery)

Figure S3



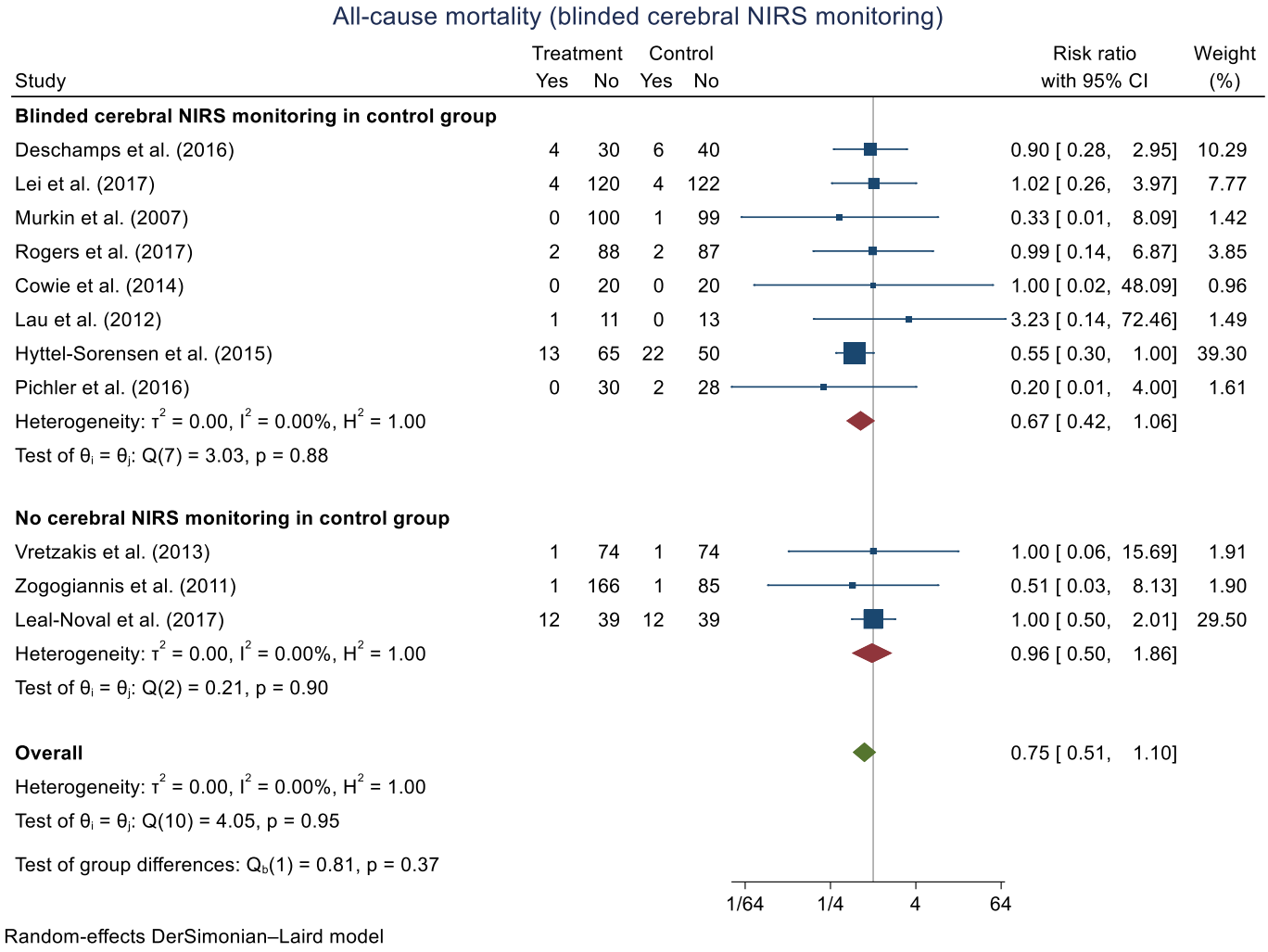
Industry funding (funding not reported compared to industry funded compared to no industry funding)

Figure S4



Random-effects DerSimonian–Laird model

Cerebral NIRS monitoring in the control group (blinded cerebral NIRS monitoring in the control group compared to no cerebral NIRS monitoring in the control group)
Figure S5



Trial Sequential Analysis

Figure S6 – TSA all-cause mortality

Trial Sequential analysis adjusted CI: 0.16 to 3.62 (p=0.1457), diversity = 0%

Bayes factor

LnRR meta-analysis = -0,29
LnSE meta-analysis = 0.20
LnRR a priori = -0.22

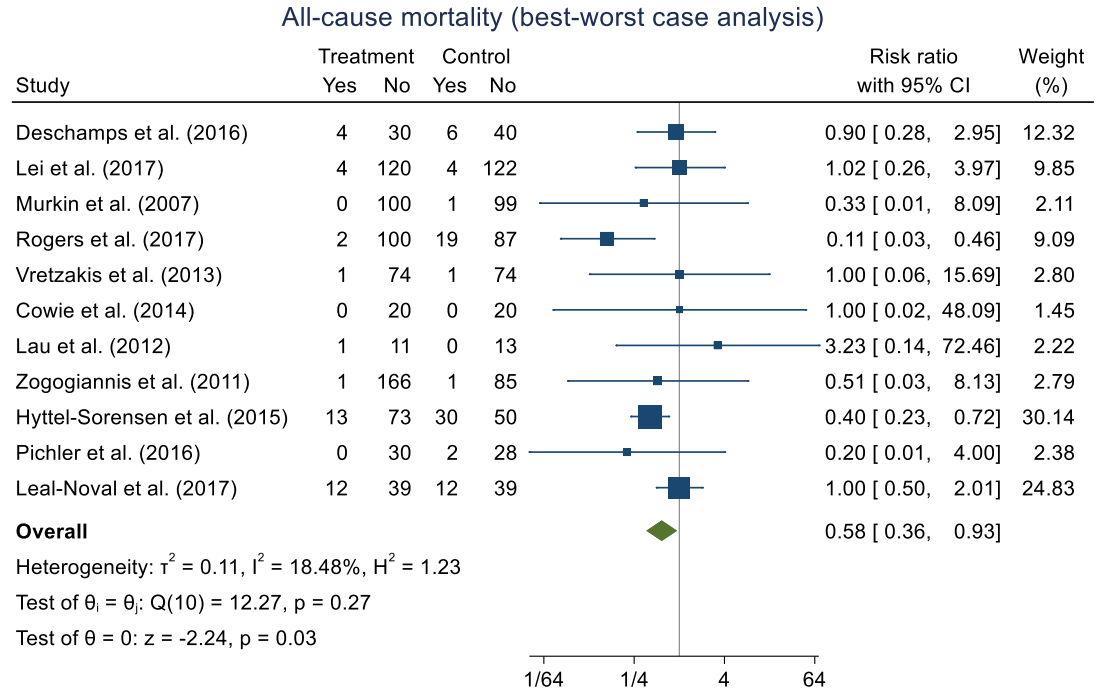
Bayes factor = 0.37

Sensitivity analyses

Best-worst case analysis

Assuming a beneficial event in the experimental group and harmful in the control group

Figure S7

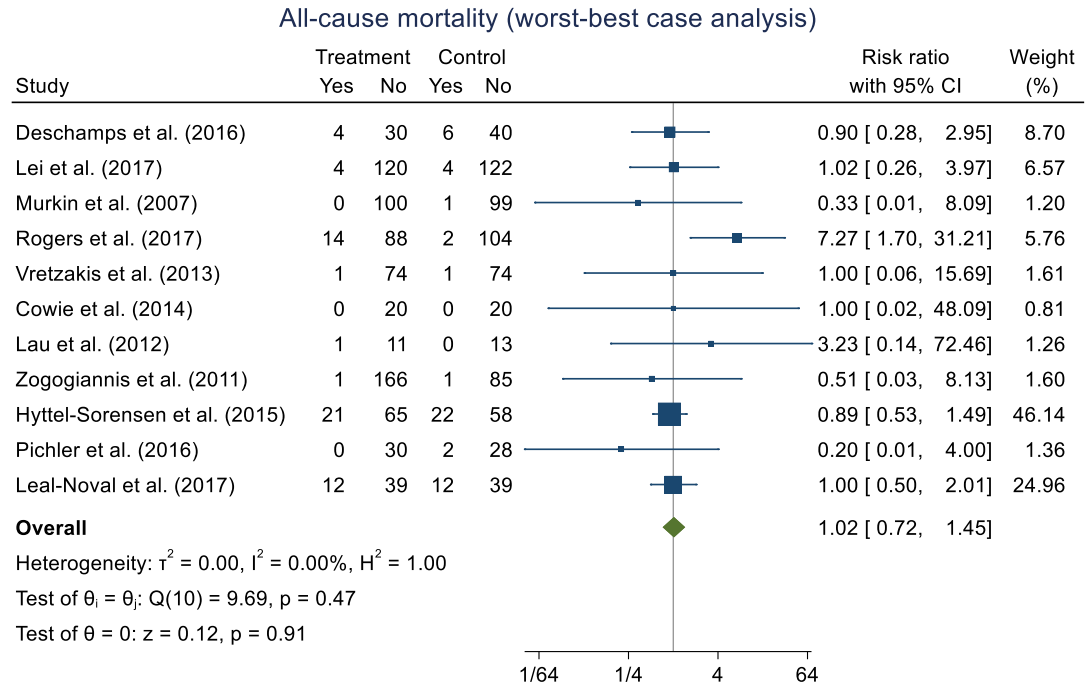


Random-effects DerSimonian–Laird model

Worst-best case analysis

Assuming a harmful event in the experimental group and beneficial in the control group

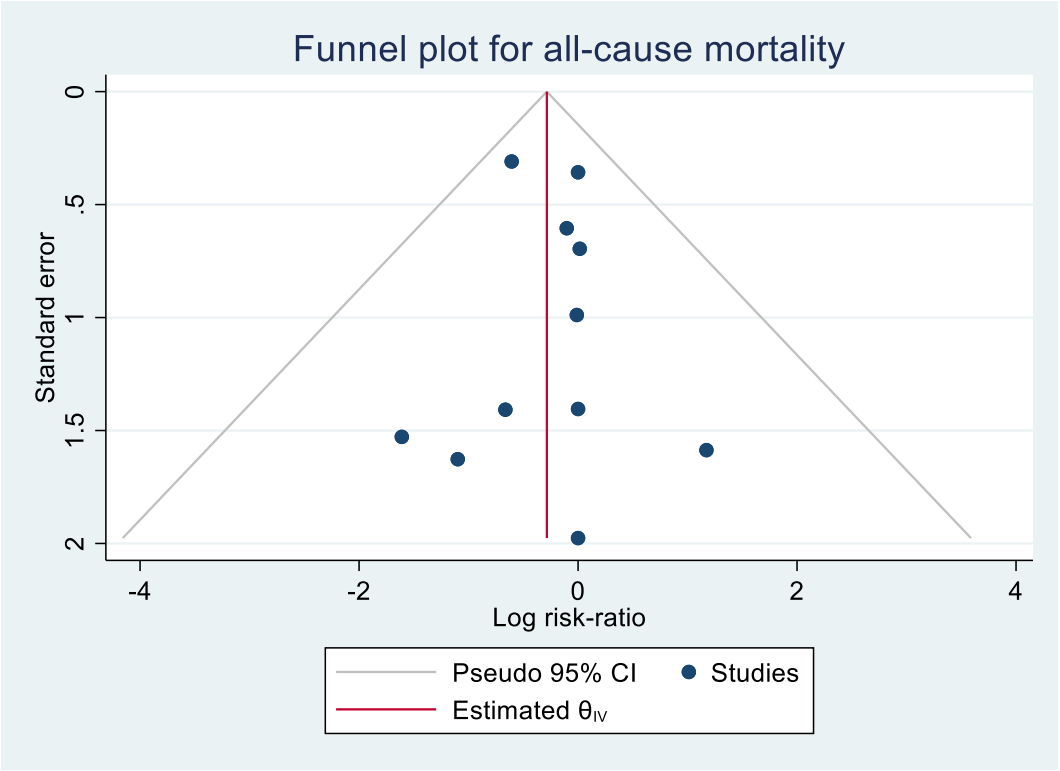
Figure S8



Random-effects DerSimonian–Laird model

Funnel plot

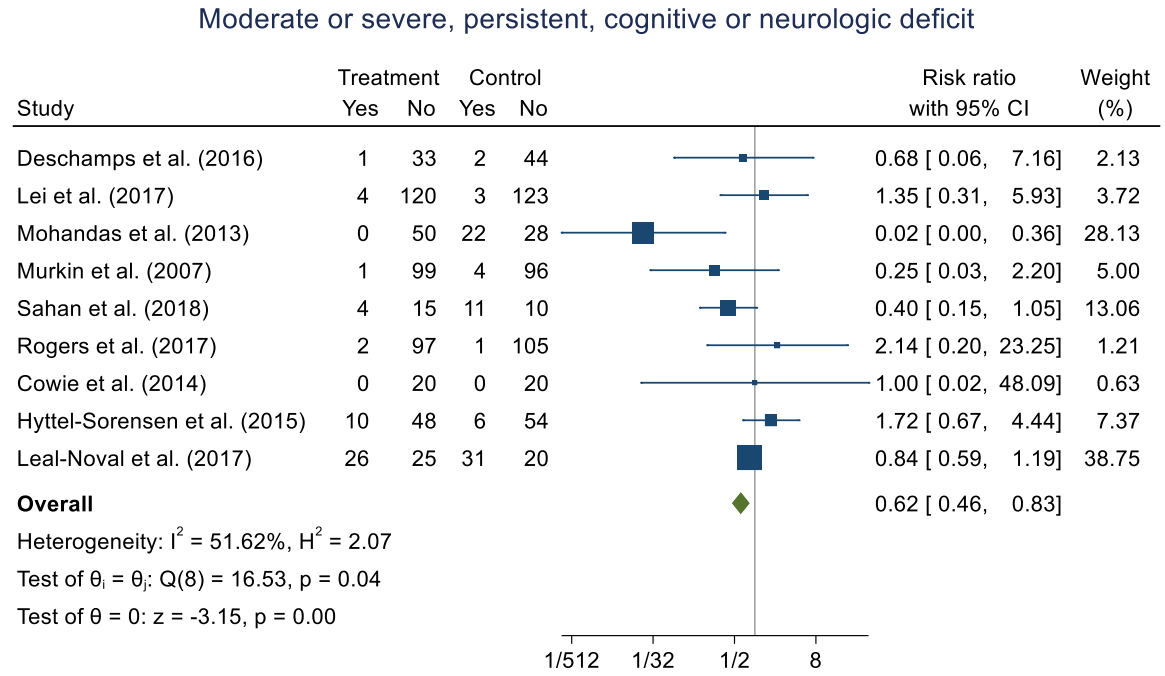
Figure S9



Moderate or severe, persistent, cognitive or neurological deficit, at maximal follow-up

