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ABSTRACT (200 words)

Objective: To evaluate therapeutic meta-analyses including both observational studies and randomized controlled trials (RCTs), how these studies were combined and whether there were differences in treatment effects.

Study design and setting: Meta-epidemiological study of meta-analyses including both observational studies and RCTs. We searched MEDLINE for the 5 leading journals of each medical category according to *Journal Citation Reports*) and Cochrane Database of Systematic Reviews, from 2014 to 2018 for eligible meta-analyses and extracted how observational studies and RCTs were combined and results for each study.

Results: Of the 102 included meta-analyses, observational studies and RCTs were combined together without a subgroup analysis in 39 (38%) and with subgroup analysis in 15 (15%); they were pooled separately for the same outcome in 11 (11%) and not for the same outcome in 9 (9%). In 28 (27%) meta-analyses, only RCTs were combined, with qualitative description of observational studies. Treatment effect estimates did not differ between observational studies and RCTs (ratio of estimates=0.98 [95% confidence interval 0.80-1.21]), with substantial heterogeneity (I^2=59%).

Conclusion: Many meta-analyses including both observational studies and RCTs pool results from both study types. Although treatment effects did not differ between them on average, we identified situations for which estimates differed.

Keywords: Meta-epidemiology, systematic review, meta-analysis, observational studies, randomized controlled trials, therapeutic intervention, comparative effectiveness research

Running title: Therapeutic meta-analyses including both randomized and observational studies

Word count: 3477

What is new?

Key findings

- Systematic reviews including both randomized controlled trials (RCTs) and observational studies frequently combine these different studies in the same meta-analysis without distinction.
- Treatment effect estimates did not differ, on average, between RCTs and observational studies within meta-analyses, but heterogeneity was substantial across meta-analyses and there were several meta-analyses for which the difference between both study types exceeded what was expected by chance alone.
- Including observational studies with RCTs in meta-analyses also frequently increased heterogeneity.

What this adds to what is known

- This study provides a global and comprehensive picture of how observational studies are combined in meta-analyses of therapeutic interventions and comparing treatment effects between these types of studies.

What is the implication, what should change now

- Given the increasing inclusion of observational studies in meta-analyses of therapeutic interventions, it is necessary to improve their methods and reporting
- In particular, observational studies and RCTs should not be combined in the same meta-analysis

BACKGROUND

Systematic reviews and meta-analyses are central to synthesize existing evidence on the efficacy and safety of healthcare interventions and inform decision making[1]. It is generally considered that systematic reviews and meta-analyses should be based on randomized controlled trials (RCTs) because these studies are more likely to provide unbiased information than other study designs[2,3]. However, RCTs may not answer all key questions regarding the balance of benefits and harms of therapeutic interventions. They frequently include a small number of highly selected patients[4–6] with a limited follow-up over time[7], which raises concerns about the generalizability of results in real-life settings[8,9] and the evaluation of safety[10]. Observational studies are frequently conducted once a treatment receives marketing approval to evaluate safety[11] or effectiveness in real life[12].

Both observational and randomized studies are considered in comparative effectiveness research[13,14], and observational studies are increasingly being included in systematic reviews of therapeutic evaluation to complement information from RCTs[15]. According to Page et al.,[16] 21% and 7% of therapeutic non-Cochrane reviews published in 2016 considered cohort and case–control studies, respectively, in addition to RCTs, a rate that has increased as compared with 2007[17].

Observational studies are more likely to be affected by biases as compared with RCTs due to lack of randomization[18]. Thus, considering both types of study together within the same meta-analysis is a challenge. Moreover, the impact on treatment effect estimates of including observational studies with RCTs in meta-analyses remains unclear.

In this study, we performed a meta-epidemiologic study of meta-analyses including both observational studies and RCTs to evaluate how these study types were combined and to compare their treatment effect estimates.

METHODS

Study design

This is a meta-epidemiologic study, reported according to the PRISMA statement[19,20].

Search strategy

We searched MEDLINE via PubMed for articles published between January 1, 2014 and January 1, 2018 by using a dedicated search algorithm combining MeSH terms and free-text words for 1) systematic reviews and meta-analyses, 2) RCTs with the Cochrane highly sensitive search strategy [21], and 3) observational studies. We restricted the search to the *Cochrane Database of Systematic Reviews* and to the 5 journals with the highest impact factor within each medical category according to *Journal Citation Reports*. The search algorithm is in **Appendix 1**.

Eligibility criteria

We included all systematic reviews with at least one meta-analysis evaluating the efficacy or safety of a therapeutic or preventive (such as vaccines) intervention and including both observational studies and RCTs. Any other topic dealing with non-therapeutic interventions, such as diagnosis or risk factor assessment, was excluded. The term “observational study” refers to cross-sectional studies, prospective or retrospective cohort studies, or case–control studies, relying on the classification provided by Ioannidis[22].

We excluded systematic reviews without a meta-analysis and studies for which a meta-analysis was not the main objective (e.g., meta-epidemiologic studies or overviews of systematic reviews). Individual patient data and network meta-analyses as well as meta-analyses of proportions were also excluded.

Selection process

To select systematic reviews meeting the eligibility criteria, one reviewer (RSB) first screened all references by examining the title and abstract and whenever necessary, the full text, then a second reviewer (AD) checked all included and excluded references and particularly reviewed all ambiguous cases.

Data collection process

We developed a data extraction form that was tested by 2 reviewers (RSB, AD) on 5 systematic reviews before starting data extraction. Then, one reviewer (RSB) extracted all data and a second reviewer (JS) independently extracted all data for half of the reviews at random. Any disagreements were resolved by discussion with a senior reviewer (AD) to reach consensus, and in case of major sources of disagreements (which occurred in only 5 cases), data for all reviews were checked by both reviewers.

The following characteristics were extracted:

General characteristics

- Publication characteristics: journal name and year of publication
- Medical condition
- Therapeutic interventions evaluated. We classified interventions as pharmacological (i.e., drug therapies, biologicals, cell or gene therapies, blood or plasma transfusion) or non-pharmacological (i.e., surgical interventions, medical devices, rehabilitation, psychotherapy, acupuncture, chiropractic therapy, lifestyle management)
- Reporting of registration in PROSPERO
- Involvement of epidemiologists or statisticians relying on the definition given by Delgado-Rodriguez and colleagues[23]
- Sources of funding and declared conflicts of interest

Observational studies considered

- Type of observational studies considered: we collected whether all types of observational studies were considered or only specific types (e.g., prospective cohort studies). We classified observational studies as cross-sectional studies, retrospective cohort studies, prospective cohort studies, or case–control studies, relying on the classification provided by Ioannidis[22].
- Justification for inclusion of observational studies: we collected whether the inclusion of observational studies was justified and if yes, how (e.g., "to study safety", "to study efficacy in real life", "to study both efficacy and safety", "lack of RCTs", "lack of long-term outcomes in RCTs").
- Outcomes for which observational studies were considered: we collected whether observational studies were considered for all outcomes or for some outcomes only and if yes, which outcomes (e.g., safety outcomes).

