

RESEARCH ARTICLE

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Meta-analyses including non-randomized studies of therapeutic interventions: a methodological review

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Abstract

Background: There is an increasing number of meta-analyses including data from non-randomized studies for therapeutic evaluation. We aimed to systematically assess the methods used in meta-analyses including non-randomized studies evaluating therapeutic interventions.

Methods: For this methodological review, we searched MEDLINE via PubMed, from January 1, 2013 to December 31, 2013 for meta-analyses including at least one non-randomized study evaluating therapeutic interventions. Etiological assessments and meta-analyses with no comparison group were excluded. Two reviewers independently assessed the general characteristics and key methodological components of the systematic review process and meta-analysis methods.

Results: One hundred eighty eight meta-analyses were selected: 119 included both randomized controlled trials (RCTs) and non-randomized studies of interventions (NRSI) and 69 only NRSI. Half of the meta-analyses ($n = 92$, 49 %) evaluated non-pharmacological interventions. “Grey literature” was searched for 72 meta-analyses (38 %). An assessment of methodological quality or risk of bias was reported in 135 meta-analyses (72 %) but this assessment considered the risk of confounding bias in only 33 meta-analyses (18 %). In 130 meta-analyses (69 %), the design of each NRSI was not clearly specified. In 131 (70 %), whether crude or adjusted estimates of treatment effect for NRSI were combined was unclear or not reported. Heterogeneity across studies was assessed in 182 meta-analyses (97 %) and further explored in 157 (84 %). Reporting bias was assessed in 127 (68 %).

Conclusions: Some key methodological components of the systematic review process—search for grey literature, description of the type of NRSI included, assessment of risk of confounding bias and reporting of whether crude or adjusted estimates were combined—are not adequately carried out or reported in meta-analyses including NRSI.

Keywords: Meta-analyses, Therapeutic evaluation, Non-randomized studies, Reporting

Background

Randomized controlled trials (RCTs) are considered the gold standard for evidence-based medicine because they are designed to minimize the risk of bias [1]. However, the applicability of their results has been criticized because of restrictive selection criteria, with, commonly, exclusion of older adults and people with co-morbidities or severe disease [2–4]. Also, conducting an RCT is sometimes impossible or inappropriate (eg, when studying rare or long-term events) [1, 3, 5], which results in critical information gaps.

In contrast, observational studies, the overarching term for all non-experimental non-randomized studies (including cohort, case-control, and cross-sectional studies) [6], generally are more likely to reflect clinical practice in real life because of their broader range of participants, longer follow-up time, and lower costs than RCTs [7–10]. With the aim of generating evidence that will guide healthcare decisions, the field of comparative effectiveness research (CER) emphasizes the need to incorporate data from observational studies to complement RCTs [8, 11–16]. A comprehensive assessment in 2009 indicated that 54 % of CER studies had an observational study design [17]. Therefore, an increasing number of systematic reviews and meta-analyses are

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including data from non-randomized studies to assess therapeutic interventions.

Similar to systematic reviews of RCTs, reviews including non-randomized studies are expected to follow the general recommendations for good conduct, such as retrieving all relevant studies and assessing their risk of bias. However, some elements should be adapted specifically to the inclusion of non-randomized studies because their study designs inherently differ from RCTs [7, 9, 14, 18–23]. Lacking randomization, they are likely subject to confounding bias, which results in an imbalance in prognostic factors associated with the outcome of interest that may severely compromise the validity of their results [24].

Previous methodological reviews evaluating systematic reviews including observational studies exist [25–28]. However, these studies have a different objective. One assessed the main characteristics of all systematic reviews indexed in Medline on November 2004 whatever the type of included studies (ie, therapeutic, epidemiological, prognostic or diagnostic studies) [27]. Two others focused on the methods and reporting of harms in systematic reviews of adverse events [26, 28]. The last one was in the field of psychiatry and did not concern therapeutic evaluation but assessment of prevalence or association [25]. Further, none of these previous reviews has evaluated the specific methodological problems raised by the inclusion of non-randomized studies.

In this study, we performed a methodological review of meta-analyses including non-randomized studies of interventions (NRSI) to evaluate key methodological components common to all meta-analyses and those specifically related to the inclusion of non-randomized studies.