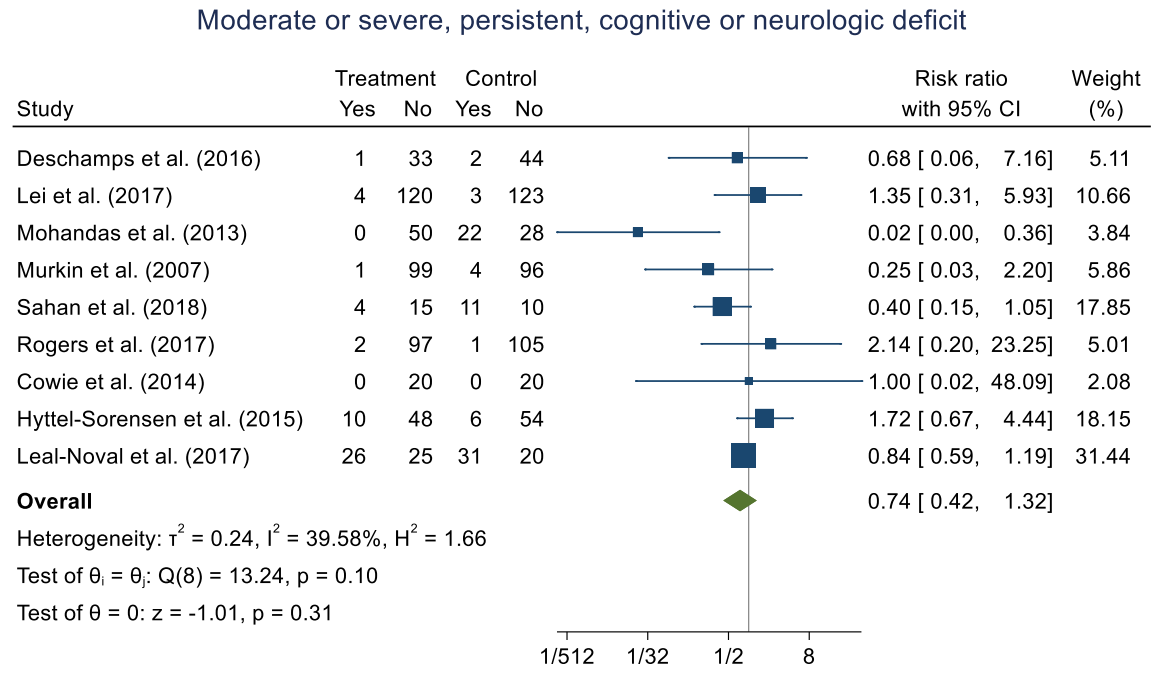
Primary analysis

Figure S10 – fixed effect



Fixed-effects Mantel–Haenszel model

Figure S11 – random effects

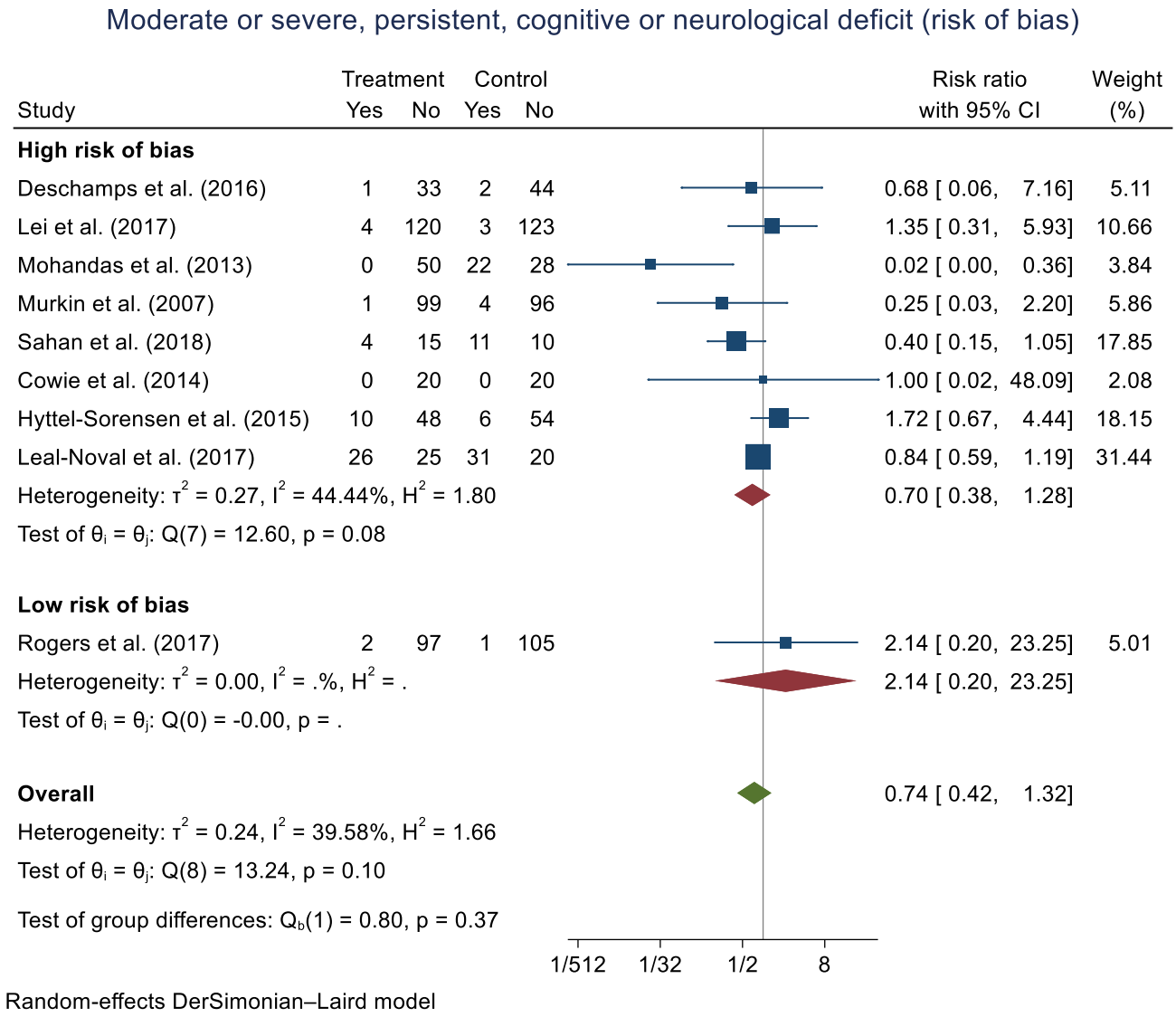


Random-effects DerSimonian–Laird model

Subgroup analyses

Risk of bias (high compared to low)

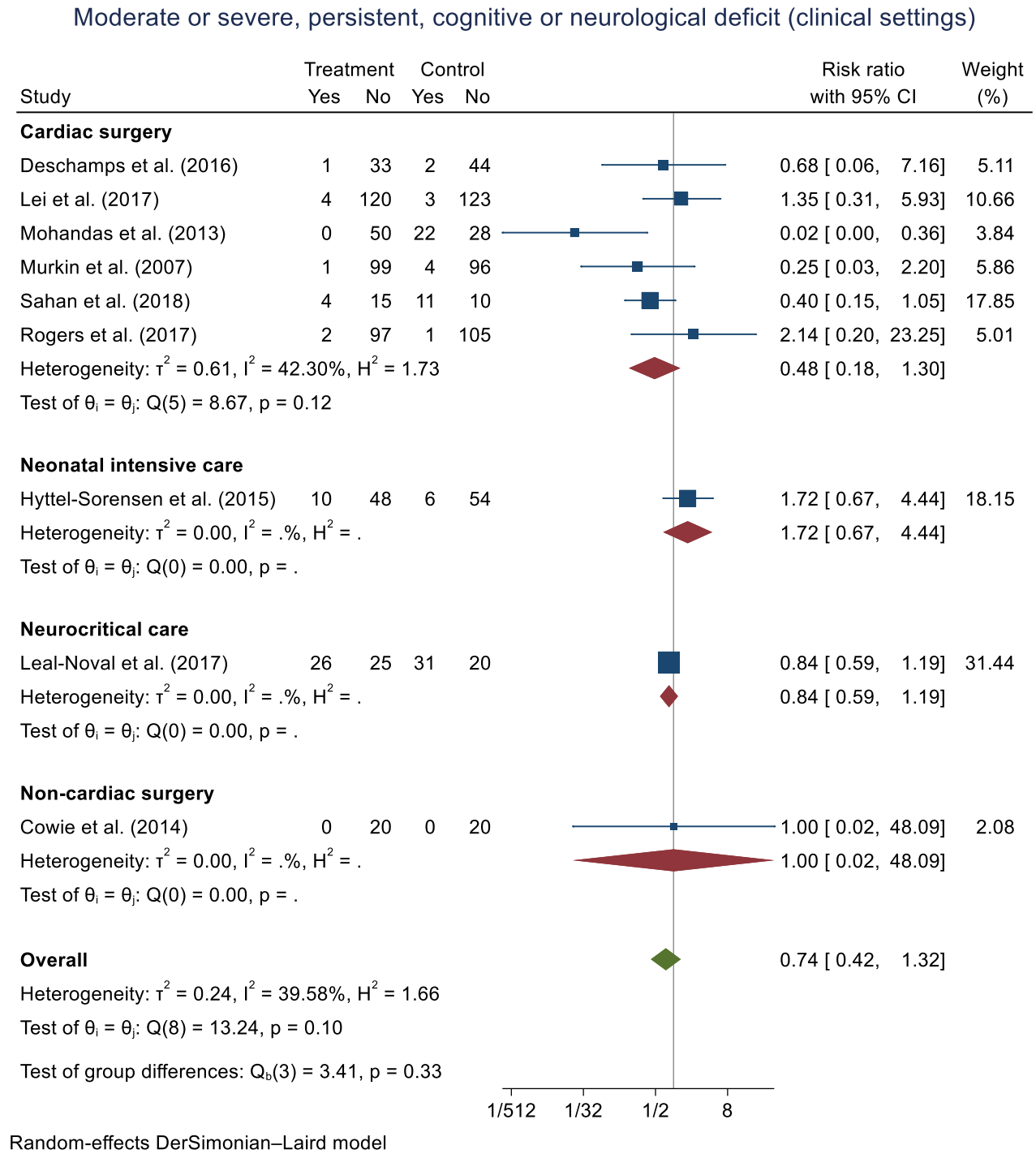
Figure S12



Random-effects DerSimonian–Laird model

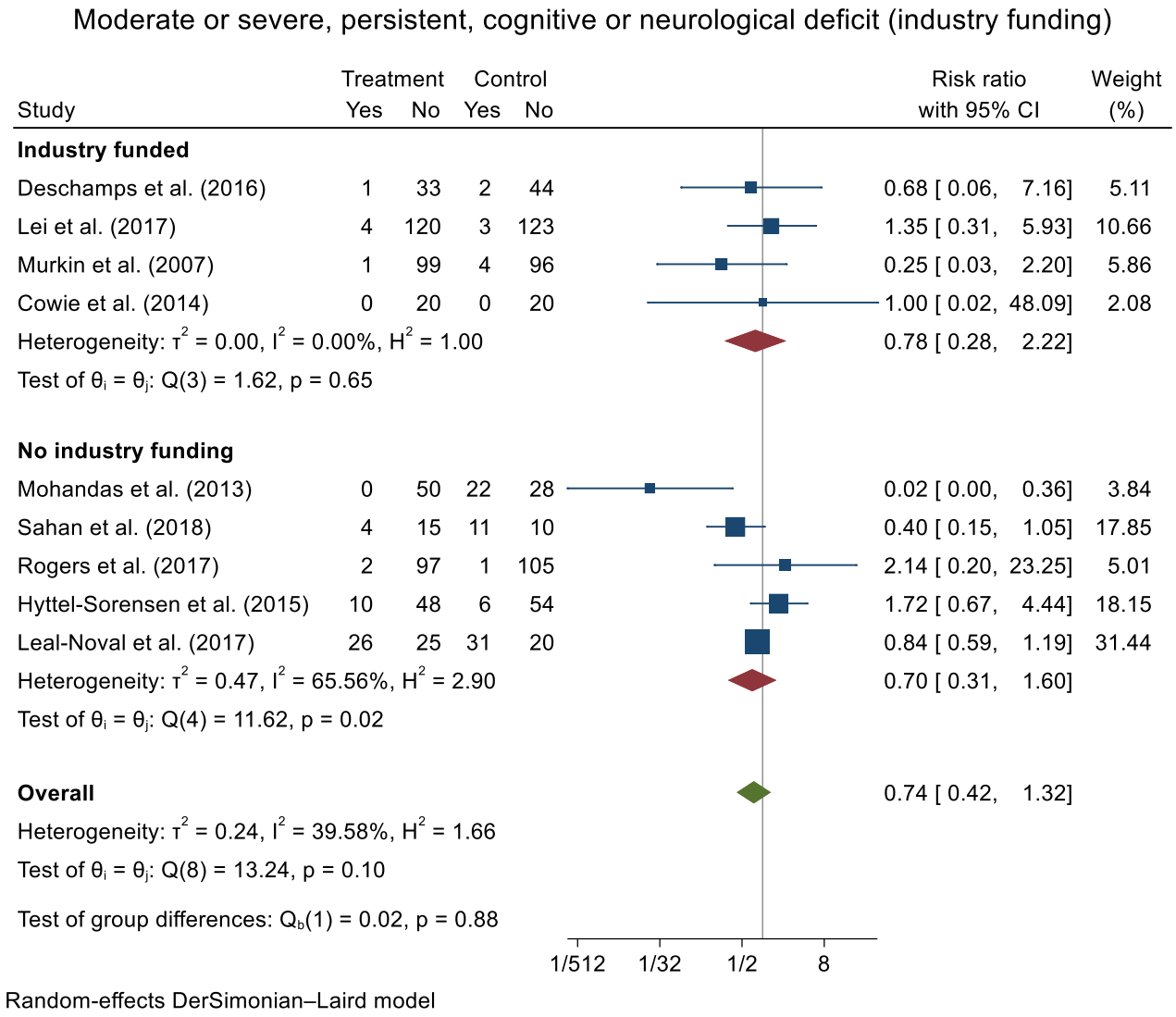
Clinical setting (cardiac surgery compared to neonatal intensive care compared to neurocritical care compared to non-cardiac surgery)