Systematic review methods

- Search strategy: we collected which electronic databases were searched and whether the authors searched for "grey" literature, and if yes, how (registries, conference abstracts, or contacting experts). We also evaluated whether specific searches were performed to identify observational studies.
- Methodological quality/risk of bias assessment: we assessed whether methodological quality or risk of bias was evaluated, differentiating tools used for RCTs and for observational studies.

Meta-analysis methods

- Combination of studies: We evaluated how observational studies and RCTs were combined. We distinguished the following cases:
    - Observational studies and RCTs combined separately (e.g., two separate meta-analyses: one for observational studies, one for RCTs) for the same outcome.
    - Both observational studies and RCTs combined in the same meta-analysis but with a subgroup analysis by type of study (RCTs vs observational studies)
    - Both observational studies and RCTs combined in the same meta-analysis without subgroup analysis
    - Only one type of study combined in a meta-analysis (e.g., RCTs) and the other (e.g., observational studies) with only a qualititative description
    - Observational studies combined for some outcomes and RCTs combined for other outcomes
- Measure of intervention effect used: odds ratio, risk ratio, hazard ratio. We also collected whether the authors reported the use of crude or adjusted estimates for observational studies and whether they mentioned the use of propensity scores.
- Meta-analysis model used: we collected whether the authors used fixed- or random-effects models to pool the data. We also collected whether and how the authors assessed heterogeneity.

Difference in effect estimates between observational studies and RCTs

We performed a meta-epidemiologic analysis to evaluate differences in estimates for the same outcome between observational studies and RCTs. For this, we focused on meta-analyses for which observational studies and RCTs were combined in the same meta-analysis (with or without subgroup analysis) or separately for the same outcome and including at least 3 studies

overall (3 studies is the minimum to conduct a meta-epidemiologic analysis). We did not consider meta-analyses for which there was only a qualitative description of observational studies and those for which observational studies and RCTs were not combined for the same outcome. Any meta-analyses involving an active treatment as a control were excluded because of uncertainty regarding the direction of the effect. We considered only meta-analyses of binary or censored outcomes. We did not consider meta-analyses of continuous outcomes because the null value is different. If several meta-analyses were eligible per review, we kept only the first one reported.

For each selected meta-analysis, one reviewer (JS) collected the number of events and the number of patients analyzed for each arm in each included study as reported in the forest plot. When the authors used adjusted estimates for observational studies, we instead collected for each study the adjusted point estimate with the 95% confidence interval (CI). We also collected point estimates and 95% CIs when raw data were not reported or in case of censored outcomes. A second reviewer (RSB) independently extracted all these data for half of the meta-analyses. Any doubts or disagreements were resolved by discussion with a third reviewer (AD) whenever necessary to reach a consensus.

We estimated the difference in effect estimates (expressed as a ratio of estimates [RE]) between observational studies and RCTs by using the two-step method described by Sterne and colleagues[24]. The effect estimates could be ORs, RRs or HRs depending on the measure reported in the included meta-analyses when raw data were not used. When raw data were used, we recalculated an OR for each study. In a first step, for each individual meta-analysis, we estimated the ratio of estimates (RE) for observational studies to estimates for RCTs, which represents the difference in estimates between both study types by using a random-effects meta-regression model to incorporate between-study heterogeneity. In a second step, we combined REs across meta-analyses by using a random-effects meta-analysis

model. We did not combine RRs, ORs and HRs but rather the difference in treatment effects (ie, the RE) across meta-analyses. An RE <1 indicates larger estimates of the intervention effect for observational studies than RCTs because all outcomes were re-coded so that an estimate <1 indicated a benefical effect of the experimental intervention. Heterogeneity across REs was assessed by the I^2 and the between–meta-analysis variance τ^2.

We performed a subgroup analysis based on how studies were combined in the original meta-analyses:

- One meta-analysis for observational studies and one for RCTs
- A single meta-analysis with subgroup analysis (RCTs vs observational studies)
- A single meta-analysis combining observational studies and RCTs without subgroup analysis

We tested the interaction between the intervention and how studies were combined by using a meta-regression model.

Finally, we explored the impact of including observational studies on meta-analysis results for meta-analyses combining RCTs and observational studies (with or without subgroups). To do so, we compared the results and conclusions on statistical significance between the meta-analysis of RCTs only and that including both RCTs and observational studies. Random-effects models were used for all meta-analyses to account for potential between-trial heterogeneity.

Statistical analysis involved using R 3.3.2 (R Core Team [2013]. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL: http://www.R-project.org/). Categorical data are described with frequencies (%).

RESULTS

Study selection and general characteristics

Our search identified 672 citations; 102 were included in this review (**Figure 1** and **Appendix 2**. Among these, the most common medical conditions were cardiovascular (n=11, 11%), obstetrics (n=11, 11%), surgery (n=11, 11%), infectious diseases (n=8, 8%) and general and internal medicine (n=8, 8%). Interventions were pharmacological in 55 (54%) meta-analyses, nonpharmacological in 42 (41%) or their combination in 5 (5%). Registration in PROSPERO was reported for only 22 (22%) meta-analyses (**Table 1**).

Type of observational studies considered

The most frequent type of observational studies considered was prospective cohort studies in 77 (75%) meta-analyses, followed by retrospective cohort studies (n=56, 55%), case–control studies (n=19, 19%) and cross-sectional studies (4, 4%). Twelve (12%) meta-analyses reported only observational studies without details. A justification for including observational studies was reported for 25 (25%) meta-analyses: lack of long-term outcomes in RCTs for 11 (11%), evaluation of safety for 9 (9%), insufficient number of RCTs for 8 (8%) and evaluation of efficacy in real life for 2 (2%).

Systematic review methods

Literature search

Most meta-analyses (n=101, 99%) reported a search in more than 1 electronic dabatase. MEDLINE, the Cochrane Library and EMBASE were the most frequently searched databases for 100 (98%), 82 (80%), and 81 (79%) meta-analyses, respectively. About half of the meta-analyses (n=53, 52%) did not report a grey literature search and the other half reported searches in registries (39 [38%]) or conference abstracts (16 [16%]). Ten meta-analyses

(10%) reported a specific search strategy to identify observational studies (**Table 2**).

Risk of bias and quality assessment

Risk of bias was assessed for RCTs and observational studies in 91 (89%) and 87 (85%) meta-analyses, respectively. The most commonly used tools for assessing risk of bias was the Cochrane Risk of Bias tool for RCTs[18] (n=48, 47%) and the Newcastle-Ottawa Scale[25] for observational studies (n=36, 35%) (**Table 2**).

Meta-analysis methods

In 39 (38%) meta-analyses, both observational studies and RCTs were combined in a single meta-analysis without subgroups; in 15 (15%), they were combined together but with a subgroup analysis (observational studies vs RCTs); in 11 (11%), observational studies and RCTs were analyzed separately for the same outcome (1 meta-analysis for observational studies and 1 for RCTs) and in 9 (9%), the meta-analyses were performed for different outcomes and thus reported separately. Finally, in 28 (27%) meta-analyses, only RCTs were combined in a meta-analysis, with only a qualitative description of observational studies. The use of adjusted estimates for observational studies was reported in only 21 (21%) meta-analyses and propensity scores in 5 (5%).