Methods

Study design

This is a methodological review of meta-analyses including NRSI for therapeutic evaluation. For clarity and consistency, we refer to this article as a “methodological review”, the systematic reviews with meta-analyses included in this methodological review as “meta-analyses”, and the studies included in these meta-analyses as “studies”.

Search strategy

Our goal was not to create an exhaustive list of all meta-analyses that include NRSI but rather to identify a relatively representative sample of recently published meta-analyses that a health professional would most likely encounter when searching for meta-analyses. We therefore searched MEDLINE via PubMed because of its wide use among health professionals, combining keywords and MeSH terms for NRSI, systematic reviews, and meta-analyses (Appendix 1). The search was conducted on January 7, 2014 and restricted to the year 2013.

Eligibility criteria

To be eligible, a meta-analysis had to examine a therapeutic or preventive intervention (such as vaccines) for efficacy or safety, include data from at least one NRSI, and be published in 2013. We excluded meta-analyses that included studies without a comparison group and meta-analyses of etiological assessment. When it was difficult to distinguish an etiological from a therapeutic evaluation, we agreed to include the former if the authors considered the inclusion of RCTs in their meta-analysis. To illustrate: a meta-analysis that investigated the association of the use of statins and risk of cancer would be considered a therapeutic evaluation if the authors planned to include RCTs. Individual patient data meta-analyses were also excluded, as were non-randomized studies that conducted a meta-analysis of the literature as secondary analysis. Finally, we did not include meta-analyses published in a language other than English or those for which the full text was not available.

Selection of relevant meta-analyses

The selection of relevant meta-analyses was conducted in 2 steps. In the first step, one reviewer (CR) excluded clearly irrelevant studies based on the title, abstract, and full text, then, a second reviewer (TF) performed the final selection, discussing all doubtful cases with a third reviewer (AD).

Data extraction

The data extraction form for this methodological review was developed from the MOOSE statement for reporting meta-analyses that include observational studies [29], the PRISMA statement for reporting systematic reviews and meta-analyses of studies evaluating healthcare interventions [30, 31], and the AMSTAR measurement tool for assessing the methodological quality of systematic reviews [32]. The data extraction form was tested by one reviewer (TF) with 10 studies before data extraction commenced.

Two reviewers (TF, CR) independently extracted all data in duplicate, resolving discrepancies with a third reviewer (AD) if necessary. The following characteristics were extracted from the full text and online appendix of each meta-analysis:

- *General characteristics:* We collected whether the journal was a specialty or a general journal, the location of the corresponding author, and the medical area. We verified whether the meta-analysis was registered on the international prospective register of systematic reviews by the University of York's Centre for Reviews and Dissemination (PROSPERO). We collected whether epidemiologists or statisticians were involved, relying on the definition given by Delgado-Rodriguez et al.[33] and assessed whether

the authors reported the funding sources and declared conflict of interests. We assessed whether the meta-analyses evaluated a pharmacological or non-pharmacological intervention. Non-pharmacological interventions were classified as surgical procedures or other interventions. We also assessed the type of studies included: only NRSI or both NRSI and RCTs.

- *Systematic review methods:*
 - Search strategy: We collected how many and which electronic databases were searched, and whether the search strategy for at least one database was provided. We collected whether reference lists and journals were hand-searched and whether the authors searched for grey literature, and if yes, how: search of registries (eg, ClinicalTrials.gov), conference abstracts, or contacting experts. We assessed whether the authors restrict their searches by language.
 - Study selection and data extraction process: We assessed whether study selection and data extraction were conducted in duplicate.
 - Contact of the study authors: We noted whether it was mentioned that study authors were contacted for clarification or additional results.
 - Methodological quality/risk of bias assessment: We assessed whether methodological quality or risk of bias assessment was conducted, what tools were used, and whether the assessment was conducted in duplicate.
- *Meta-analysis methods:*
 - Studies combined: We assessed the types of NRSI included. NRSI were categorized as concurrent (prospective) cohort, nonconcurrent (retrospective) cohort, case-control, or historically controlled studies according to the definition by Ioannidis et al. [21]. We also assessed whether the authors combined the results from NRSI and RCTs and whether they combined results from different types of NRSI (eg, cohort and case-control studies).
 - Meta-analysis model: We collected whether the authors used crude or adjusted estimates for NRSI and whether they used fixed- or random-effects models to pool the data. For adjusted estimates, we also collected whether the confounding factors taken into account were listed.
 - Assessment and exploration of heterogeneity: We collected whether and how the authors assessed heterogeneity and whether they conducted meta-regression, subgroup, or sensitivity analyses to explore heterogeneity.