Figure S13

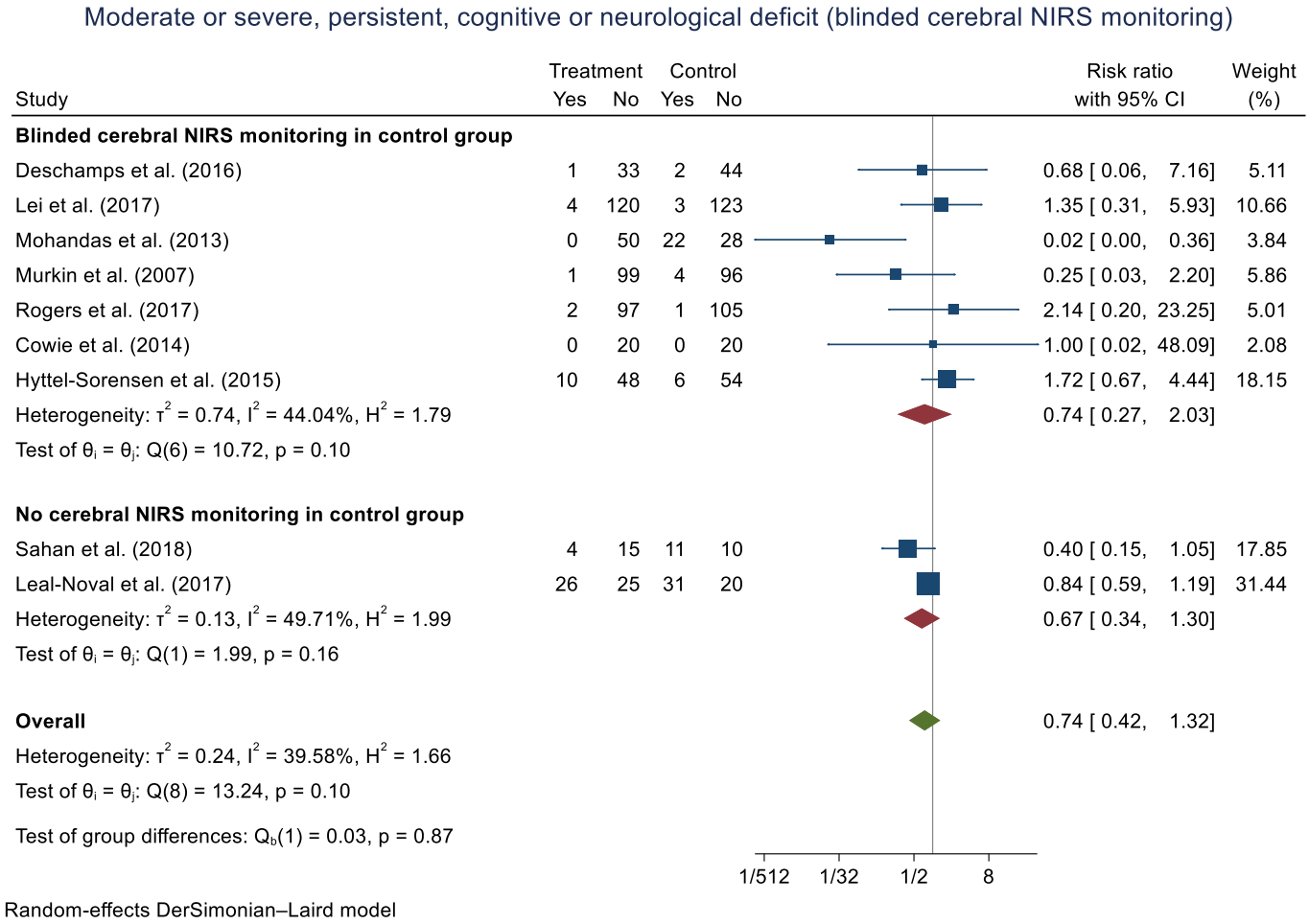


Industry funding (funding not reported compared to industry funded compared to no industry funding)

Figure S14



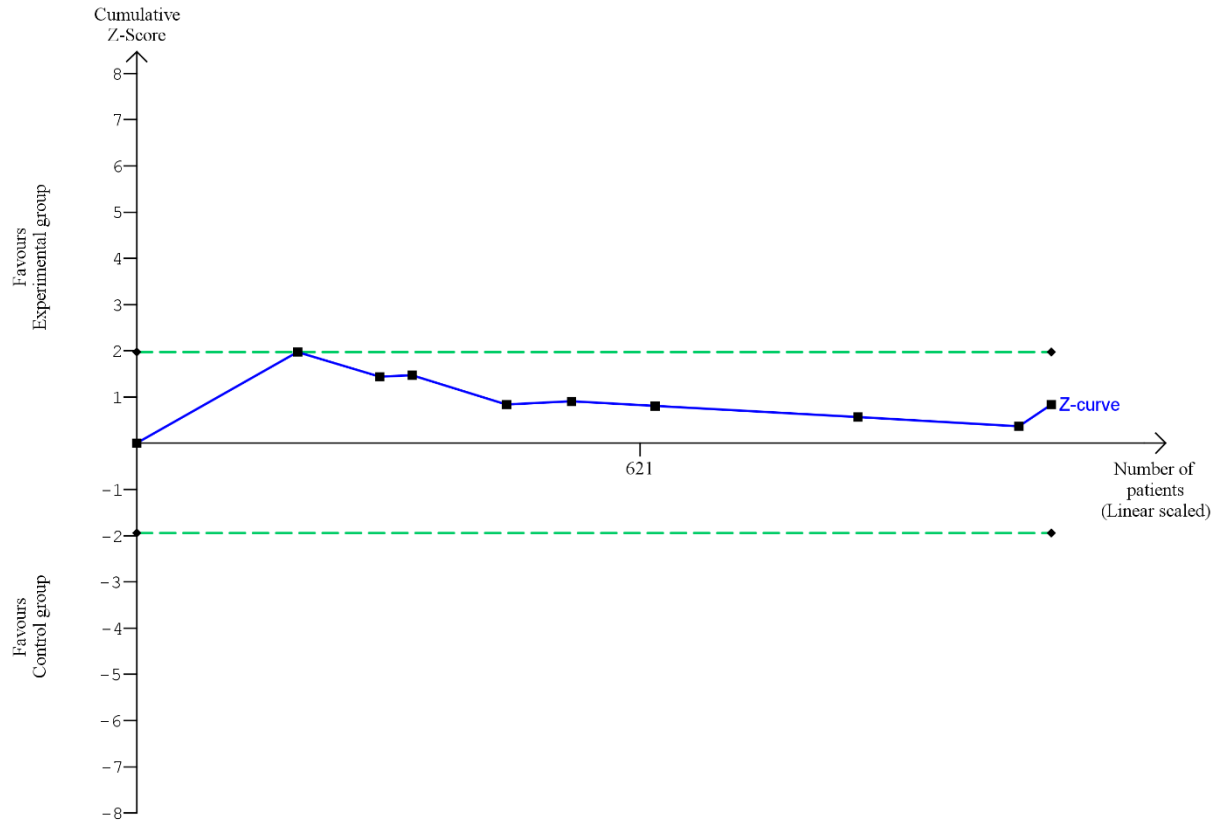
Cerebral NIRS monitoring in the control group (blinded cerebral NIRS monitoring in the control group compared to no cerebral NIRS monitoring in the control group)
Figure S15



Trial Sequential Analysis

Figure S16 – TSA moderate or severe, persistent, cognitive or neurologic deficit

Boundary DARIS Pc 13.8; RR 20%; alpha 2.5%; beta 10%; diversity 78.9 is ignored due to too little information size (3.4% out of 33679).



Bayes factor

LnRR meta-analysis = -0,30
LnSE meta-analysis = 0.29
LnRR a priori = -0.22

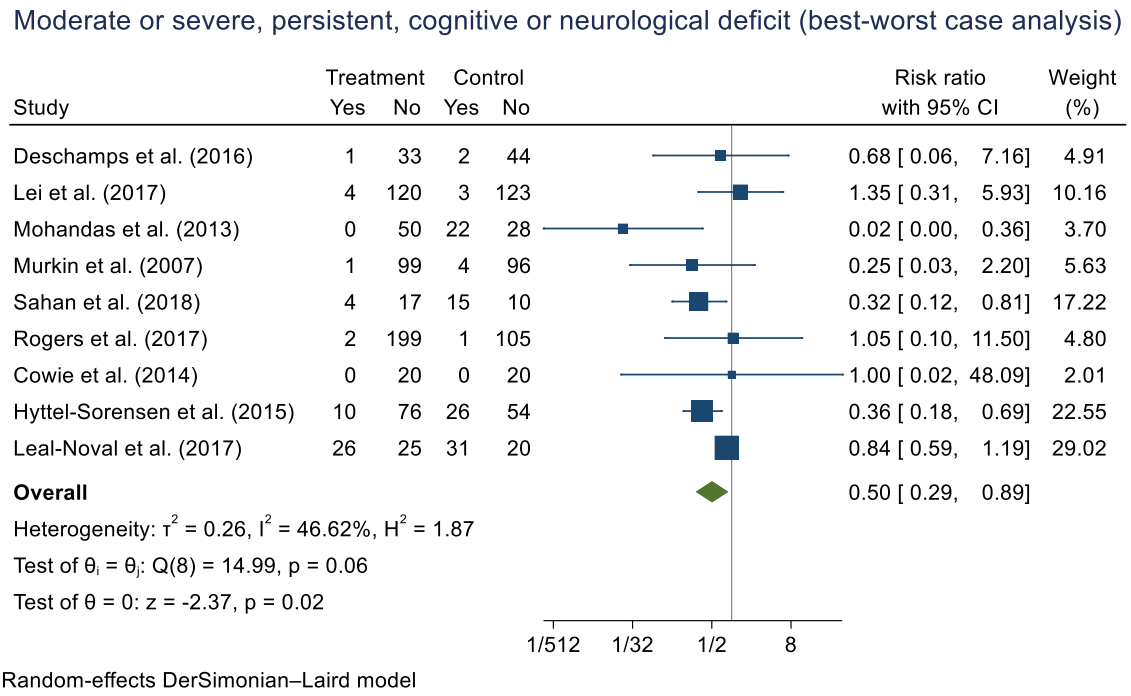
Bayes factor = 0.60

Sensitivity analyses

Best-worst case analysis

Assuming a beneficial event in the experimental group and harmful in the control group

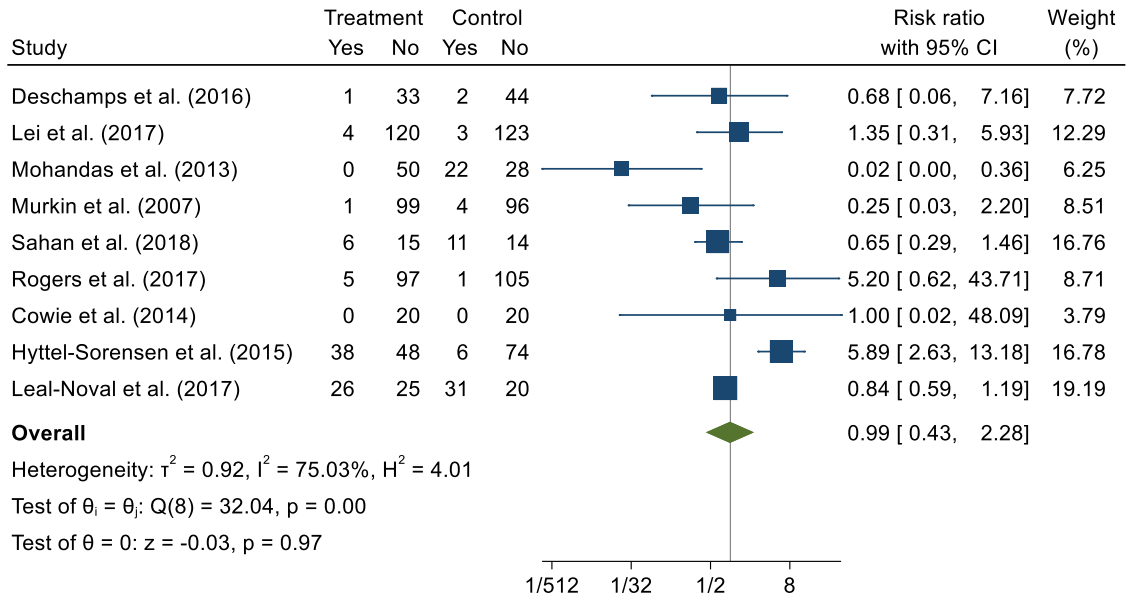
Figure S17



Worst-best case analysis

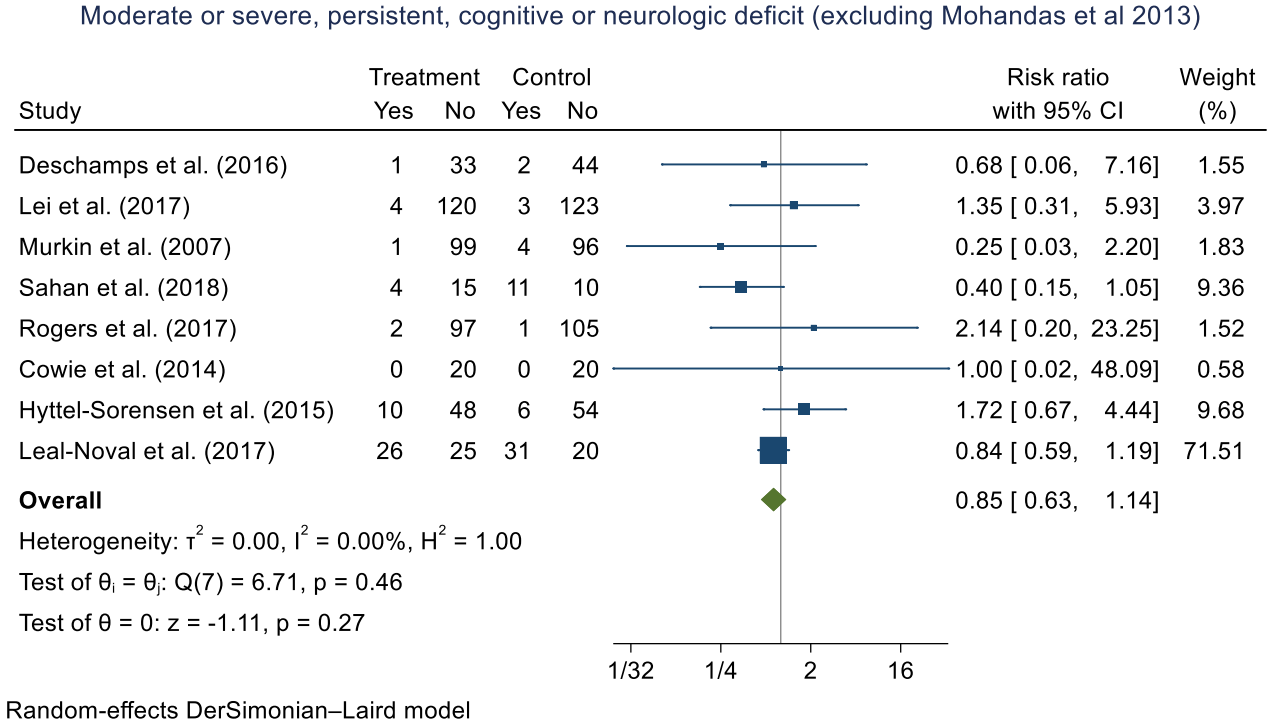
Assuming a harmful event in the experimental group and beneficial in the control group