The analysis involved a random-effects model only for 60 (59%) meta-analyses, both a fixed-effect and random-effects model for 13 (13%) and a fixed-effect model only for 12 (12%). Almost all meta-analyses assessed heterogeneity (n=99, 97%). The I^2 statistics was reported in 97 (95%), Cochran Q test in 70 (69%) and τ^2 in 31 (30%) (**Table 3**).

Difference in effect estimates between observational studies and RCTs

In 31 (30%) meta-analyses combining at least 3 observational studies and RCTs, either in the same meta-analysis (with or without subgroup analysis) or separately for the same binary or

censored outcome, we found no statistically significant difference in effect estimates, on average, between observational studies and RCTs (RE=0.98, 95% CI 0.80-1.21), but heterogeneity across meta-analyses was substantial (I^2=59%, between–meta-analysis variance τ^2=0.14). Heterogeneity was particularly important in the subgroup of meta-analyses combining together RCTs and observational studies without subgroup (I^2 =68%, τ^2=0.30). Overall, the difference in effect estimates exceeded what was expected by chance in 4 (13%) meta-analyses, with observational studies showing a significantly larger estimate in 2 and RCTs showing a significantly larger estimate in 2. The difference in effect estimates between observational studies and RCTs did not significantly differ by how studies were combined (p-value for interaction=0.63) (**Figure 2**). We did not include one meta-analysis[26] in this meta-epidemiologic analysis because the authors reported 3 separate analyses for observational studies: one with unadjusted estimates, one with adjusted estimates and one with propensity-matched estimates (RCTs were also combined separately). The combined relative risk was 1.76 (95% CI 1.57-1.97) for unadjusted observational studies, 1.61 (95% CI 1.31-1.97) for adjusted observational studies, 1.18 (95% CI 1.09-1.26) for propensity-matched observational studies and 0.99 (95% CI 0.93-1.05) for RCTs.

Effect of including observational studies on meta-analysis conclusion

The results comparing the meta-analyses restricted to RCTs only and that including both observational studies and RCTs are reported in **Figure 3**. For the 9 meta-analyses in which observational studies and RCTs were combined with a subgroup analysis, estimates were close and conclusions consistent. In contrast, for the 17 meta-analyses combining observational studies and RCTs without a subgroup analysis, statistical significance was modified by the inclusion of observational studies in 12, including 1 with conflicting results.

Overall, heterogeneity was frequently increased when observational studies were considered in the meta-analysis.

DISCUSSION

In this meta-epidemiologic study, we provide a complete overview of meta-analyses of therapeutic interventions including both observational studies and RCTs and compared effect estimates between both study types. In most cases, including observational studies in addition to RCTs was not justified by the authors in the study report. Many combined the study types together, which raises concerns because of their methodological differences. Our meta-epidemiologic analysis based on 31 meta-analyses of binary or censored outcomes found no difference in effect estimates, on average. However, we found substantial heterogeneity across meta-analyses, and the difference in estimates between observational studies and RCTs exceeded what was expected by chance in 4 meta-analyses. When comparing results of meta-analyses including both observational studies and RCTs and meta-analyses restricted to RCTs only, the conclusion was modified by the inclusion of observational studies in 12/17. We also found that including observational studies frequently increased heterogeneity in meta-analysis.

The percentage of PROSPERO registration was 22%, a rate higher than that observed by Page and colleagues in 2014, which might be explained by a possible slight improvement over time and/or by our restriction to high-impact-factor journals, that may be more likely to require PROSPERO registration.

Although Cochrane recommends focusing on adjusted estimates for observational studies to account for confounding factors, the use of adjusted estimates was reported for few meta-analyses and the use of estimates accounting for a propensity score to limit the risk of confounding by indication even less. Most authors did not report anything about use of adjusted or crude estimates in meta-analyses for observational studies. Because, poor reporting does not necessarily mean poor methods, we checked whether the effect calculated

by the authors for each observational study corresponded to the number of events/patients analyzed presented in the forest plot. This was the case for all studies, which suggests that when the authors did not report having used adjusted estimates and when they reported number of events/patients analyzed, they did not use adjusted estimates. Accounting for adjusted estimates complicates the analysis because it implies directly combining estimates rather than the number of events/patients analyzed. In addition, it raises a problem if the authors of individual studies did not use the same measure of association (eg, OR or RR) because it may not be appropriate to combine them directly within the same meta-analysis. We cannot exclude that some authors combined different measures of association. We cannot exclude either that some authors used inappropriate measures of association for some study types when raw data were available. This could be the case for example if they calculated a risk ratio in case-control studies.

We found consistent results with previous studies comparing effect estimates between RCTs and observational studies. Most of them found no difference between the study types, as shown in a Cochrane review published in 2014[12]. A large part of this literature concerned a particular topic, such as femoral neck fractures[27] or breast cancer surgery[28], or a particular intervention, such as anticoagulants[29]. Two previous reviews compared adverse events estimates between RCTs and observational studies[10,30]. Two other studies compared cohort studies with propensity score analysis and RCTs.[31,32]

Our study goes beyond this previous literature because we were interested in comparing effect estimates between both study types and also evaluating the situations for which the results of these studies were considered together and how they were combined.

There are several reasons for why we did not find an overall difference in effect estimates between observational studies and RCTs. First, the review authors may have combined both

study types because results did not greatly differ. Second, we found substantial heterogeneity across meta-analyses. We identified 4 meta-analyses (13% of the sample used) for which differences in effect estimates exceeded what was expected by chance alone, 2 of which showed larger effect estimates in RCTs than observational studies. Therefore, the lack of difference in effect estimates we observed on average does not imply that RCTs and observational studies can be combined; rather, it suggests that there are situations in which effect estimates greatly differ, and these particular situations could be explored further. The difference in populations may explain some of the differences in effect estimates we found. Another potential explanation may be the risk of confounding bias in observational studies. All these factors may operate in different directions, thereby contributing to the increased heterogeneity we observed when including observational studies.

Therefore, we recommend analyzing RCTs and observational studies in separate meta-analyses. We also recommend better justification for including observational studies in meta-analyses and the use of adjusted estimates for observational studies with the reporting of confounding factors accounted for. Some of these recommendations are not new, because the Cochrane handbook includes a specific section dedicated to the inclusion of non-randomized studies, recommending not to combine RCTs and observational studies in the same meta-analysis. We hope our study may help highlight these important points and improve both the methodology and reporting in these meta-analyses.

Our study has some limitations. Our sample may not be representative of all meta-analyses including both observational studies and RCTs because we focused on those published in the journals with the highest impact factor for each medical specialty or in the *Cochrane Database of Systematic Reviews*. Our meta-epidemiologic analysis was based on meta-analyses of binary or censored outcomes, so our results cannot be extrapolated to continuous

outcomes. Finally, our meta-epidemiologic analysis may lack power.