- Assessment of reporting bias: We collected information on whether the authors assessed reporting bias, and how.

Statistical analysis

The analysis of the data consisted of descriptive statistics, providing numbers and percentages for qualitative variables and median (minimum, maximum, or inter-quartile range) for quantitative variables. The results were stratified for meta-analyses including only NRSI and those including both NRSI and RCTs. We did not assess statistical differences between these strata. Statistical analysis involved use of R 3.0.2. (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/>).

Results

Study selection

Our MEDLINE search identified 3602 citations; Among the 341 potentially relevant meta-analyses, 188 were eligible for this review (Fig. 1). Complete references for the included meta-analyses and meta-analyses excluded are in Appendixes 2 and 3, respectively.

General characteristics (Table 1)

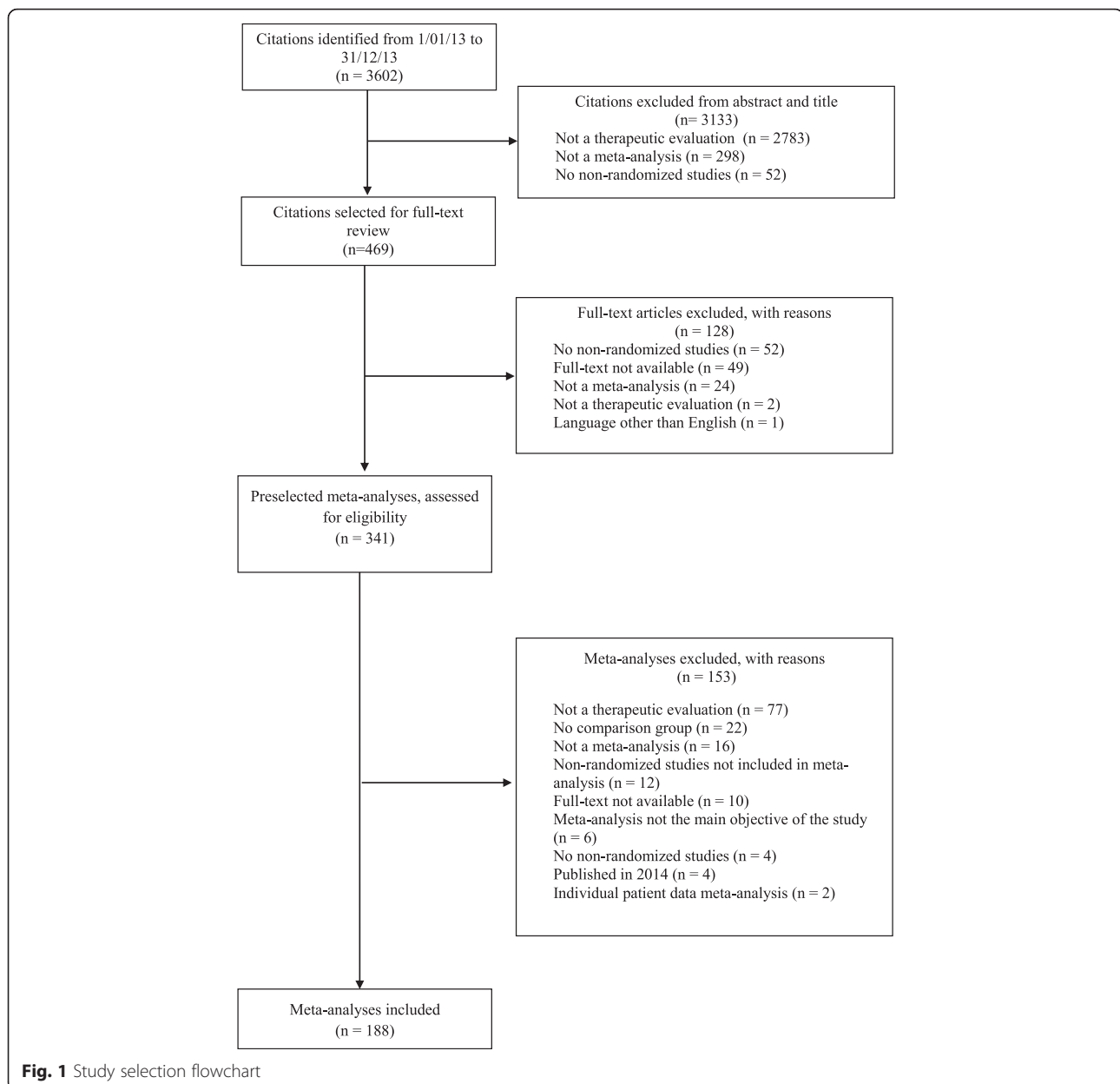
Among the 188 included meta-analyses, 49 (26 %) were of surgery, 33 (18 %) cardiology, and 25 (13 %) oncology. Half of the meta-analyses assessed non-pharmacological interventions ($n = 92$, 49 %); 74 involved surgical procedures. Approximately one third ($n = 69$, 37 %) included only NRSI, and two thirds included both NRSI and RCTs ($n = 119$, 63 %).