Figure S18



Heterogeneity (excluding Mohandas et al 2013)

Figure S19



Proportion of participants with one or more serious adverse events

Primary analysis

Figure S20 – fixed effect

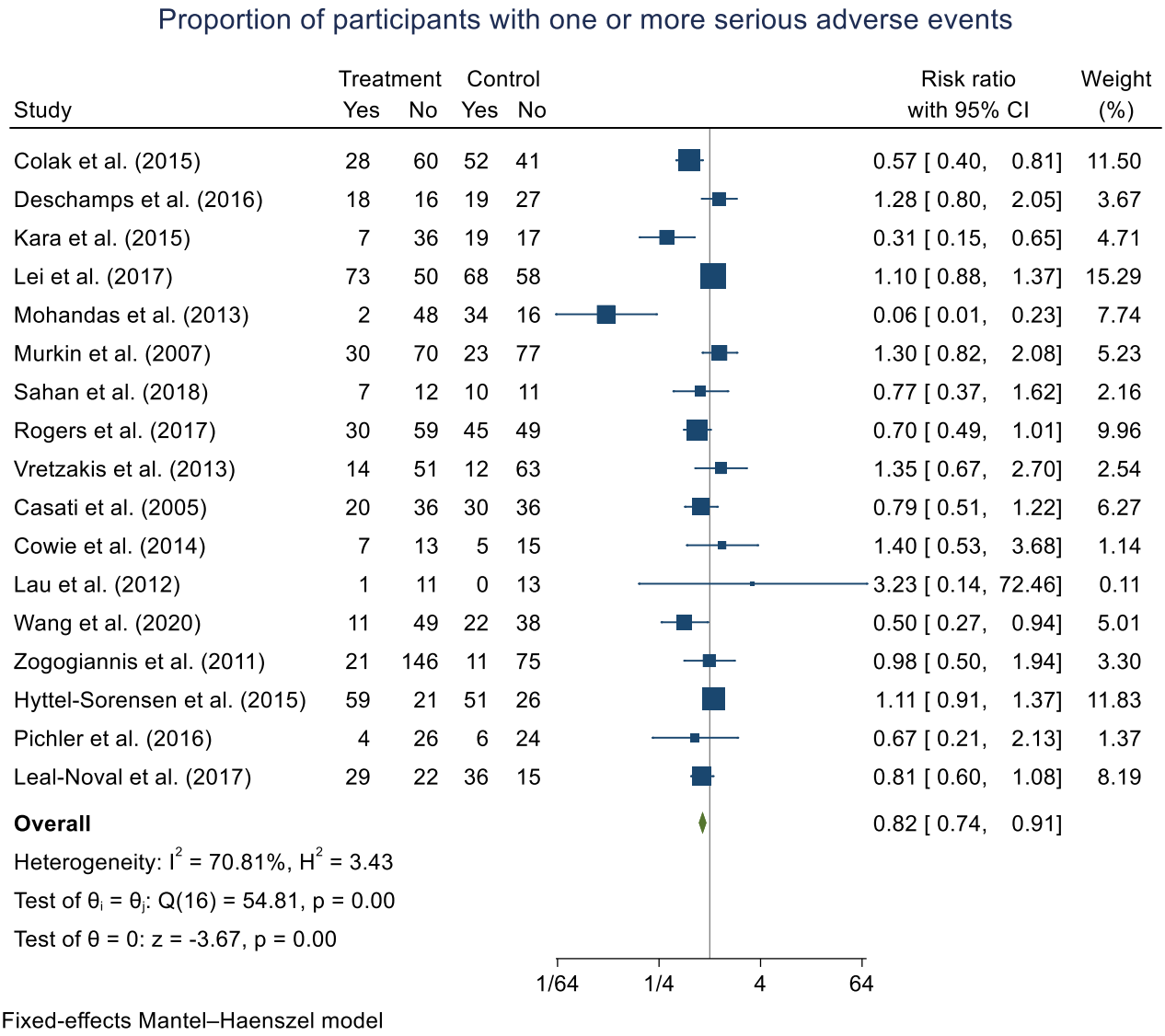
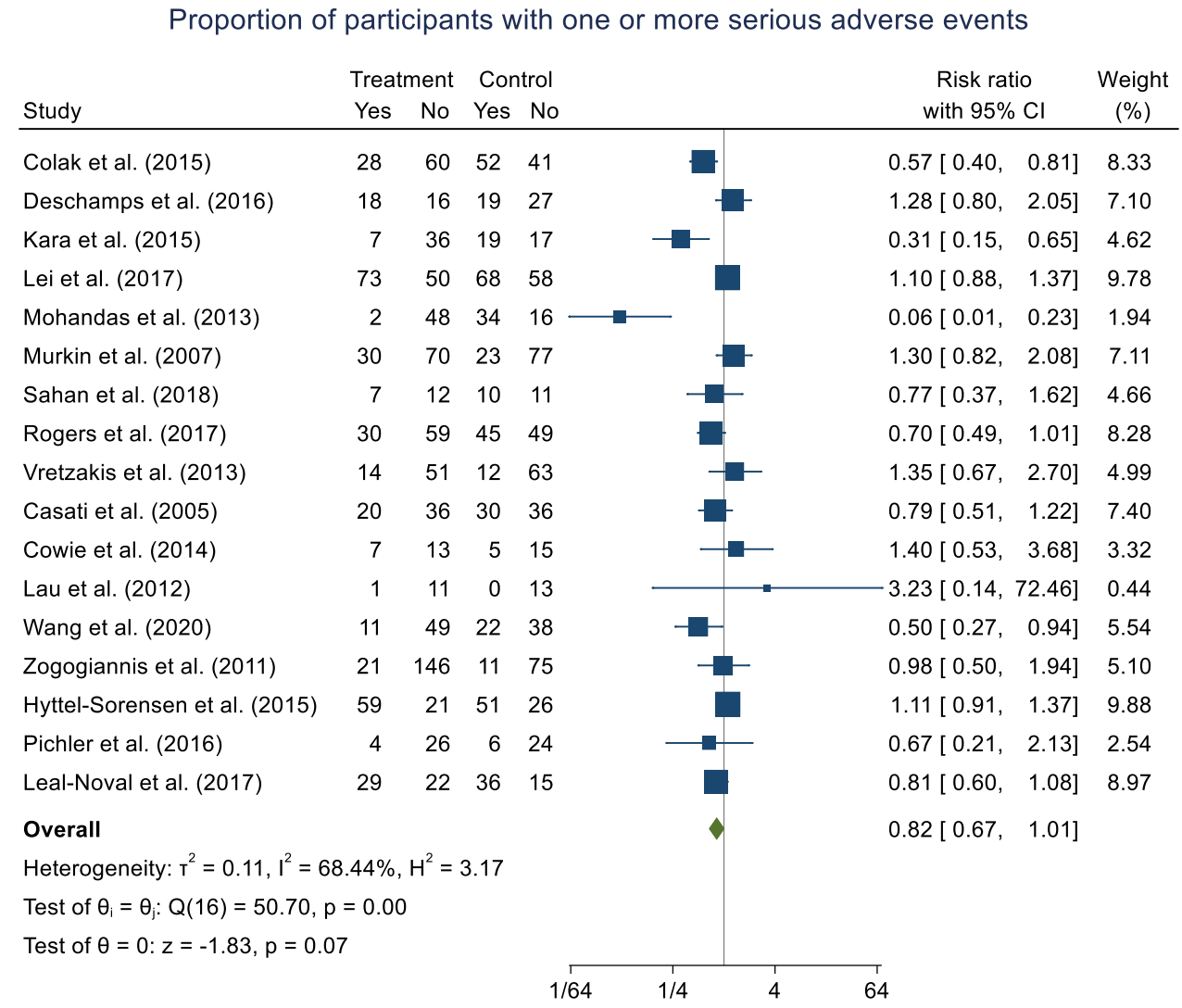


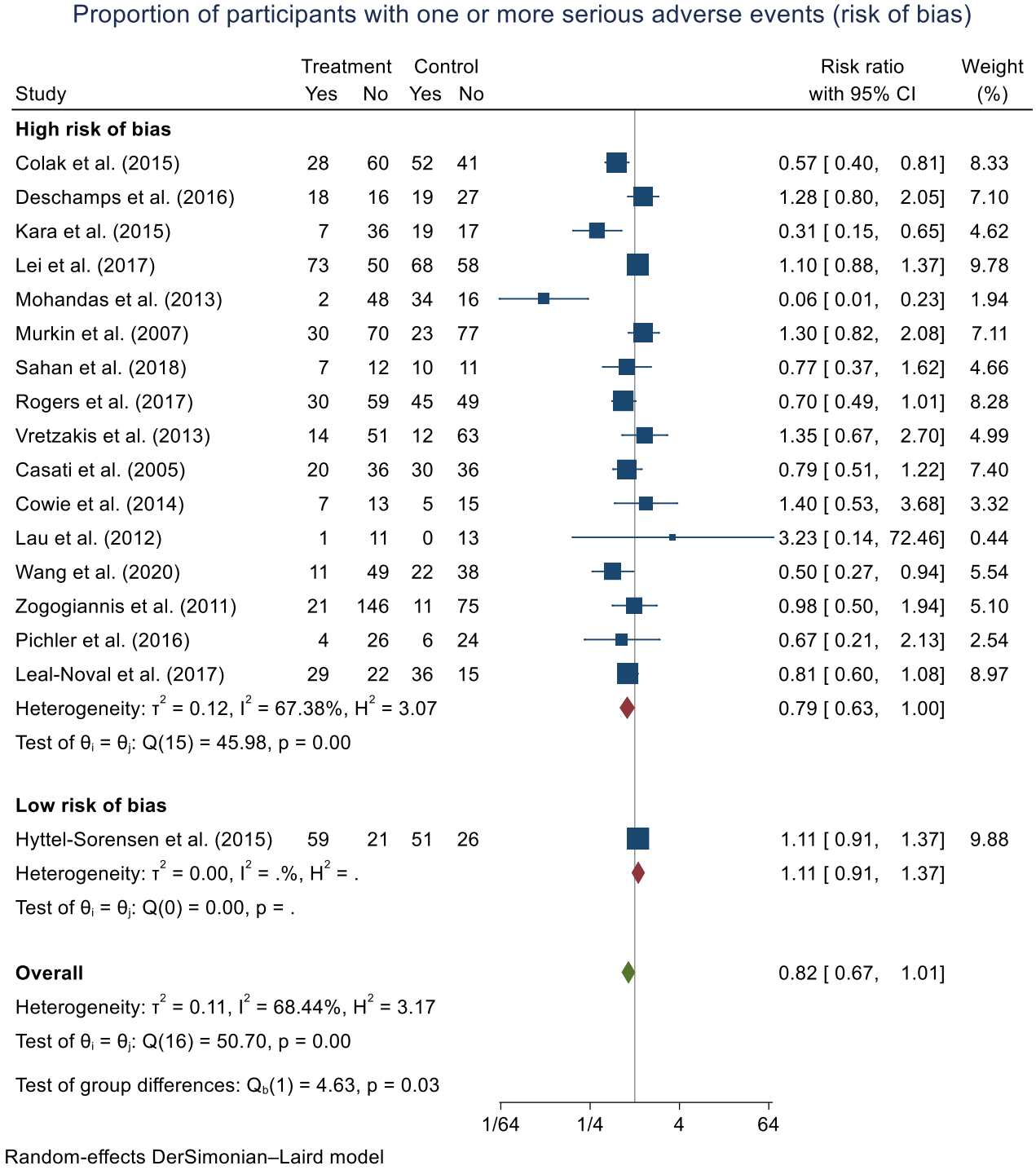
Figure S21 – random effects



Subgroup analyses

Risk of bias (high compared to low)