Conclusions

Many meta-analyses combined observational studies with RCTs in a single meta-analysis, which is not appropriate because of the methodological differences between the study types. Despite no difference in effect estimates, on average, between RCTs and observational studies, heterogeneity was substantial across topics, and we identified a few situations for which differences between both study types exceeded what was expected by chance alone. Given the increasing interest for observational studies in comparative effectiveness research, improving how these reviews are conducted and reported is crucial.

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Authors' contributions:

Rene Bun participated in the design of the study, selection and acquisition of data, conducted statistical analyses, interpreted the data and wrote the manuscript.

Jordan Scheer participated in the design of the study, selection and acquisition of data, conducted statistical analyses, interpreted the data and wrote the manuscript.

Rene Bun and Jordan Scheer contributed equally.

Sylvie Guillo participated in the elaboration of the search algorithm and critically reviewed the manuscript.

Florence Tubach interpreted the data and critically reviewed the manuscript.

Agnes Dechartres participated in the design of the study, selection and acquisition of data, conducted statistical analyses, interpreted the data and wrote the manuscript.

Agnes Dechartres is the guarantor. She had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Figure titles and legends

Figure 1: Flow diagram of the selection of meta-analyses. MA, meta-analysis; RCT, randomized controlled trial.

Figure 2: Differences in treatment effect estimates between randomized controlled trials (RCTs) and observational studies by meta-epidemiologic analysis

Difference in treatment effect estimates is expressed as ratio of estimates (RE). An RE < 1 indicates that observational studies yielded larger estimates of the intervention effect or adverse events than did RCTs. Subgroups represent the 3 different types of study combinations: 1) two separate meta-analyses (1 meta-analysis for observational studies and 1 for RCTs); 2) one meta-analysis performed with subgroups (observational studies vs RCTs); 3) one meta-analysis pooling results of observational studies and RCTs . Heterogeneity across studies was assessed with the I^2, τ^2, and Cochran Q statistic.

The ratio of estimates was a ratio of ORs in all studies except Lee (2017) and Filippini (2017), for which it was a ratio of HRs, and Cheungpasitporn (2015), Lok (2016), Muranushi (2016), Nair (2016), Kunutsor (2017) and Boundy (2016), for which it was a ratio of RRs.

OBS: observational studies; RCT: randomized controlled trial; RE: ratio of estimates; RE model: random-effects model; OR= odds ratio; RR=risk ratio.

Figure 3: Effect of including observational studies on meta-analysis conclusion

Green dots indicate effect estimates from a meta-analysis restricted to RCTs only. Black squares indicate effect estimates from a meta-analysis considering all studies (RCTs and observational studies). Heterogeneity across studies was assessed with the I^2. HBV: Hepatitis

B virus; NSAIDs: non-steroidal anti-inflammatory drugs; PTSD: post-traumatic stress disorder; RAS: renin-angiotensin system; RCT: randomized controlled trial.

Tables

Table 1: General characteristics of 102 therapeutic meta-analyses published between 2014-2018 and including both observational studies and randomized controlled trials (RCTs)

General characteristics	***n (%)*** ***N=102***
Medical condition	
Cardiac and cardiovascular systems	11 (11)
Obstetrics and gynecology	11 (11)
Surgery	11 (11)
Infectious diseases	8 (8)
Medicine, general and internal	8 (8)
Psychiatry	6 (6)
Gastroenterology and hepatology	5 (5)
Clinical neurology	4 (4)
Ophtalmology	4 (4)
Peripheral vascular disease	4 (4)
Rehabilitation	4 (4)
Urology and nephrology	4 (4)
Anesthesiology	3 (3)
Endocrinology and metabolism	3 (3)
Geriatrics	3 (3)
Pediatry	3 (3)
Others	10 (10)
Type of intervention	
Pharmacological	55 (54)
Non-pharmacological	42 (41)
Both pharmacological and non-pharmacological	5 (5)
*PROSPERO registration reported**	
Yes	22 (22)
No	80 (80)
Epidemiologist and/or biostatisticians involved	
Yes	29 (28)
No	73 (72)
Conflicts of interest reported	102 (100)
Yes	39 (38)
No	63 (62)

* PROSPERO was the only register reported by authors

Table 2: Systematic review methods of 102 therapeutic meta-analyses published in 2014-2018 and including both RCTs and observational studies

Review methods characteristics	***n (%)*** ***N=102***
Electronic search	101 (99)
If yes, which database :	
MEDLINE via PubMed	100 (98)
Cochrane Library (CENTRAL)	82 (80)
EMBASE	81 (79)
CINAHL	28 (27)
Scopus	22 (22)
Web of Science	15 (15)
PsychINFO	10 (10)
LILACS	5 (5)
Not reported	1 (1)
"Grey" literature search	49 (48)
If yes, which source :	
Registries (e.g., ClinicalTrials.gov)	39 (38)
Conference abstracts	16 (16)
Not reported	53 (52)
Specific search strategy to identify observational studies	10 (10)
Not reported	92 (90)
Assessment of methodological quality/risk of bias for RCTs	91 (89)
If reported, which tool:	
Cochrane Risk of Bias tool	48 (47)
Own tool	11 (11)
Down and Black checklist	9 (9)
GRADE	8 (8)
Jadad score	5 (5)
Others	9 (9)
Assessment of methodological quality/risk of bias without details	1 (1)
Not reported	11 (11)
Assessment of methodological quality /risk of bias for observational studies	87 (85)
If reported, which tool:	
Newcastle Ottawa Scale	36 (35)
Cochrane Risk of Bias tool	13 (13)
Down and Black checklist	10 (10)
Own tool	9 (9)
GRADE	7 (7)
MINORS	3 (3)
Others	6 (6)
Assessment of methodological quality/risk of bias without details	3 (3)
Not reported	15 (15)

Table 3: Meta-analysis methods of 102 therapeutic meta-analyses published in 2014-2018 and including both RCTs and observational studies

Characteristics of meta-analysis methods	***n (%) N=102***
Combination of studies	
A single meta-analysis with both RCTs and observational studies	39 (38)
Only qualitative description of observational studies	28 (27)
A single meta-analysis with subgroup analysis (RCT vs observational studies)	15 (15)
Two distinct meta-analyses for the same outcome (1 for RCTs and 1 for observational studies)	11 (11)
Distinct meta-analyses for different outcomes for RCTs and observational studies	9 (9)
Measure of effect used	
Risk ratio	35 (34)
Standardized mean difference	29 (28)
Odds ratio	28 (27)
Hazard ratio	5 (5)
Others	5 (5)
Adjusted estimates reported for observational studies	
Yes	21 (21)
No (raw data used)	6 (6)
Not reported	75 (73)
Propensity score reported	5 (5)
Analysis strategy used	
Random-effects model	60 (59)
Both fixed- and random-effects models	13 (13)
Fixed-effect model	12 (12)
Fixed-effect model, unless high heterogeneity, then random-effects model	12 (12)
Some outcomes with fixed-effects model, some with random-effects model	3 (3)
Not reported/unclear	2 (2)
Heterogeneity assessment	
I^2	97 (95)
Cochran Q X^2 test	70 (69)
τ^2 (between–meta-analysis variance)	31 (30)
Not reported/unclear	3 (3)