In total, 36 meta-analyses (19 %) involved epidemiologists or statisticians. Conflict of interest was declared in 166 (88 %), with 26 reporting a potential conflict of interest. About one-third of the meta-analyses did not report a source of funding ($n = 69$, 37 %).

Systematic review methods (Table 2)

Literature search

Overall, all but one of the meta-analyses reported the search of at least 1 electronic database and 147 (78 %) reported the search of > 2 electronic databases. One third provided the search strategy for each database ($n = 62$, 33 %). MEDLINE, Embase, and the Cochrane Library were most frequently searched (187 [99 %], 149 [79 %], and 126 (67 %) meta-analyses, respectively). In addition to the search of electronic databases, 162 meta-analyses (86 %) reported screening the reference lists of included studies, and 12 (6 %) reported hand-searching journals. About one-third of the meta-analyses ($n = 72$, 38 %) reported searching for grey literature: 41 (22 %) conference abstracts, 33 (18 %) registries, and 15 (8 %) contacted



experts. For 82 meta-analyses (44 %), the authors reported that they did not restrict their searches by language.

Methodological quality/risk of bias assessment

Methodological quality or risk of bias of included studies was assessed in 135 (72 %) meta-analyses.

For the 119 meta-analyses including RCTs and NRSI, risk of bias was assessed in 88 (74 %) with 4 assessing risk of bias for RCTs only. RCTs were assessed with the Cochrane Risk of Bias tool in 42 (35 %) meta-analyses. The assessment of risk of bias involved the same tool for both RCTs and NRSI in 27 (23 %) meta-analyses. For the assessment of NRSI,

a variety of tools were used. The most frequently used tool was the Newcastle-Ottawa Scale ($n = 68$). GRADE and the Cochrane Collaboration Risk of Bias Tool were used in 13 and 10 meta-analyses, respectively. In 37 meta-analyses, authors used other tools; in 12, they developed their own tools; and in 12, they were unclear about the methods used for assessing methodological quality/risk of bias. Overall, the authors have considered the risk of confounding bias in their risk of bias assessment in 33 meta-analyses (18 %). Of the 135 meta-analyses with an assessment of risk of bias, 87 (64 %) reported having performed it in duplicate.

Table 1 General characteristics of therapeutic meta-analyses published in 2013 and including non-randomized studies of intervention ($n = 188$)