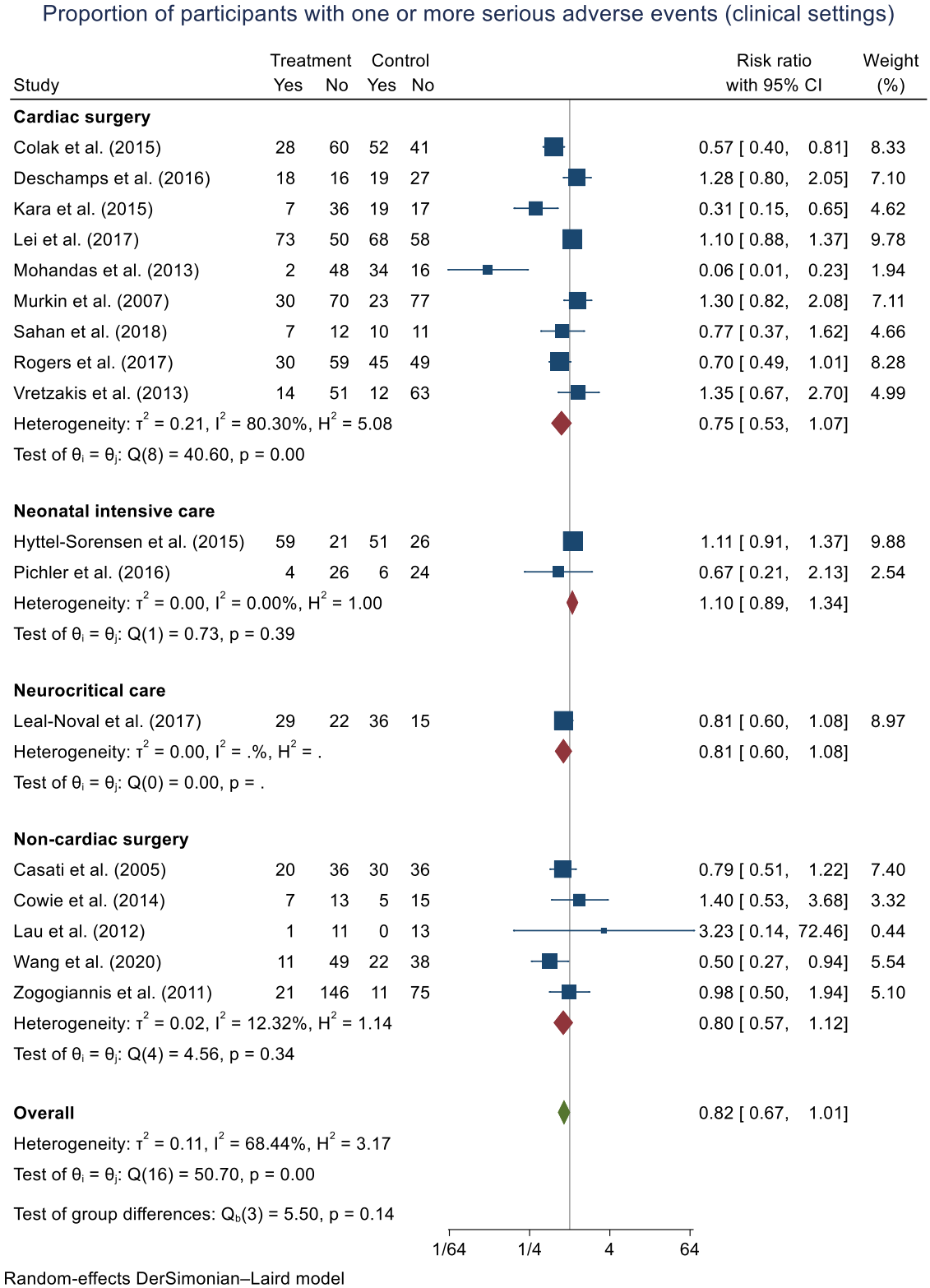
Figure S22



Random-effects DerSimonian–Laird model

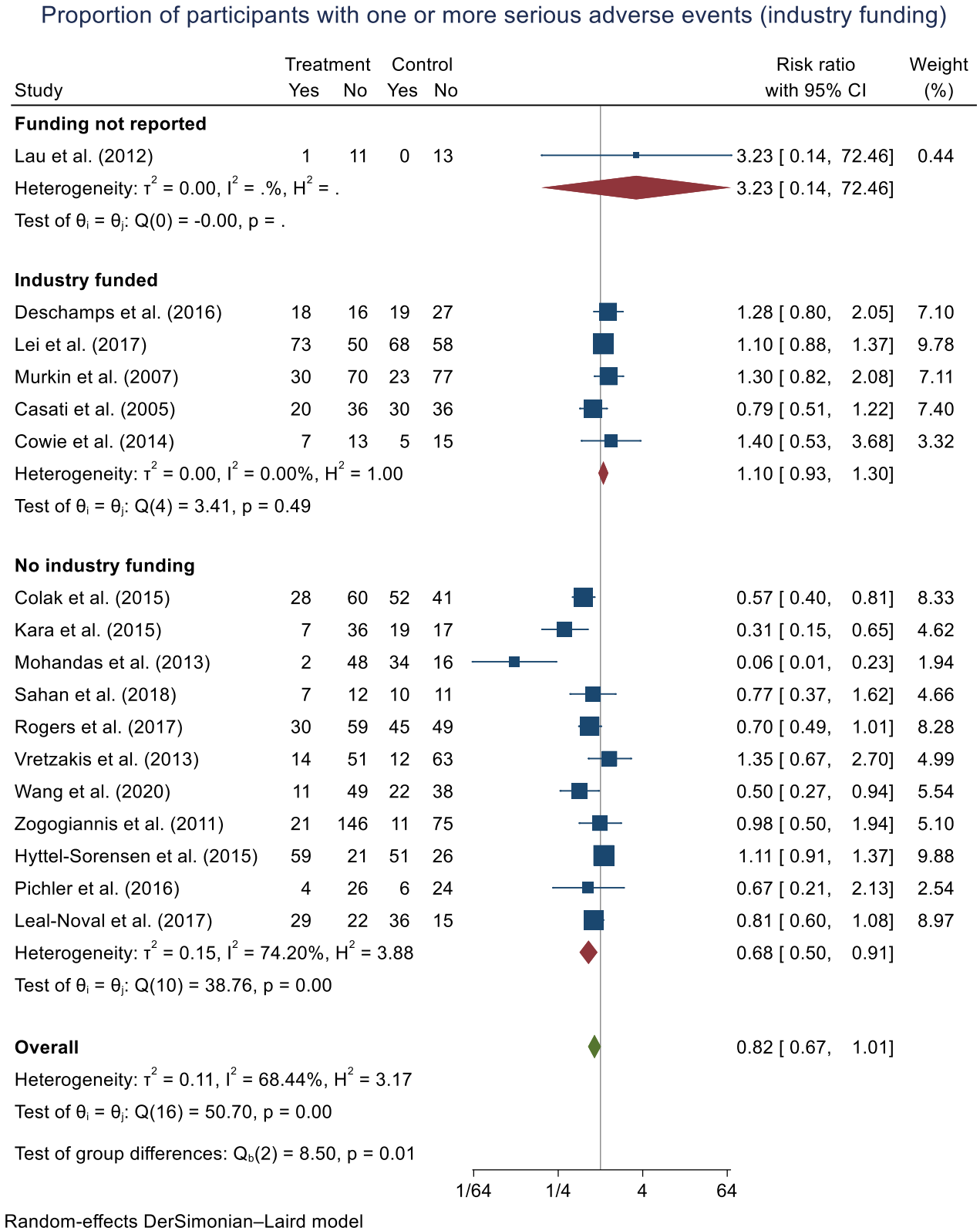
Clinical setting (cardiac surgery compared to neonatal intensive care compared to neurocritical care compared to non-cardiac surgery)

Figure S23

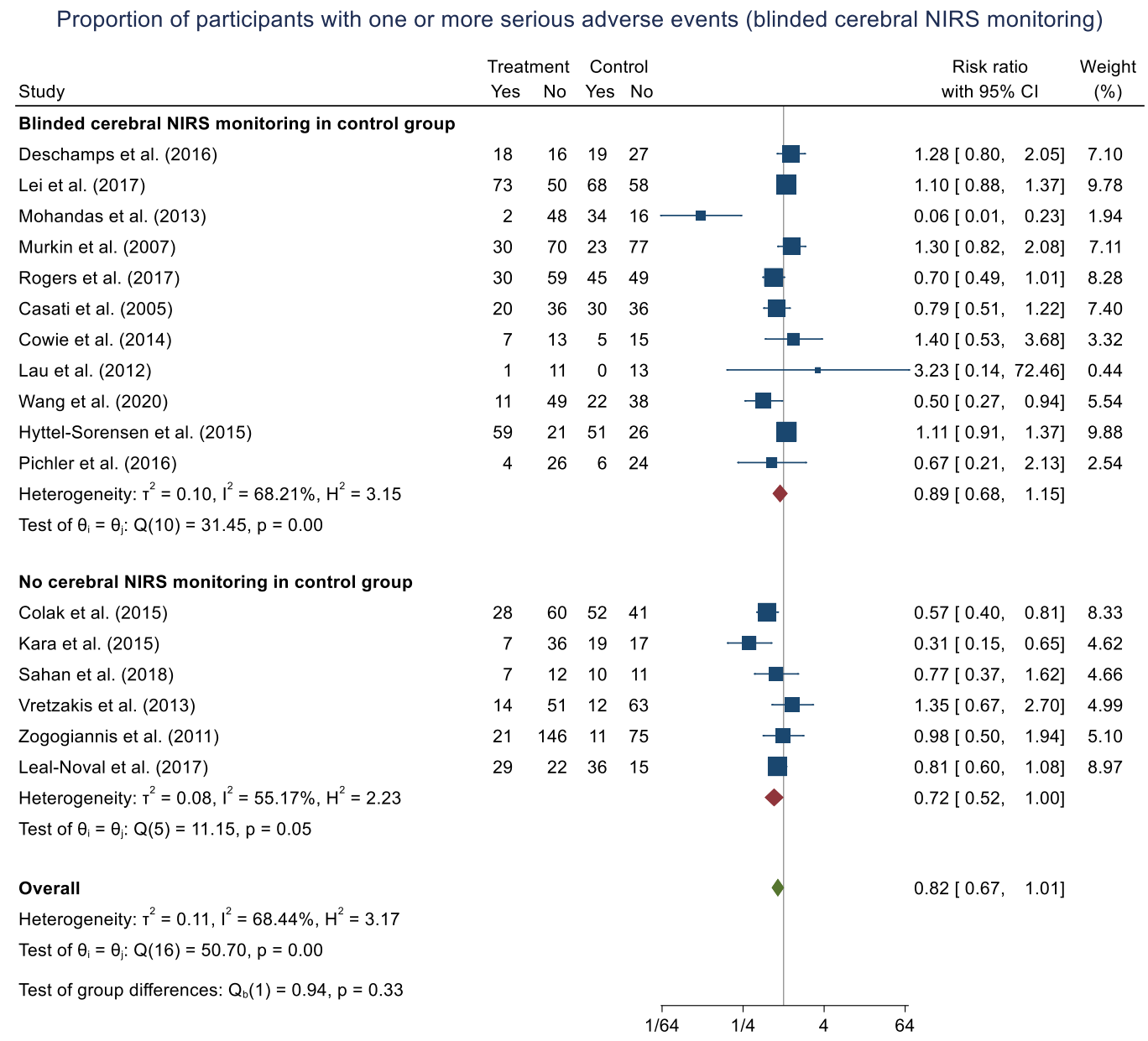


Industry funding (funding not reported compared to industry funded compared to no industry funding)

Figure S24



Cerebral NIRS monitoring in the control group (blinded cerebral NIRS monitoring in the control group compared to no cerebral NIRS monitoring in the control group)
Figure S25



Trial Sequential Analysis

Figure S26 – TSA proportion of participants with one or more serious adverse events

Trial Sequential analysis adjusted CI: 0.56 to 1.20 (p=0.07)

Bayes factor

LnRR meta-analysis = -0.20
LnSE meta-analysis = 0.10
LnRR a priori = -0.22

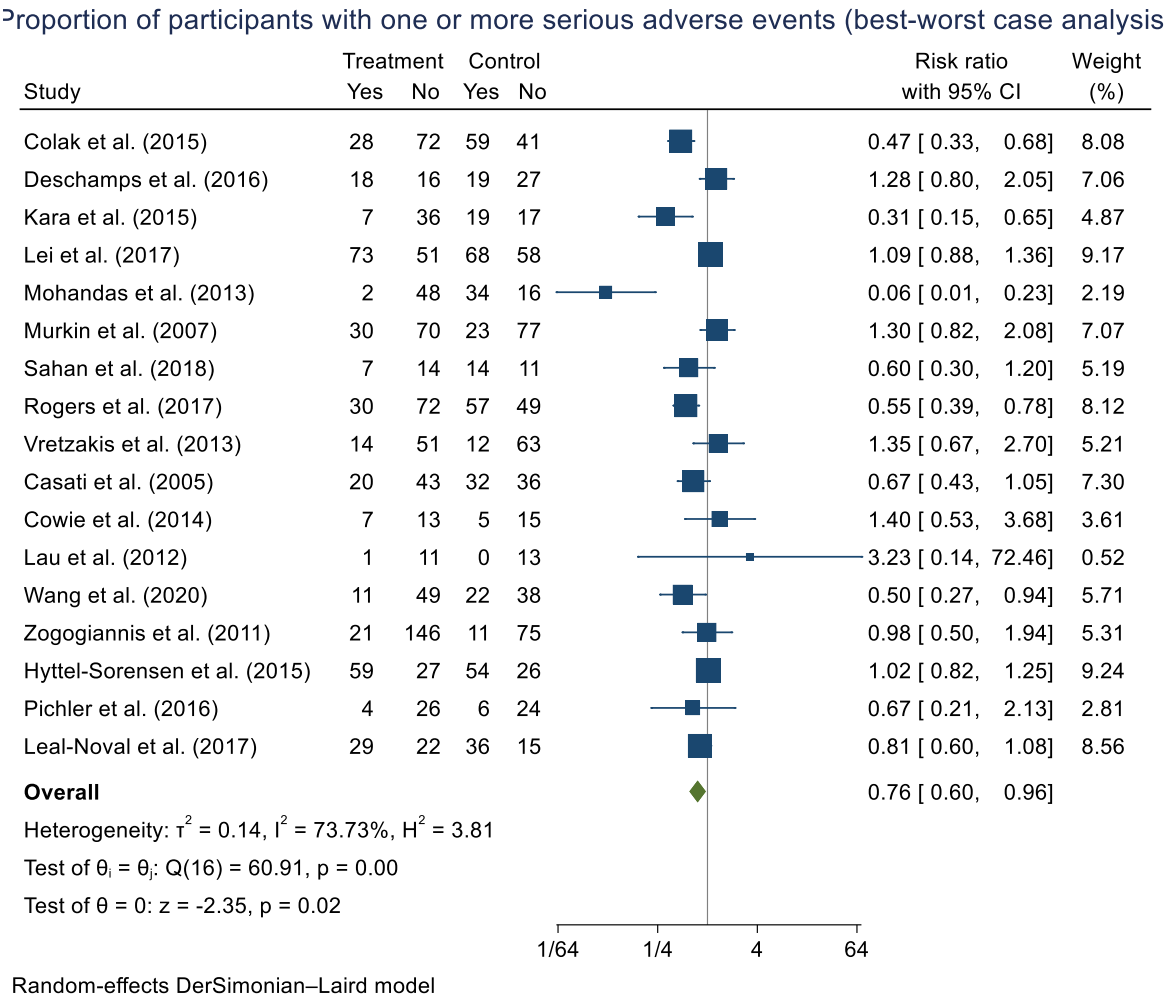
Bayes factor = 0.14

Sensitivity analyses

Best-worst case analysis

Assuming a beneficial event in the experimental group and harmful in the control group