Appendix 1: Search strategy (PubMed equation)

#1 randomized controlled trial [pt]
#2 controlled clinical trial [pt]
#3 randomized [tiab]
#4 placebo [tiab]
#5 clinical trials as topic [mesh: noexp]
#6 randomly [tiab]
#7 trial [ti]
#8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#9 animals [mh] NOT humans [mh]
#10 #8 NOT #9

#11 “observational” [tiab]
#12 observational studies as topic [mh]
#13 observational study [pt]
#14 “prospective” [tiab]
#15 prospective study [mh]
#16 “retrospective” [tiab]
#17 retrospective study [mh]
#18 “cohort” [tiab]
#19 cohort studies [mh]
#20 “cross-sectional” [tiab]
#21 cross sectional study [mh]
#22 “case control” [tiab]
#23 case control study [mh]
#24 “case series” [tiab]

#25 “epidemiologic” [tiab]
#26 “epidemiological” [tiab]
#27 epidemiologic studies [mh]

#28 #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27

#29 “systematic review” [tiab]
#30 “systematic reviews” [tiab]
#31 “meta-analysis” [tiab]
#32 “meta-analyses” [tiab]
#33 meta analysis [pt]
#34 “overview” [tiab]
#35 #29 OR #30 OR #31 OR #32 OR #33 OR #34

#36 #10 AND # 28 AND #35

#37 #36 * AND “2014/1/1”[pdat] : “2018/1/1”[pdat] AND List of Journals*

* List of Journals

("The Cochrane database of systematic reviews"[Journal] OR "British journal of anaesthesia"[Journal] OR "Anesthesiology"[Journal] OR "Pain"[Journal] OR "Anaesthesia"[Journal] OR "Journal of neurosurgical anesthesiology"[Journal] OR "European heart journal"[Journal] OR "Journal of the American College of Cardiology"[Journal] OR "Circulation"[Journal] OR "Nature reviews. Cardiology"[Journal] OR "Circulation research"[Journal] OR "The Lancet. Neurology"[Journal] OR "Nature reviews. Neurology"[Journal] OR "Acta neuropathologica"[Journal] OR "Brain : a journal of neurology"[Journal] OR "JAMA neurology"[Journal] OR "Journal of the American Academy of Dermatology"[Journal] OR "The Journal of investigative dermatology"[Journal] OR "JAMA dermatology"[Journal] OR "Pigment cell & melanoma research"[Journal] OR "The British journal of dermatology"[Journal] OR "The lancet. Diabetes & endocrinology"[Journal] OR "Nature reviews. Endocrinology"[Journal] OR "Cell metabolism"[Journal] OR "Endocrine reviews"[Journal] OR "Diabetes care"[Journal] OR "Gastroenterology"[Journal] OR "Gut"[Journal] OR "Nature reviews. Gastroenterology & hepatology"[Journal] OR "Hepatology (Baltimore, Md.)"[Journal] OR "Journal of hepatology"[Journal] OR "Ageing research reviews"[Journal] OR "Aging cell"[Journal] OR ("The journals of

gerontology. Series A, Biological sciences and medical sciences"[Journal]) OR "Journal of the American Medical Directors Association"[Journal] OR "Neurobiology of aging"[Journal] OR ("The journals of gerontology. Series A, Biological sciences and medical sciences"[Journal]) OR "Journal of the American Geriatrics Society"[Journal] OR "The Gerontologist"[Journal] OR ("The journals of gerontology. Series B, Psychological sciences and social sciences"[Journal]) OR "International journal of geriatric psychiatry"[Journal] OR "Circulation research"[Journal] OR "Blood"[Journal] OR "Leukemia"[Journal] OR "Haematologica"[Journal] OR "The Lancet. Haematology"[Journal] OR "The Lancet. Infectious diseases"[Journal] OR "The lancet. HIV"[Journal] OR "Emerging infectious diseases"[Journal] OR "Clinical infectious diseases : an official publication of the Infectious Diseases Society of America"[Journal] OR "Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin"[Journal] OR Journal of ginseng research[Journal] OR ("Phytomedicine : international journal of phytotherapy and phytopharmacology"[Journal]) OR "The American journal of Chinese medicine"[Journal] OR "Journal of ethnopharmacology"[Journal] OR "Planta medica"[Journal] OR "The New England journal of medicine"[Journal] OR "Lancet (London, England)"[Journal] OR "JAMA"[Journal] OR "BMJ (Clinical research ed.)"[Journal] OR "Annals of internal medicine"[Journal] OR "Nature medicine"[Journal] OR "Science translational medicine"[Journal] OR "Annual review of medicine"[Journal] OR "The Journal of clinical investigation"[Journal] OR "The Journal of clinical investigation"[Journal] OR Human reproduction update[Journal] OR ("American journal of obstetrics and gynecology"[Journal]) OR ("Obstetrics and gynecology"[Journal]) OR ("BJOG : an international journal of obstetrics and gynaecology"[Journal]) OR "Human reproduction (Oxford, England)"[Journal] OR "CA: a cancer journal for clinicians"[Journal] OR "Nature reviews. Cancer"[Journal] OR "The Lancet. Oncology"[Journal] OR "The Lancet. Oncology"[Journal] OR "Journal of clinical oncology : official journal of the American Society of Clinical Oncology"[Journal] OR ("Progress in retinal and eye research"[Journal]) OR "Ophthalmology"[Journal] OR "JAMA ophthalmology"[Journal] OR "American journal of ophthalmology"[Journal] OR "The ocular surface"[Journal] OR ("The American journal of sports medicine"[Journal]) OR ("The Journal of bone and joint surgery. American volume"[Journal]) OR ("Osteoarthritis and cartilage"[Journal]) OR ("Arthroscopy : the journal of arthroscopic & related surgery : official publication of the Arthroscopy Association of North America and the International Arthroscopy Association"[Journal])

OR "Journal of physiotherapy"[Journal] OR "Head & neck"[Journal] OR "Trends in hearing"[Journal] OR "JAMA ophthalmology"[Journal] OR "Hearing research"[Journal] OR ("Ear and hearing"[Journal]) OR "Circulation"[Journal] OR "Circulation research"[Journal] OR "Hypertension (Dallas, Tex. : 1979)"[Journal] OR ("Arteriosclerosis, thrombosis, and vascular biology"[Journal]) OR "Stroke"[Journal] OR ("JAMA pediatrics"[Journal]) OR ("Journal of the American Academy of Child and Adolescent Psychiatry"[Journal]) OR "Pediatrics"[Journal] OR "Pediatric diabetes"[Journal] OR "Archives of disease in childhood. Fetal and neonatal edition"[Journal] OR "World psychiatry : official journal of the World Psychiatric Association (WPA)"[Journal] OR "JAMA psychiatry"[Journal] OR "The American journal of psychiatry"[Journal] OR "Molecular psychiatry"[Journal] OR "The lancet. Psychiatry"[Journal] OR ("Neurorehabilitation and neural repair"[Journal]) OR "Journal of physiotherapy"[Journal] OR ("Journal of neuroengineering and rehabilitation"[Journal]) OR ("IEEE transactions on neural systems and rehabilitation engineering : a publication of the IEEE Engineering in Medicine and Biology Society"[Journal]) OR ("Archives of physical medicine and rehabilitation"[Journal]) OR "The Lancet. Respiratory medicine"[Journal] OR ("American journal of respiratory and critical care medicine"[Journal]) OR "The European respiratory journal"[Journal] OR "The European respiratory journal"[Journal] OR ("The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation"[Journal]) OR "Annals of the rheumatic diseases"[Journal] OR "Nature reviews. Rheumatology"[Journal] OR "Arthritis & rheumatology (Hoboken, N.J.)"[Journal] OR "Rheumatology (Oxford, England)"[Journal] OR ("Osteoarthritis and cartilage"[Journal]) OR "Annals of surgery"[Journal] OR "JAMA surgery"[Journal] OR ("Journal of neurology, neurosurgery, and psychiatry"[Journal]) OR ("The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation"[Journal]) OR ("American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons"[Journal]) OR ("The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation"[Journal]) OR ("American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons"[Journal]) OR ("Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation"[Journal]) OR ("Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association"[Journal]) OR