Characteristic	Included NRSI only	Included NRSI&RCTs	All meta-analyses
	($n = 69$) No (%)	($n = 119$) No (%)	($n = 188$) No (%)
Journal type			
Specialty	59 (86)	99 (83)	158 (84)
General	10 (14)	20 (17)	30 (16)
Location of corresponding author			
Asia	26 (38)	38 (32)	64 (34)
Europe	22 (32)	39 (33)	61 (32)
North-America	18 (26)	33 (28)	51 (27)
Other	3 (4)	9 (7)	12 (7)
Medical area			
Surgery	21 (30)	28 (24)	49 (26)
Cardiology	8 (12)	25 (21)	33 (18)
Oncology	6 (9)	19 (16)	25 (13)
Other	34 (49)	47 (39)	81 (43)
Type of intervention			
Pharmacological	36 (52)	56 (47)	92 (49)
Non-pharmacological	32 (46)	60 (50)	92 (49)
<i>Surgical procedures</i>	30 (43)	44 (37)	74 (39)
<i>Other</i>	2 (3)	16 (13)	18 (10)
Both pharmacological and non-pharmacological	1 (1)	3 (3)	4 (2)
Epidemiologists or statisticians involved	17 (25)	19 (16)	36 (19)
Declaration of conflict of interests	64 (93)	102 (86)	166 (88)
Potential conflict of interests	9 (13)	17 (14)	26 (14)
Funding source			
Public	30 (43)	36 (30)	66 (35)
No specific funding	10 (14)	29 (24)	39 (21)
Private	2 (3)	7 (6)	9 (5)
Both public and private	3 (4)	2 (2)	5 (3)
Not reported/unclear	24 (35)	45 (38)	69 (37)
Registration on PROSPERO	0	3 (3)	3 (2)

NRSI non-randomized studies of intervention; RCTs randomized controlled trials

Meta-analysis methods (Table 3)

Studies combined

For 130 meta-analyses (69 %), the authors did not clearly report the design for each individual study. Among the meta-analyses that included both NRSI and RCTs ($n = 119$), for 88 (74 %), the results of NRSI and RCTs were combined.

Concerning NRSI combined, 52 meta-analyses (28 %) included only cohort studies and 5 only prospective cohort studies; 46 meta-analyses (24 %) combined cohort and case-control studies, and 23 (12 %) included all types of NRSI. The other 67 meta-analyses (36 %) included “observational studies” (without further details

($n = 28$, 15 %), “prospective and retrospective studies” ($n = 23$, 12 %), and only “retrospective studies” ($n = 16$, 9 %).

Crude or adjusted estimates used for NRSI

For 131 meta-analyses (70 %), whether crude or adjusted estimates of treatment effect from the NRSI were used for the meta-analysis was unclear or not reported. For the remaining meta-analyses, the authors reported combining crude and adjusted estimates for 22 (12 %), only adjusted estimates for 21 (11 %), and only crude estimates for 6 (3 %). For 8 meta-analyses (4 %), the authors

Table 2 Systematic review methods of therapeutic meta-analyses published in 2013 and including non-randomized studies ($n = 188$)

Characteristic	Included NRSI only	Included NRSI&RCTs	All Meta-analyses
	($n = 69$) No (%)	($n = 119$) No (%)	($n = 188$) No (%)
Search strategy			
No. of electronic databases searched, median [IQR]	3 [2–4]	3 [3, 4]	3 [3, 4]
> 2 databases searched	51 (74)	96 (81)	147 (78)
Electronic databases searched ^a			
Medline/PubMed/Ovid	69 (100)	118 (99)	187 (99)
EMBASE	52 (75)	97 (82)	149 (79)
Cochrane	45 (65)	81 (68)	126 (67)
Web of science/web of knowledge	14 (20)	22 (18)	36 (19)
Time-frame of search strategy reported	62 (90)	109 (92)	171 (91)
Time end of search-publication date (months), median [min-max]	10 [0–24]	9 [1–51]	10 [0–51]
Search strategy provided for at least one database	18 (26)	44 (37)	62 (33)
Searched reference lists for relevant studies	57 (83)	105 (88)	162 (86)
Hand searched journals	5 (7)	7 (6)	12 (6)
Searched for grey literature ^a			
Conference abstracts	14 (20)	27 (23)	41 (22)
Registries (eg, ClinicalTrials.gov)	8 (12)	25 (21)	33 (18)
Experts	6 (9)	9 (8)	15 (8)
No restriction by language reported	20 (29)	62 (52)	82 (44)
Study selection			
Duplicate study selection	47 (68)	84 (71)	131 (70)
Methodological quality/risk of bias			
Assessment of MQ/RoB	47 (68)	88 (74)	135 (72)
Tools used for RCTs ^a			
Cochrane RoB Tool [41]	NA	42 (35)	NA
Jadad scale [42]	NA	22 (18)	NA
GRADE [43]	NA	9 (8)	NA
Other	NA	21 (18)	NA
Authors made their own tool	NA	3 (3)	NA
Unclear	NA	7 (6)	NA
Tools used for NRSI ^a			
Newcastle-Ottawa scale [44]	25 (36)	43 (36)	68 (36)
GRADE [43]	5 (7)	8 (7)	13 (7)
Cochrane RoB Tool [41]	3 (4)	7 (6)	10 (5)
Other tools	13 (19)	24 (20)	37 (20)
Authors made their own tool	6 (9)	6 (5)	12 (6)
Unclear	3 (4)	9 (8)	12 (6)
Confounding taken into account in risk of bias	13 (19)	20 (17)	33 (18)
Same tool used for RCTs and NRSI	NA	27 (23)	NA
Duplicate MQ/RoB assessment	30/47 (64)	57/88 (65)	87/135 (64)