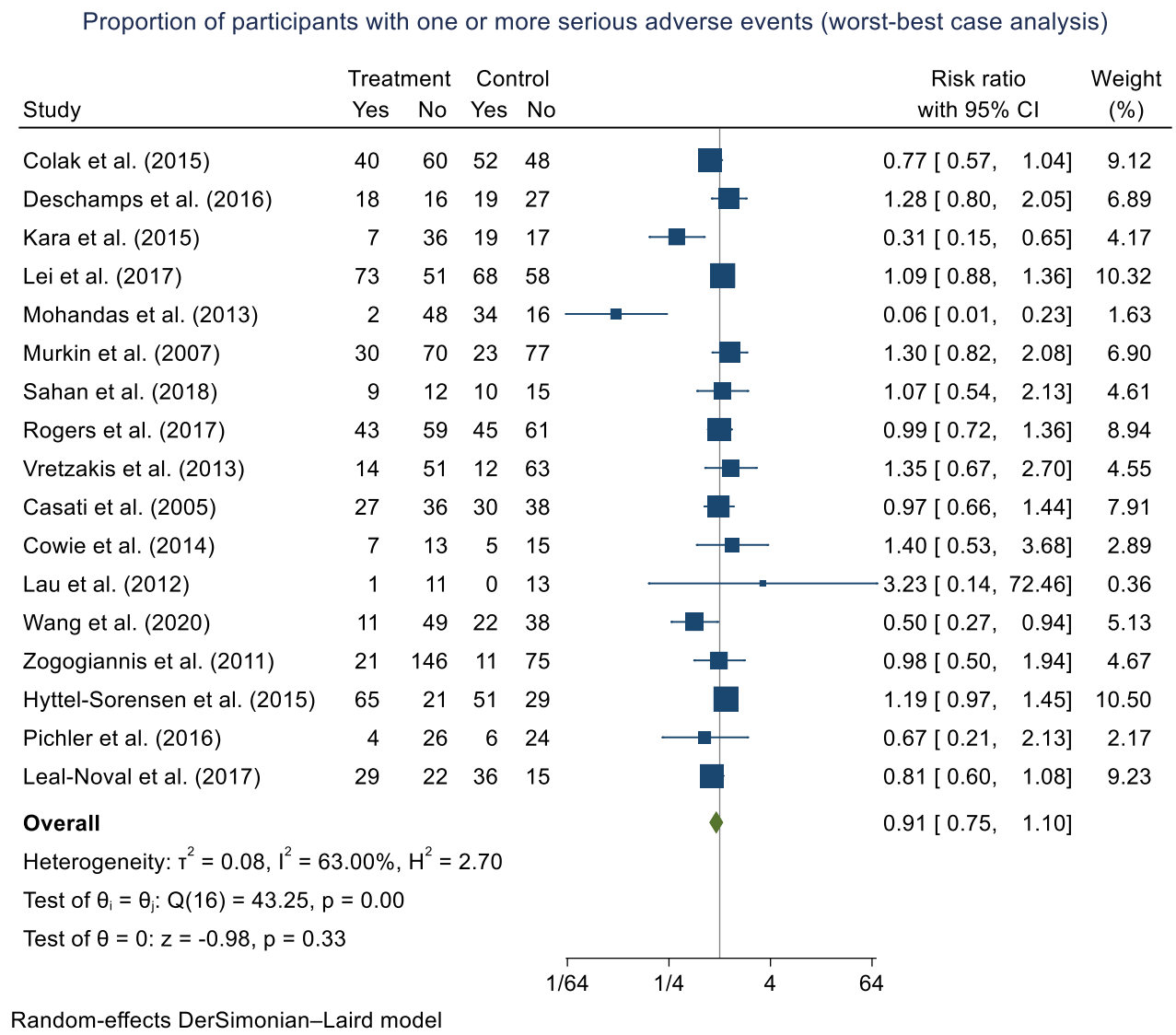
Figure S27



Worst-best case analysis

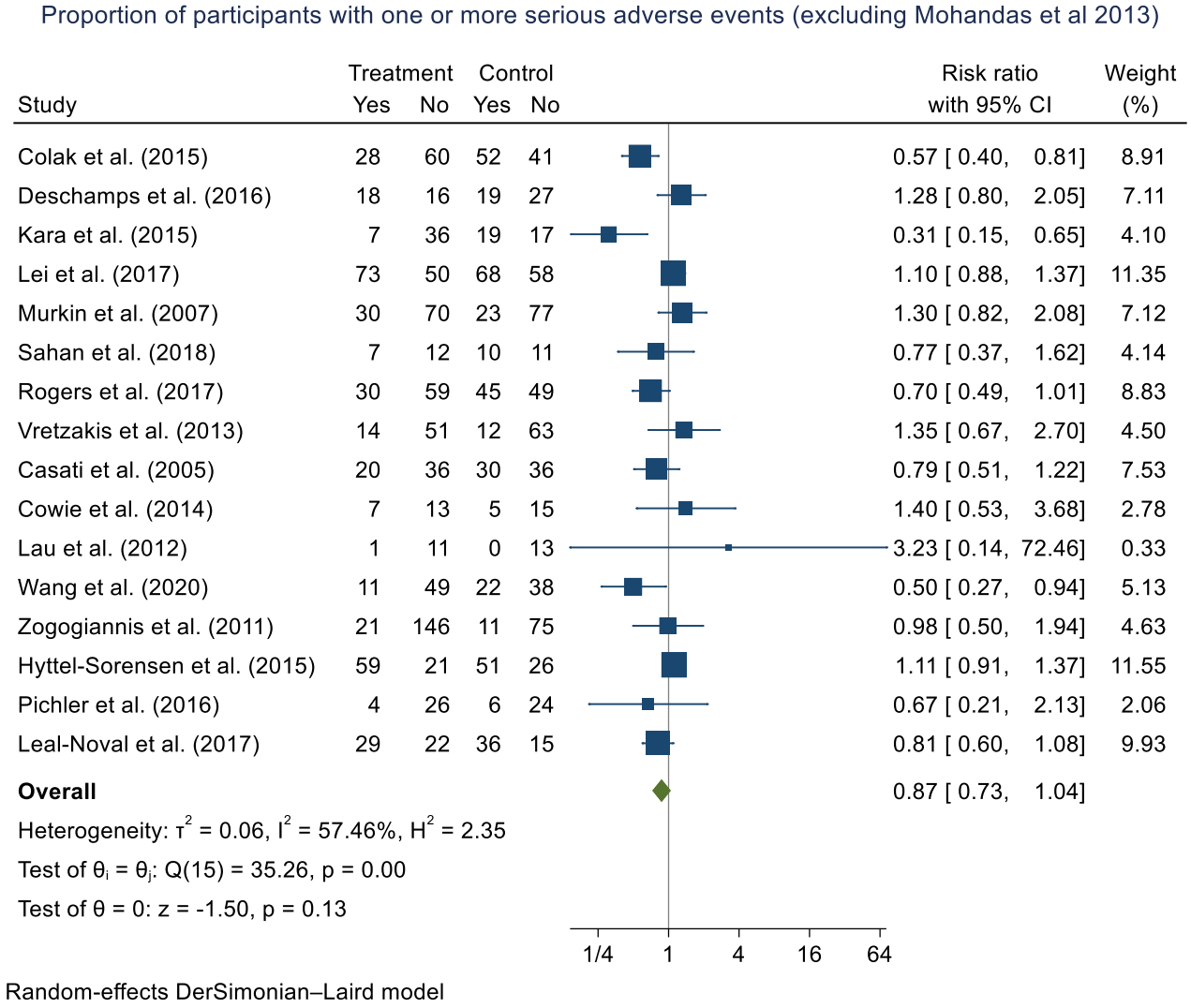
Assuming a harmful event in the experimental group and beneficial in the control group

Figure S28



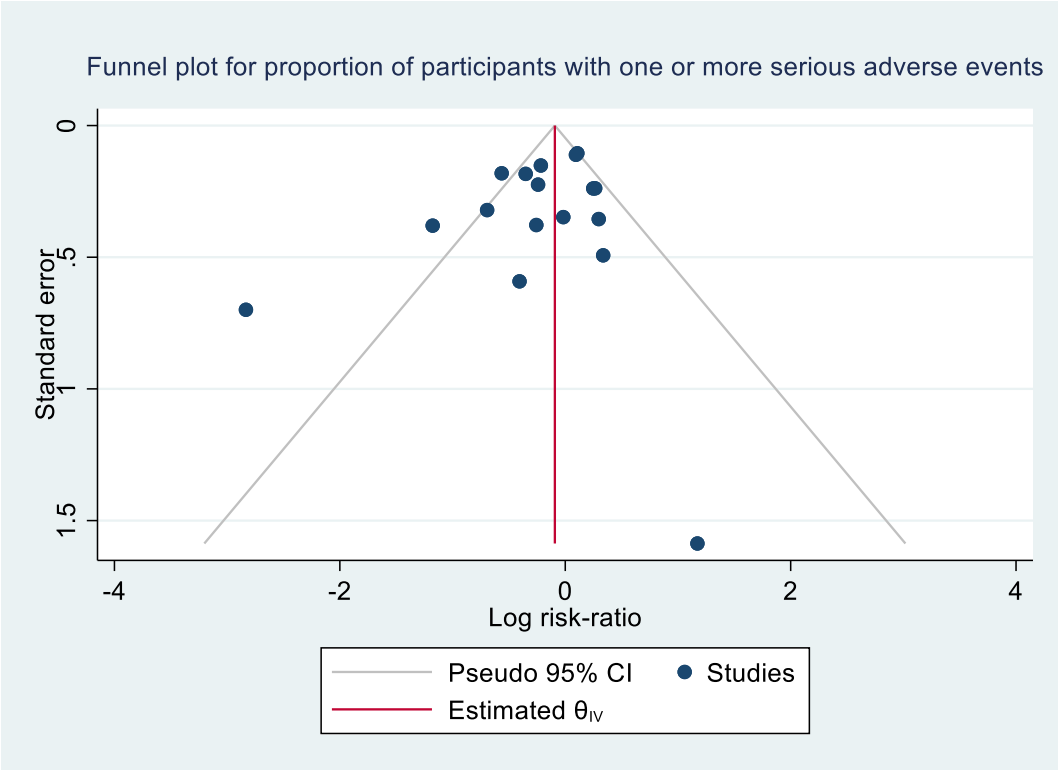
Heterogeneity (excluding Mohandas et al. 2013)

Figure S29



Funnel plot

Figure S30

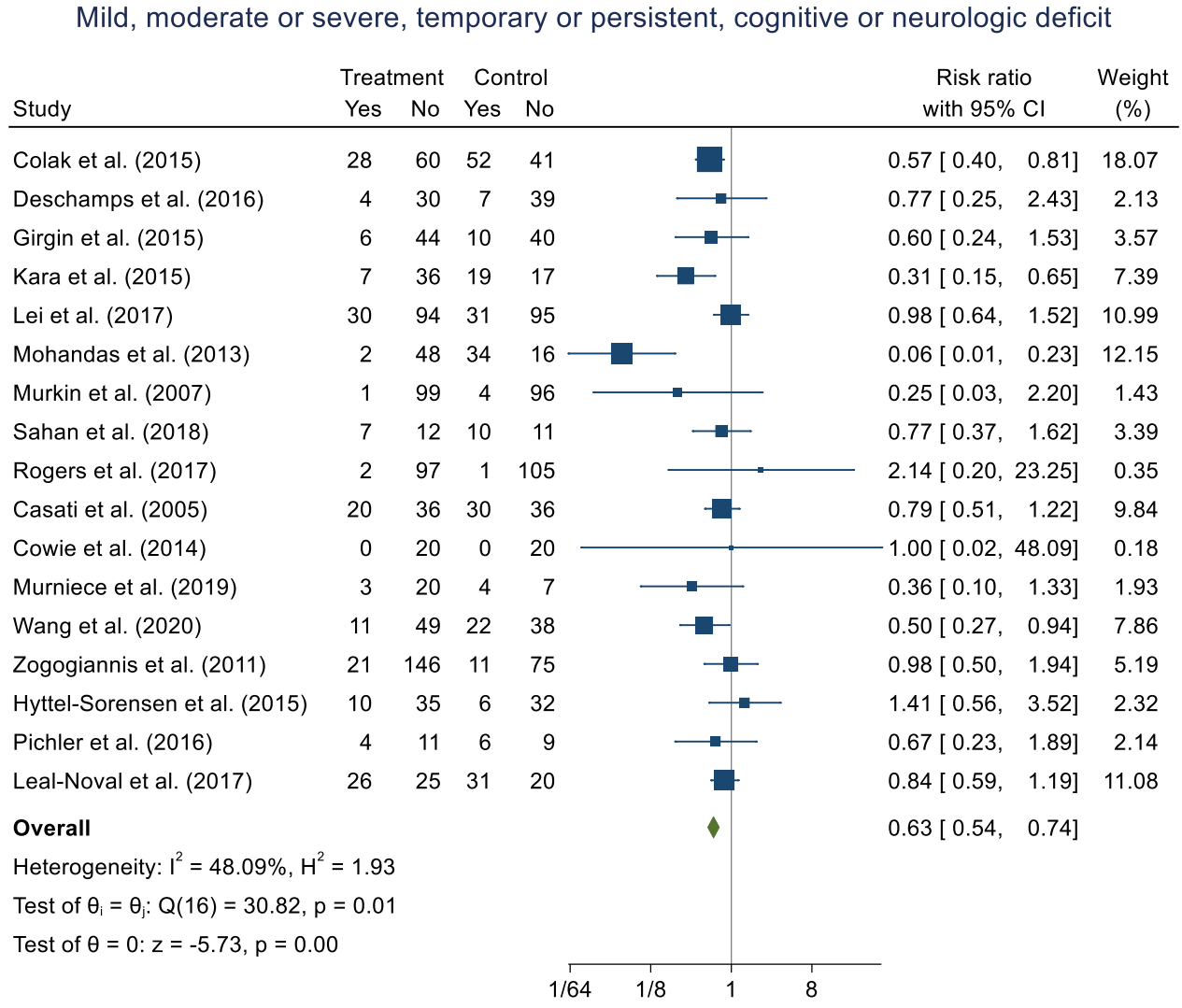


Harbord test: p=0.60

Mild, moderate or severe, temporary or persistent, cognitive or neurological deficit