"Xenotransplantation"[Journal] OR "European urology"[Journal] OR "Nature reviews. Nephrology"[Journal] OR "Journal of the American Society of Nephrology : JASN"[Journal] OR "Kidney international"[Journal] OR "Nature reviews. Urology"[Journal])

Appendix 2: List of included meta-analyses (n=102)

1. Athappan G, Chacko P, Patvardhan E, Gajulapalli RD, Tuzcu EM, Kapadia SR. Late stroke: comparison of percutaneous coronary intervention versus coronary artery bypass grafting in patients with multivessel disease and unprotected left main disease: a meta-analysis and review of literature. Stroke. 2014;45:185–93.

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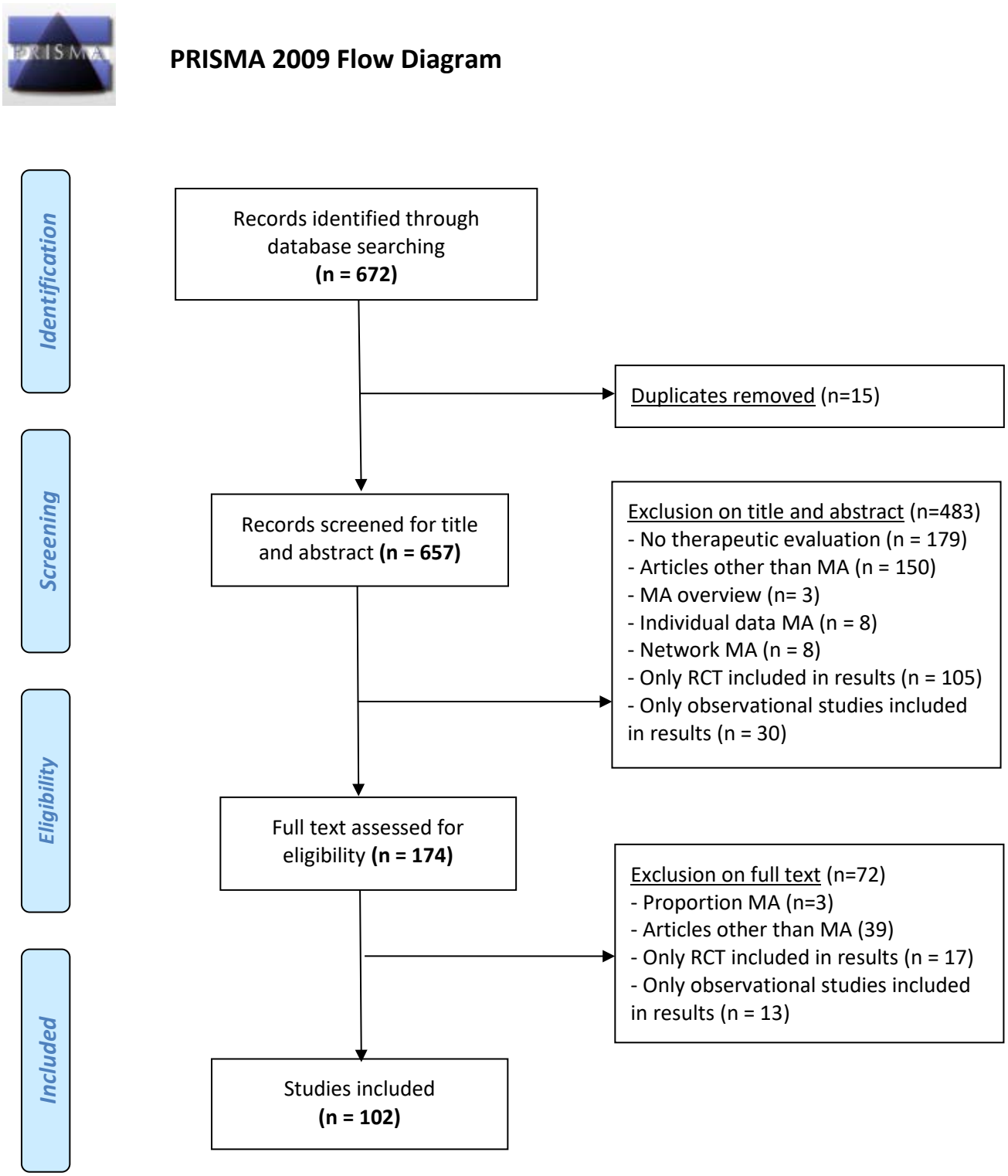
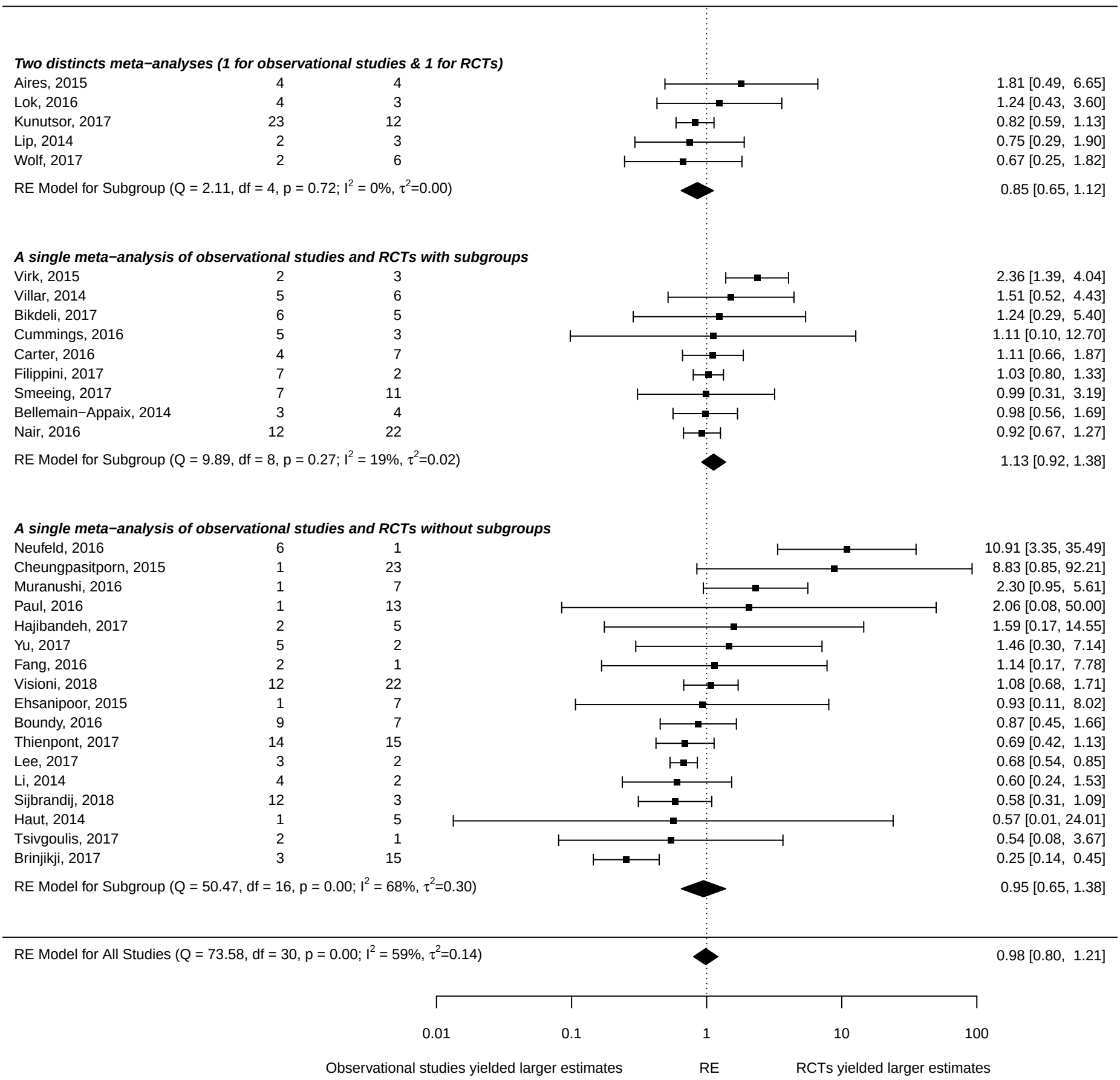
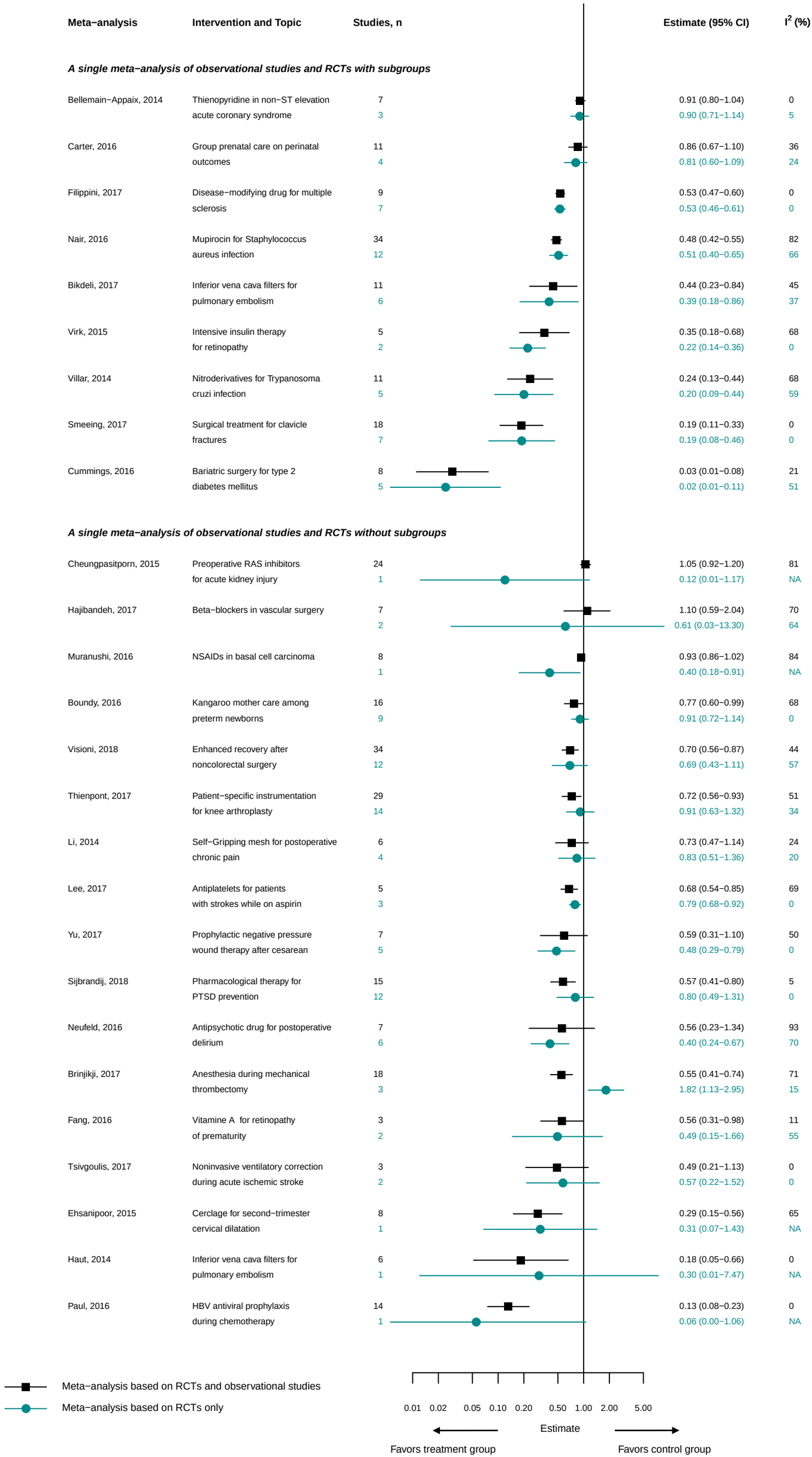
Figure 1: Flow diagram of the selection process