Table 2 Systematic review methods of therapeutic meta-analyses published in 2013 and including non-randomized studies ($n = 188$) (Continued)

Data extraction			
Duplicate data extraction	52 (75)	86 (72)	138 (73)
Contact authors for clarification or additional results	18 (26)	43 (36)	61 (32)

Data are no. (%), unless indicated. *IQR* interquartile range; *MQ* methodological quality; *NRSI* non-randomized studies of interventions; *RCTs* randomized controlled trials; *Cochrane RoB* Cochrane risk of bias tool; *NA* Not applicable

^aMore than one item could have been reported for each meta-analysis

extracted both the crude and adjusted estimates and used them separately in 2 meta-analyses. Among the 51 meta-analyses involving adjusted estimates, 17 (33 %) did not report the confounding factors adjusted for.

Meta-analysis model

A random-effects model was used for half of the meta-analyses ($n = 95$). For 52 (28 %), a fixed-effects model was used primarily but then replaced with a random-effects model if high heterogeneity was observed in the model. For 26 meta-analyses (14 %), the authors used both fixed- and random-effects models, and for 9 (5 %), a fixed-effects model. The type of model was not reported or was unclear for 6 meta-analyses (3 %). We found 2 network meta-analyses (1 %).

Heterogeneity assessment

Almost all meta-analyses assessed heterogeneity ($n = 182$, 97 %). The I^2 statistic was used in 164 meta-analyses (87 %), Cochran Q χ^2 test in 115 (61 %), and between-study variance τ^2 in 6 (3 %). Heterogeneity was explored in 157 meta-analyses (84 %) by subgroup analyses ($n = 126$, 67 %), sensitivity analyses ($n = 109$, 58 %) and meta-regression analyses ($n = 34$, 18 %).

For 44 of 88 (50 %) meta-analyses combining results from RCTs and NRSI, a subgroup or sensitivity analysis was based on the type of study (RCT vs NRSI). For 28 meta-analyses (15 %), subgroup or sensitivity analyses were based on the type of NRSI included.

Reporting bias assessment

Reporting bias was assessed in 127 meta-analyses (68 %) by standard funnel plots ($n = 111$, 59 %), Egger's test ($n = 68$, 36 %), or Begg's test ($n = 42$, 22 %). Overall, 82 of the 105 meta-analyses (78 %) including 10 or more studies reported having assessed reporting bias.

Discussion

We systematically assessed key methodological components of a large sample of therapeutic meta-analyses including NRSI in a variety of medical areas. Our results highlight some important methodological shortcomings. Only 38 % of the meta-analyses reported having searched for grey literature. Specific

points related to the inclusion of NRSI raise concerns, with 69 % of the meta-analyses not reporting the study design of the included NRSI, and 70 % not reporting whether crude or adjusted estimates were combined.

Strengths and limitations of study

To the best of our knowledge, no previous study has comprehensively assessed both key methodological components common to all systematic reviews and elements specific to the inclusion of non-randomized studies. Other studies that previously evaluated methods or reporting of systematic reviews including NRSI concentrated on the reporting of harms [26, 28] and on systematic reviews in psychiatric epidemiology [25].

Our study has some limitations. The representativeness of our sample could be debated because we searched for studies in only one online database (MEDLINE), and limited our selection to meta-analyses in English. In addition, for the assessment of the methods, we depended completely on the reporting; we did not assess protocols or contact the authors if methods were not clearly reported. Even though poor reporting does not necessarily reflect poor conduct, it may severely limit the reader's comprehension of the systematic review process [34].