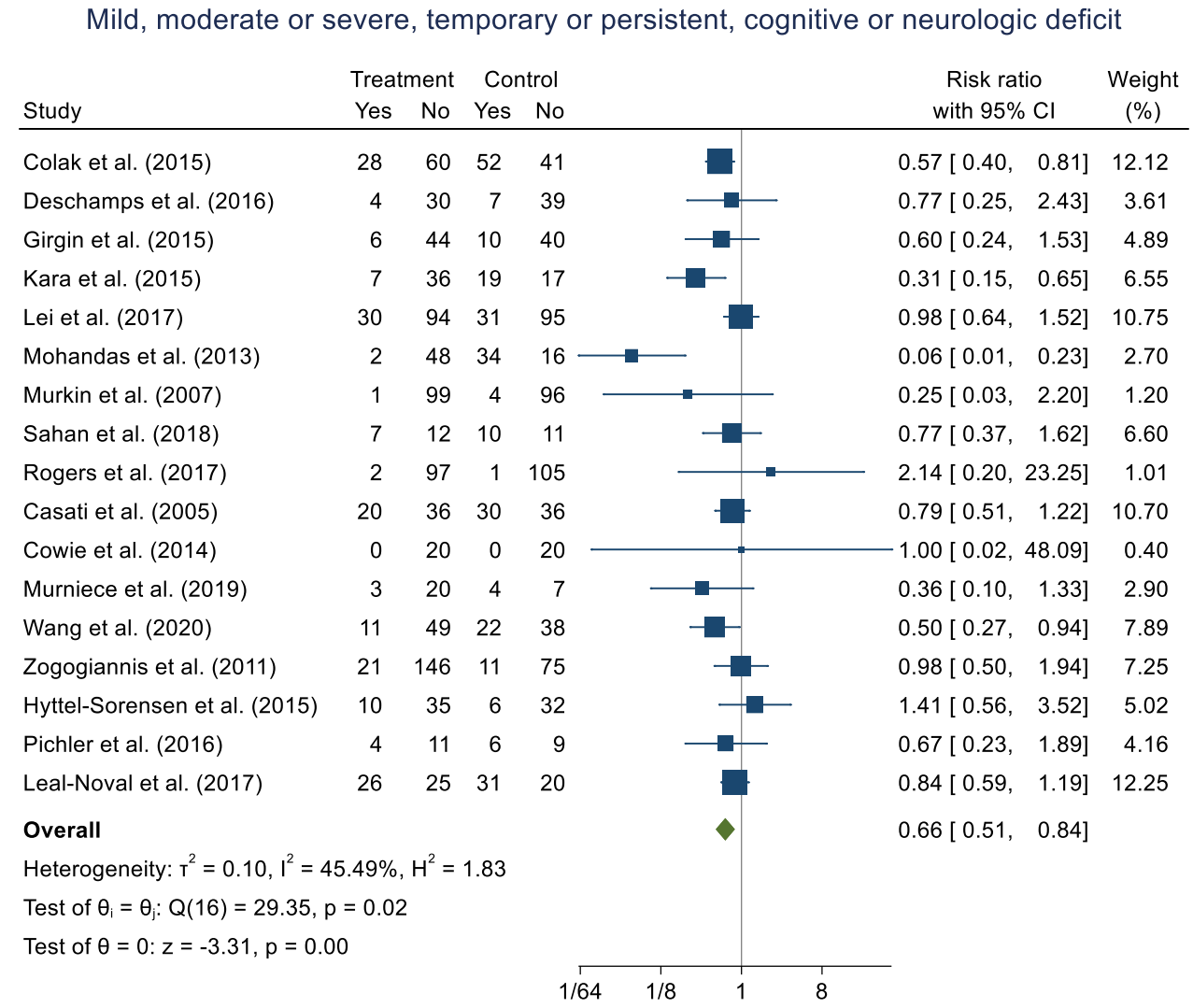
Primary analysis

Figure S31 – fixed effect



Fixed-effects Mantel–Haenszel model

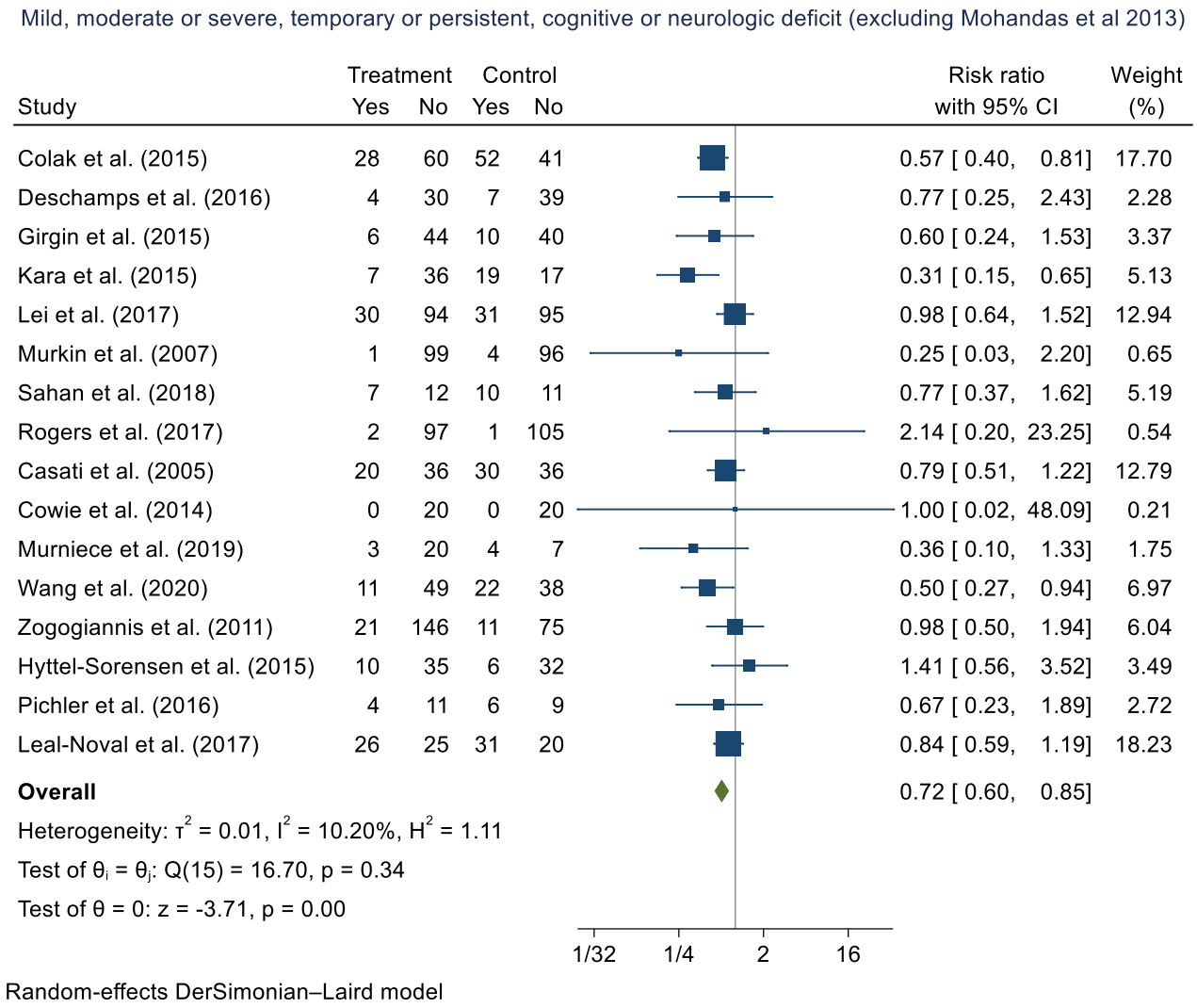
Figure S32 – random effects



Sensitivity analysis

Heterogeneity (excluding Mohandas et al. 2013)