Author and Year
RCTs, n
Observational, n
RE [95% CI]
Two distincts meta−analyses (1 for observational studies & 1 for RCTs)
Aires, 2015 4 4 1.81 [0.49, 6.65]
Lok, 2016 4 3 1.24 [0.43, 3.60]
Kunutsor, 2017 23 12 0.82 [0.59, 1.13]
Lip, 2014 2 3 0.75 [0.29, 1.90]
Wolf, 2017 2 6 0.67 [0.25, 1.82]
RE Model for Subgroup (Q = 2.11, df = 4, p = 0.72; I² = 0%, τ²=0.00) 0.85 [0.65, 1.12]
A single meta−analysis of observational studies and RCTs with subgroups
Virk, 2015 2 3 2.36 [1.39, 4.04]
Villar, 2014 5 6 1.51 [0.52, 4.43]
Bikdeli, 2017 6 5 1.24 [0.29, 5.40]
Cummings, 2016 5 3 1.11 [0.10, 12.70]
Carter, 2016 4 7 1.11 [0.66, 1.87]
Filippini, 2017 7 2 1.03 [0.80, 1.33]
Smeeing, 2017 7 11 0.99 [0.31, 3.19]
Bellemain−Appaix, 2014 3 4 0.98 [0.56, 1.69]
Nair, 2016 12 22 0.92 [0.67, 1.27]
RE Model for Subgroup (Q = 9.89, df = 8, p = 0.27; I² = 19%, τ²=0.02) 1.13 [0.92, 1.38]
A single meta−analysis of observational studies and RCTs without subgroups
Neufeld, 2016 6 1 10.91 [3.35, 35.49]
Cheungpasitporn, 2015 1 23 8.83 [0.85, 92.21]
Muranushi, 2016 1 7 2.30 [0.95, 5.61]
Paul, 2016 1 13 2.06 [0.08, 50.00]
Hajibandeh, 2017 2 5 1.59 [0.17, 14.55]
Yu, 2017 5 2 1.46 [0.30, 7.14]
Fang, 2016 2 1 1.14 [0.17, 7.78]
Visioni, 2018 12 22 1.08 [0.68, 1.71]
Ehsanipoor, 2015 1 7 0.93 [0.11, 8.02]
Boundy, 2016 9 7 0.87 [0.45, 1.66]
Thienpont, 2017 14 15 0.69 [0.42, 1.13]
Lee, 2017 3 2 0.68 [0.54, 0.85]
Li, 2014 4 2 0.60 [0.24, 1.53]
Sijbrandij, 2018 12 3 0.58 [0.31, 1.09]
Haut, 2014 1 5 0.57 [0.01, 24.01]
Tsivgoulis, 2017 2 1 0.54 [0.08, 3.67]
Brinjikji, 2017 3 15 0.25 [0.14, 0.45]
RE Model for Subgroup (Q = 50.47, df = 16, p = 0.00; I² = 68%, τ²=0.30) 0.95 [0.65, 1.38]
RE Model for All Studies (Q = 73.58, df = 30, p = 0.00; I² = 59%, τ²=0.14) 0.98 [0.80, 1.21]
0.01
0.1
1
10
100
Observational studies yielded larger estimates
RE
RCTs yielded larger estimates


Meta−analysis
Intervention and Topic
Studies, n
Estimate (95% CI)
I2 (%)
A single meta−analysis of observational studies and RCTs with subgroups
Bellemain−Appaix, 2014
Thienopyridine in non−ST elevation
7
0.91 (0.80−1.04)
0
acute coronary syndrome
3
0.90 (0.71−1.14)
5
Carter, 2016
Group prenatal care on perinatal
11
0.86 (0.67−1.10)
36
outcomes
4
0.81 (0.60−1.09)
24
Filippini, 2017
Disease−modifying drug for multiple
9
0.53 (0.47−0.60)
0
sclerosis
7
0.53 (0.46−0.61)
0
Nair, 2016
Mupirocin for Staphylococcus
34
0.48 (0.42−0.55)
82
aureus infection
12
0.51 (0.40−0.65)
66
Bikdeli, 2017
Inferior vena cava filters for
11
0.44 (0.23−0.84)
45
pulmonary embolism
6
0.39 (0.18−0.86)
37
Virk, 2015
Intensive insulin therapy
5
0.35 (0.18−0.68)
68
for retinopathy
2
0.22 (0.14−0.36)
0
Villar, 2014
Nitroderivatives for Trypanosoma
11
0.24 (0.13−0.44)
68
cruzi infection
5
0.20 (0.09−0.44)
59
Smeeing, 2017
Surgical treatment for clavicle
18
0.19 (0.11−0.33)
0
fractures
7
0.19 (0.08−0.46)
0
Cummings, 2016
Bariatric surgery for type 2
8
0.03 (0.01−0.08)
21
diabetes mellitus
5
0.02 (0.01−0.11)
51
A single meta−analysis of observational studies and RCTs without subgroups
Cheungpasitporn, 2015
Preoperative RAS inhibitors
24
1.05 (0.92−1.20)
81
for acute kidney injury
1
0.12 (0.01−1.17)
NA
Hajibandeh, 2017
Beta−blockers in vascular surgery
7
1.10 (0.59−2.04)
70
2
0.61 (0.03−13.30)
64
Muranushi, 2016
NSAIDs in basal cell carcinoma
8
0.93 (0.86−1.02)
84
1
0.40 (0.18−0.91)
NA
Boundy, 2016
Kangaroo mother care among
16
0.77 (0.60−0.99)
68
preterm newborns
9
0.91 (0.72−1.14)
0
Visioni, 2018
Enhanced recovery after
34
0.70 (0.56−0.87)
44
noncolorectal surgery
12
0.69 (0.43−1.11)
57
Thienpont, 2017
Patient−specific instrumentation
29
0.72 (0.56−0.93)
51
for knee arthroplasty
14
0.91 (0.63−1.32)
34
Li, 2014
Self−Gripping mesh for postoperative
6
0.73 (0.47−1.14)
24
chronic pain
4
0.83 (0.51−1.36)
20
Lee, 2017
Antiplatelets for patients
5
0.68 (0.54−0.85)
69
with strokes while on aspirin
3
0.79 (0.68−0.92)
0
Yu, 2017
Prophylactic negative pressure
7
0.59 (0.31−1.10)
50
wound therapy after cesarean
5
0.48 (0.29−0.79)
0
Sijbrandij, 2018
Pharmacological therapy for
15
0.57 (0.41−0.80)
5
PTSD prevention
12
0.80 (0.49−1.31)
0
Neufeld, 2016
Antipsychotic drug for postoperative
7
0.56 (0.23−1.34)
93
delirium
6
0.40 (0.24−0.67)
70
Brinjikji, 2017
Anesthesia during mechanical
18
0.55 (0.41−0.74)
71
thrombectomy
3
1.82 (1.13−2.95)
15
Fang, 2016
Vitamine A for retinopathy
3
0.56 (0.31−0.98)
11
of prematurity
2
0.49 (0.15−1.66)
55
Tsivgoulis, 2017
Noninvasive ventilatory correction
3
0.49 (0.21−1.13)
0
during acute ischemic stroke
2
0.57 (0.22−1.52)
0
Ehsanipoor, 2015
Cerclage for second−trimester
8
0.29 (0.15−0.56)
65
cervical dilatation
1
0.31 (0.07−1.43)
NA
Haut, 2014
Inferior vena cava filters for
6
0.18 (0.05−0.66)
0
pulmonary embolism
1
0.30 (0.01−7.47)
NA
Paul, 2016
HBV antiviral prophylaxis
14
0.13 (0.08−0.23)
0
during chemotherapy
1
0.06 (0.00−1.06)
NA
Meta−analysis based on RCTs and observational studies
Meta−analysis based on RCTs only
0.01
0.02
0.05
0.10
0.20
0.50
1.00
2.00
5.00
Estimate
Favors treatment group
Favors control group