Before being able to apply the results of any meta-analysis to patient care, health professionals need to evaluate the credibility of the methods of the meta-analysis [35]. One of the key methodological elements is the search for relevant studies. Because not all studies (and particularly those with negative results) are published in scientific journals, a meta-analysis must involve a search for grey literature to try to avoid such publication bias (a type of reporting bias) [24, 35]. However, we found that only 38 % of our meta-analyses reported having searched for grey literature. Because of no mandatory registration for NRSI as for RCTs, most NRSI are not registered, so searching for grey literature of NRSI is difficult [36]. However, a recent study found that for 32 % of the observational studies registered at ClinicalTrials.gov, unpublished results could be retrieved [37]. In contrast, we found that many meta-analyses assessed reporting bias (68 %). Reviewers may have compensated for the absence of searching for grey

Table 3 Meta-analysis methods of therapeutic meta-analyses published in 2013 and including non-randomized studies ($n = 188$)

Characteristic	Included NRSI only	Included NRSI&RCTs	All meta-analyses
	($n = 69$) No (%)	($n = 119$) No (%)	($n = 188$) No (%)
Studies combined			
Type of studies included			
Only prospective cohort studies	2 (3)	3 (3)	5 (3)
Only cohort studies	18 (26)	34 (29)	52 (28)
Including also case-control studies	18 (26)	28 (23)	46 (24)
Including all types of NRSI	5 (7)	18 (15)	23 (12)
Other	28 (41)	39 (33)	67 (36)
"Observational studies"	6 (9)	22 (18)	28 (15)
"Prospective and retrospective studies"	11 (16)	12 (10)	23 (12)
"Retrospective studies"	11 (16)	5 (4)	16 (9)
Did not clearly report design for each study	43 (62)	87 (73)	130 (69)
Meta-analysis combining results of NRSI and RCTs	NA	88 (74)	NA
Results also presented separately	NA	44/88 (50)	NA
Meta-analysis combining studies of different designs	39 (57)	61 (51)	100 (53)
Meta-analysis model			
Network meta-analysis	0	2 (2)	2 (1)
Crude or adjusted estimates used			
Combined crude and adjusted estimates	10 (14)	12 (10)	22 (12)
Adjusted	8 (12)	13 (11)	21 (11)
Both crude and adjusted estimates separately	4 (6)	4 (3)	8 (4)
Crude	2 (3)	4 (3)	6 (3)
Not reported/unclear	45 (65)	86 (72)	131 (70)
If adjusted, list of confounding factors	15/22 (68)	19/29 (66)	34/51 (67)
Type of model			
Random-effects model	39 (57)	56 (47)	95 (50)
Fixed-effects model, unless high heterogeneity, then random-effects model	19 (28)	33 (28)	52 (28)
Both fixed- and random-effects models	5 (7)	21 (18)	26 (14)
Fixed-effects model	3 (4)	6 (5)	9 (5)
Not reported/unclear	3 (4)	3 (3)	6 (3)
Heterogeneity assessment & exploration			
Heterogeneity assessed ^a	66 (96)	116 (97)	182 (97)
I^2	57 (83)	107 (90)	164 (87)
Cochran Q χ^2 test	41 (59)	74 (62)	115 (61)
τ^2	4 (6)	2 (2)	6 (3)
Heterogeneity explored ^a	54 (82)	103 (87)	157 (84)
Meta-regression analysis	13 (19)	21 (18)	34 (18)
Subgroup analysis	44 (64)	82 (69)	126 (67)
Sensitivity analysis	35 (51)	74 (62)	109 (58)

Table 3 Meta-analysis methods of therapeutic meta-analyses published in 2013 and including non-randomized studies ($n = 188$) (Continued)

Reporting bias assessment ^a	49 (71)	78 (66)	127 (68)
Standard funnel plot	41 (59)	70 (59)	111 (59)
Egger's test	32 (46)	36 (30)	68 (36)
Begg's test	18 (26)	24 (20)	42 (22)
Among MAs with ≥ 10 studies, reporting bias assessed	24/29 (83)	58/76 (76)	82/105 (78)

MAs meta-analyses; NRSI non-randomized studies of intervention; RCTs randomized controlled trials

^aMore than one item could have been reported for each meta-analysis

literature by assessing reporting bias. Evaluating reporting bias does not exempt the reviewers from searching for grey literature because the assessment of Funnel plot asymmetry may be subjective and statistical methods to test for asymmetry of the plot may lack power [38, 39].