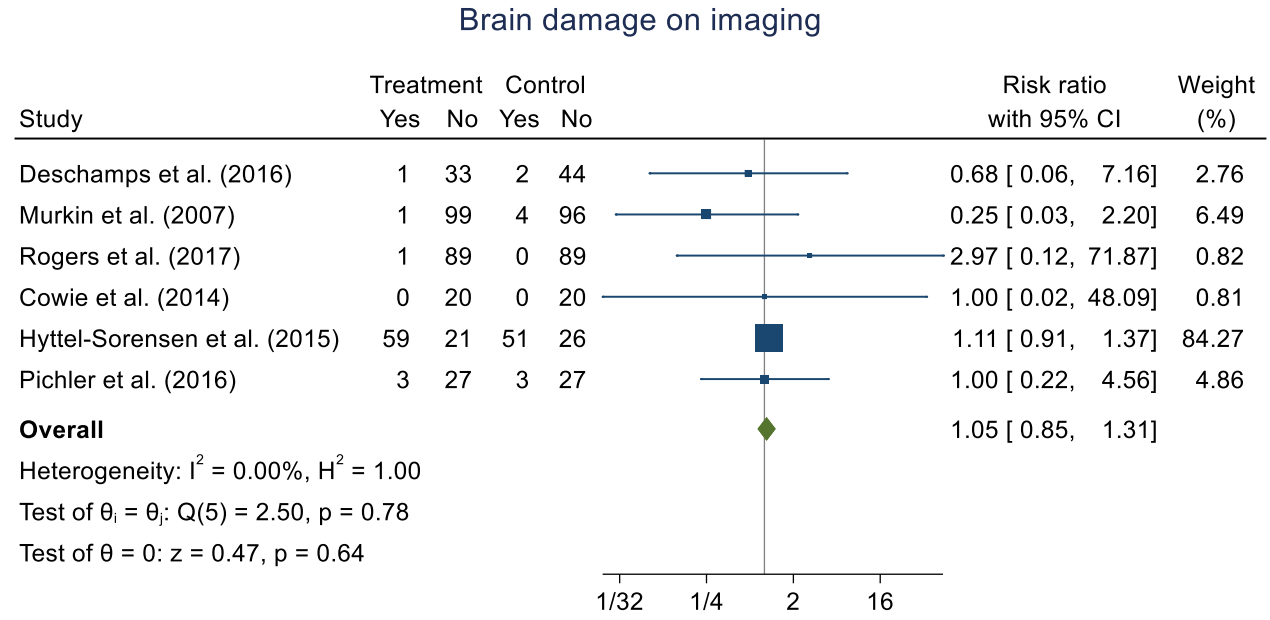
Figure S33



Brain damage on imaging at maximal follow-up

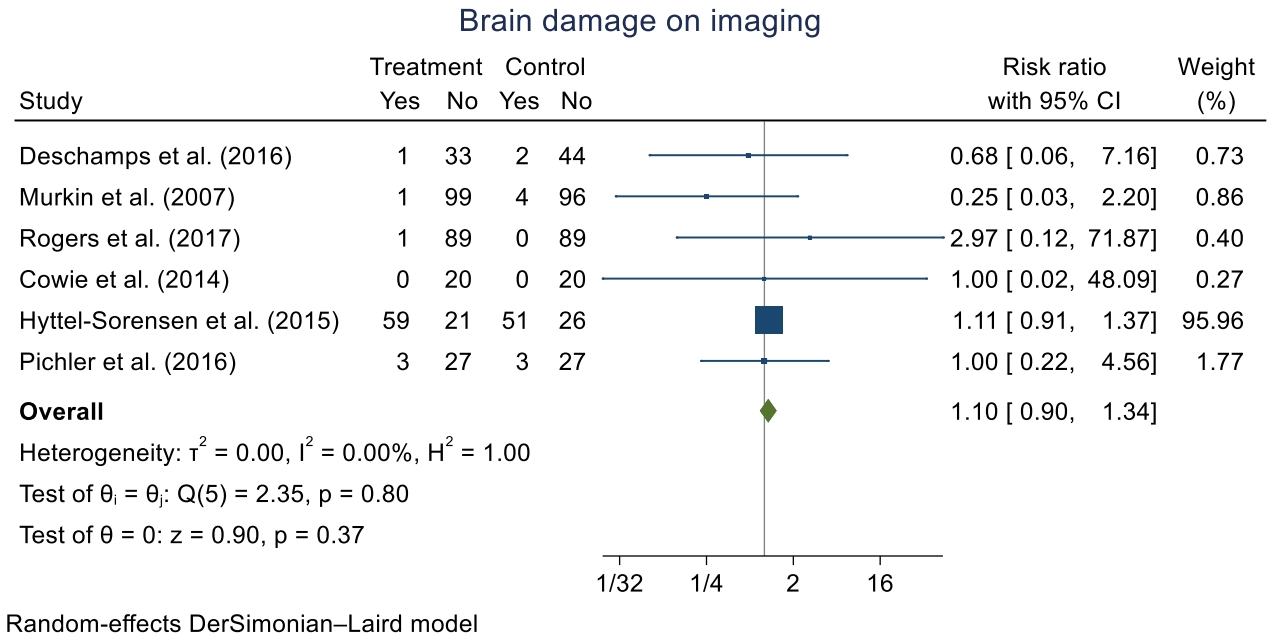
Primary analysis

Figure S34 – fixed effect



Fixed-effects Mantel–Haenszel model

Figure S35 – random effects

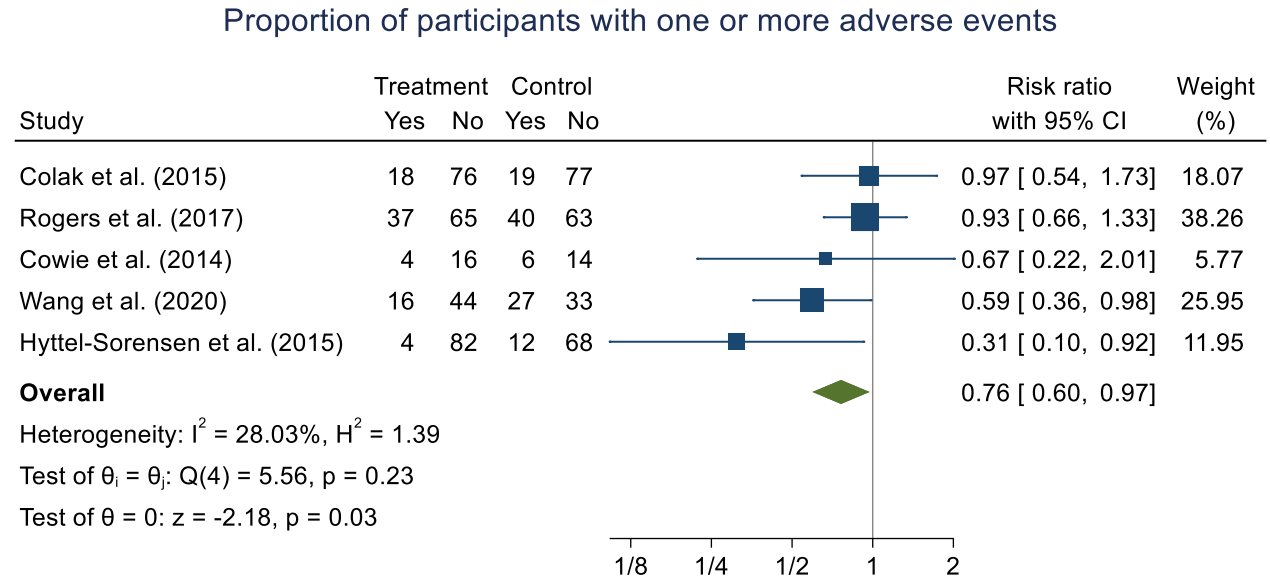


Random-effects DerSimonian–Laird model

Proportion of participants with one or more adverse events

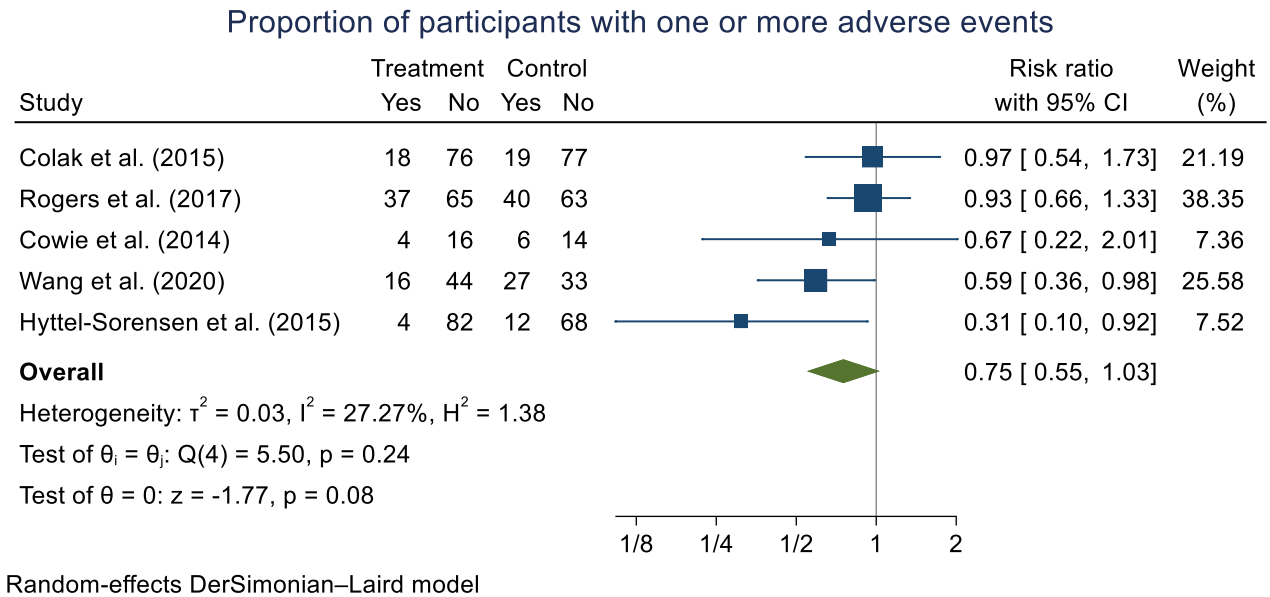
Primary analysis

Figure S36 – fixed effect



Fixed-effects Mantel–Haenszel model

Figure S37 – random effects



Random-effects DerSimonian–Laird model

Any evidence of a negative impact on the brain

Primary analysis

Figure S38 – fixed effect

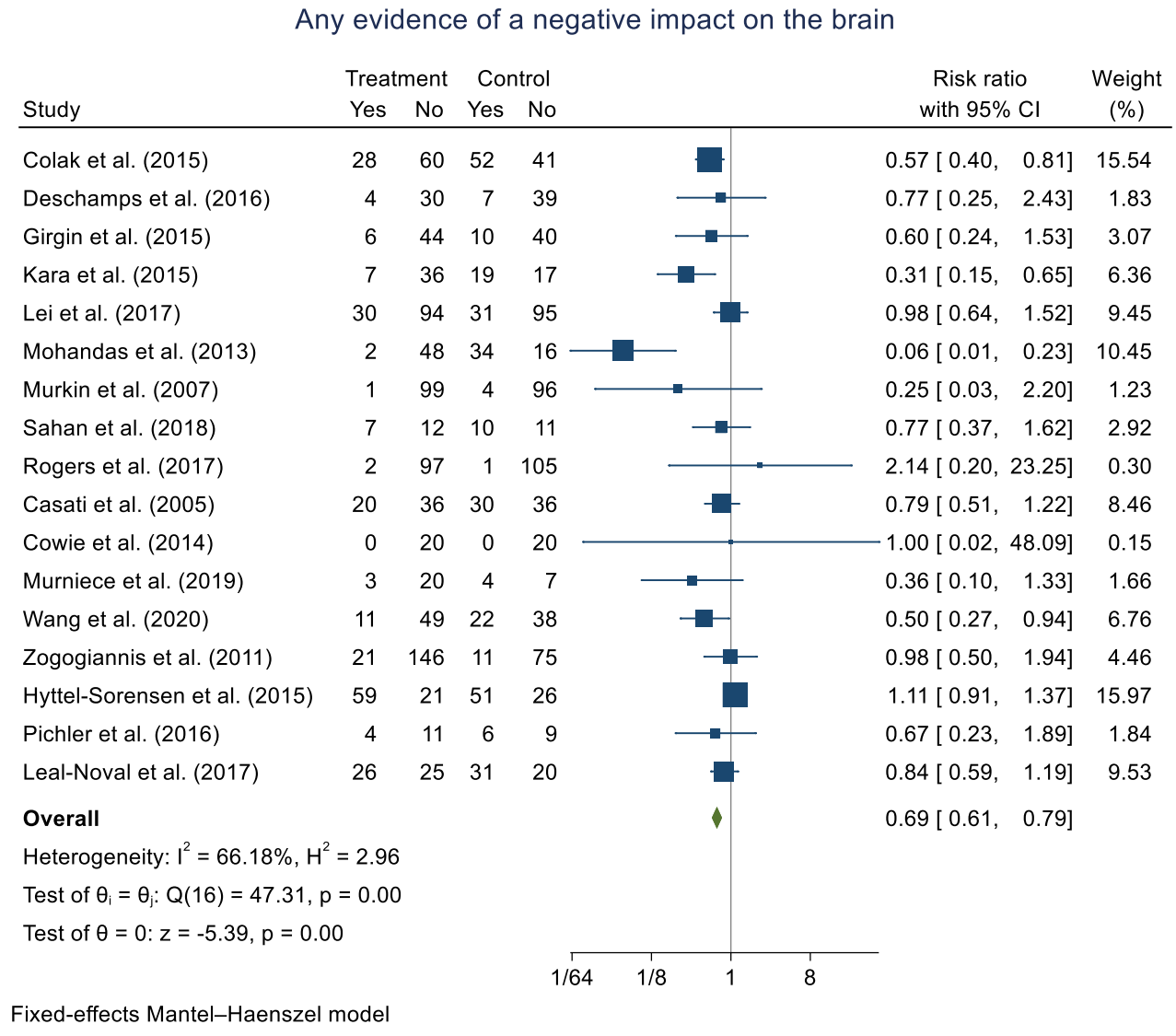
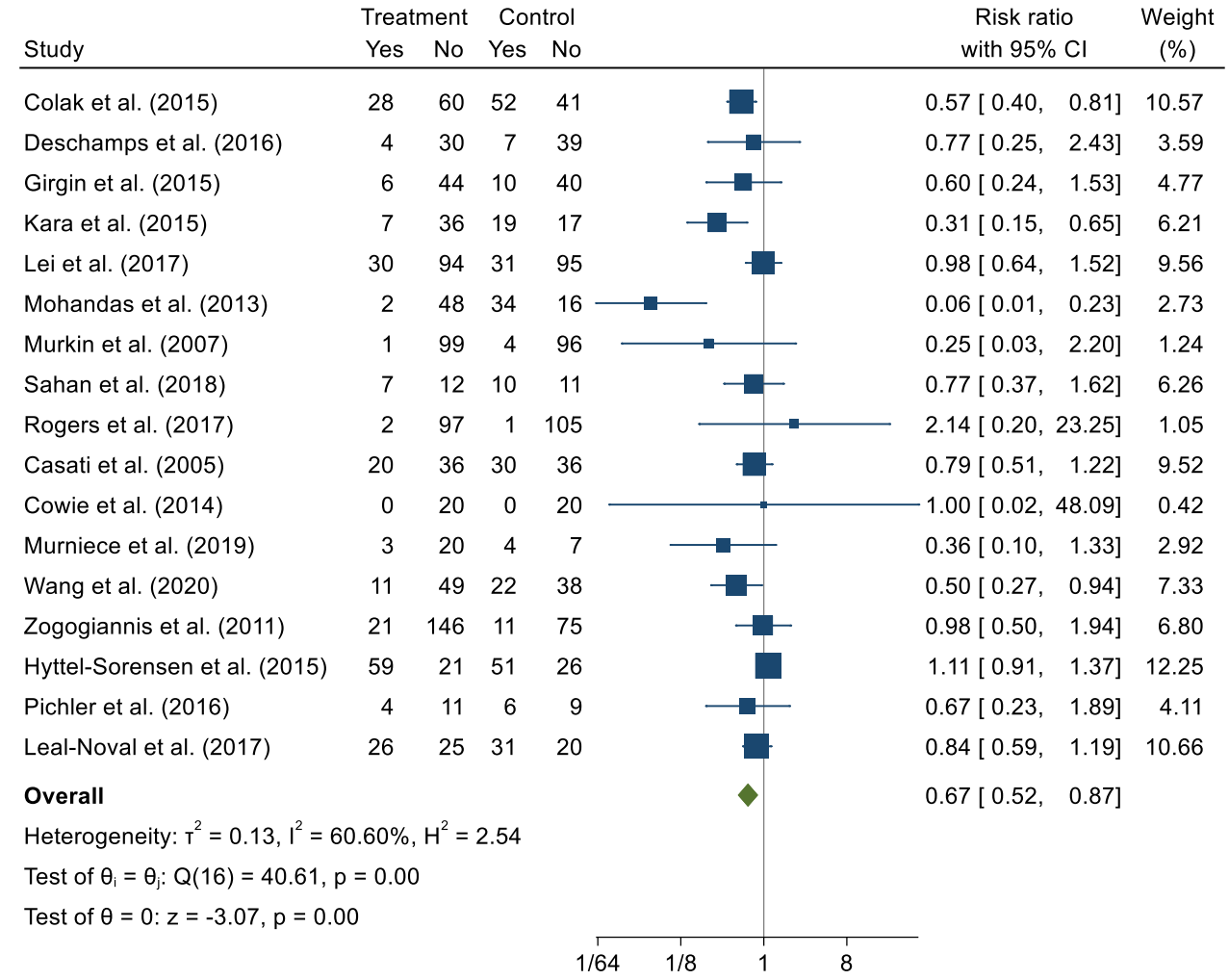


Figure S39 – random effects

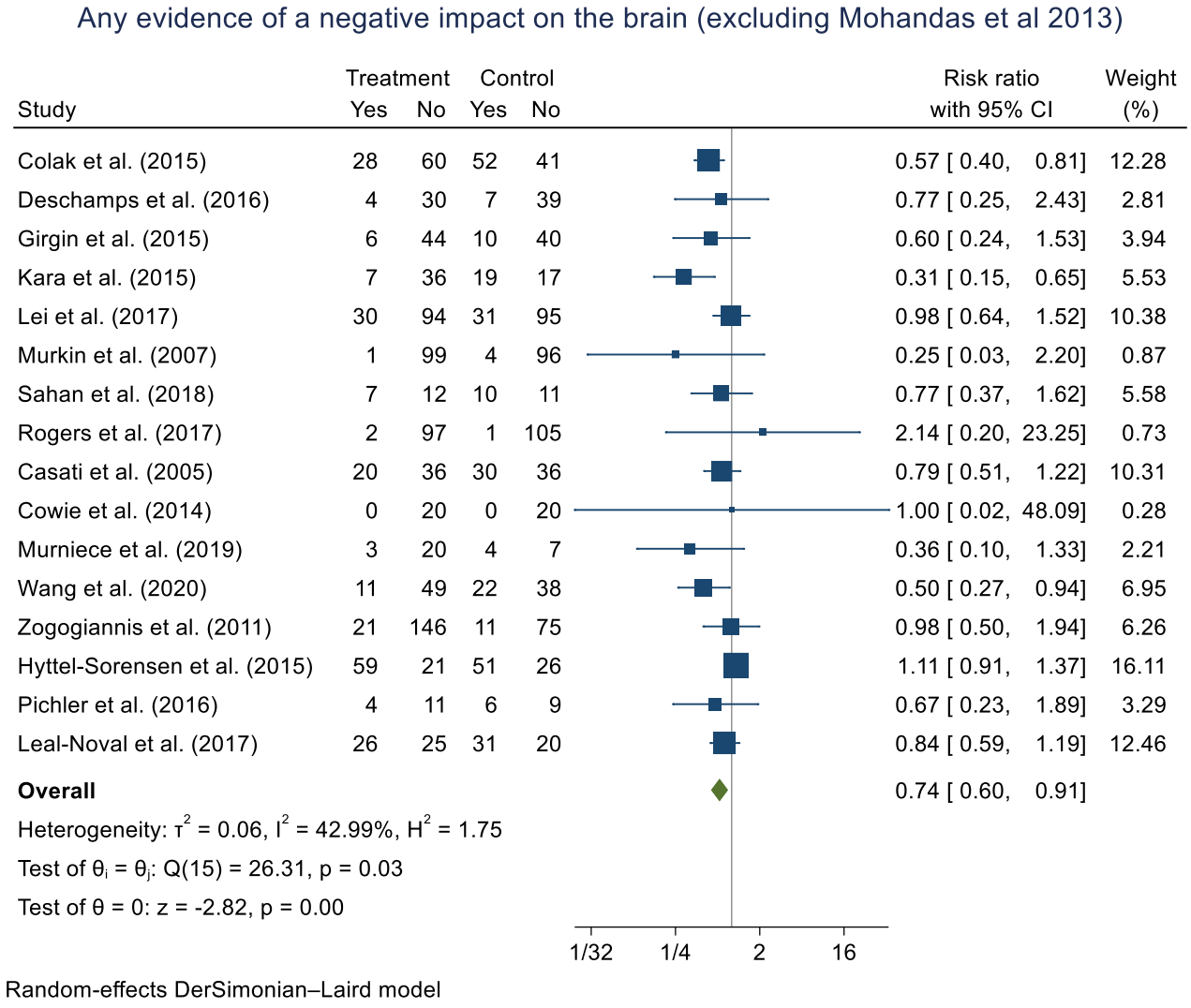


Random-effects DerSimonian–Laird model

Sensitivity analysis

Heterogeneity (excluding Mohandas et al. 2013)

Figure S40



Appendix E: Datafile for statistical analysis program

Please go to

LINK FIGSHARE: https://figshare.com/s/2b667e81c89b031f2156

For full access to the datafile used in Stata to conduct the statistical analyses for this systematic review with meta-analysis

Appendix F: Synthax for STATA/SE 17.0

Please go to

LINK FIGSHARE: https://figshare.com/s/dd48f8aec10b1718e83f

For full access to the Synthax used in Stata to conduct the statistical analyses for this systematic review with meta-analysis

Appendix G: Correspondence with the trialists

Please go to

LINK FIGSHARE: https://figshare.com/s/9bf7f10d3e82ca7924d4

For full access to the correspondence with the trialists in order to obtain unpublished data.