Another critical part of the systematic review process is assessing the methodological quality or risk of bias of the studies included, because the validity of the meta-analysis could be questionable with problems in the design and conduct of individual studies [40]. We found that 72 % of our meta-analyses reported having assessed the methodological quality or risk of bias but only 33 (18 %) considered the risk of confounding bias in their assessment. The Cochrane Collaboration has recognized the need to improve the assessment of risk of bias for NRSI and is currently developing a tool for this.

Finally, we found specific issues related to the inclusion of NRSI. In 69 % of the meta-analyses, the study design for each included study was unclear. The risk of bias may vary depending on the type of NRSI, with case-control studies generally considered as having a higher risk of bias than cohort studies. A description of the type of studies included in the meta-analysis is crucial. In addition, NRSI are prone to confounding; an imbalance in prognostic factors associated with the outcome of interest [24]. NRSI are expected to at least present adjusted estimates from multivariate analyses [3, 4]. Many of our meta-analyses (70 %) did not report or were unclear about whether the crude or adjusted estimates of NRSI were combined. Among the meta-analyses involving adjusted estimates, 33 % did not report the confounding factors adjusted for. This information was likely poorly reported in the individual studies, but then the reviewers should contact the authors for clarification or report it clearly in the meta-analysis.

Conclusions

Some key methodological components of the systematic review process – search for grey literature, description of the type of NRSI included, assessment of risk of confounding bias and reporting of whether crude or adjusted estimates were combined—are not

adequately reported in meta-analyses including NRSI. Attention should be paid to improving these elements in such meta-analyses to have an increased confidence in their results.

Ethics

Not applicable. This article reports a meta-research study.

Consent

Not needed. This study does not include human participants.

Availability of supporting data

Data are available upon request for academic researchers.

Appendices

Appendix 1 Search strategy

Pubmed Search Equation

1.	"observational" [tiab]
2.	"cohort" [tiab]
3.	cohort studies [mh]
4.	"epidemiologic" [tiab]
5.	"epidemiological" [tiab]
6.	"systematic review" [tiab]
7.	"systematic reviews" [tiab]
8.	"meta-analysis" [tiab]
9.	"meta-analyses" [tiab]
10.	meta analysis [pt]
11.	"overview" [tiab]
12.	#1 OR #2 OR #3 OR #4 OR #5
13.	#6 OR #7 OR #8 OR #9 OR #10 OR #11
14.	#12 AND #13

Date of search: 7 January 2014

Search limits: Published between 1 January 2013 and 31 December 2013.

Citations retrieved: 3602.

Appendix 2 List of included meta-analyses (N = 188)

Meta-analyses including observational studies and randomized controlled trials (N = 119)

Study ID	Reference of included citation
35	Abdelaal, E., S. V. Rao, et al. (2013). "Same-day discharge compared with overnight hospitalization after uncomplicated percutaneous coronary intervention: a systematic review and meta-analysis." <i>JACC Cardiovasc Interv</i> 6(2): 99–112.
51	Abubakar, I., L. Pimpin, et al. (2013). "Systematic review and meta-analysis of the current evidence on the duration of protection by bacillus Calmette-Guerin vaccination against tuberculosis." <i>Health Technol Assess</i> 17(37): 1–372, v-vi.
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1161	Chu, H., L. Zhao, et al. (2013). "Sulbactam-based therapy for <i>Acinetobacter baumannii</i> infection: a systematic review and meta-analysis." <i>Braz J Infect Dis</i> 17(4): 389–394.
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Appendix 3: List of excluded meta-analyses (N = 153)

Reason for exclusion:

Not a therapeutic evaluation (n = 77)

Study ID	Reference of included citation
177	Almenawer, S. A., I. Bogza, et al. (2013). "The value of scheduled repeat cranial computed tomography after mild head injury: single-center series and meta-analysis." <i>Neurosurgery</i> 72(1): 56–62; discussion 63–54.
335	Atlantis, E., P. Fahey, et al. (2013). "Endogenous testosterone level and testosterone supplementation therapy in chronic obstructive pulmonary disease (COPD): a systematic review and meta-analysis." <i>BMJ Open</i> 3(8).
2050	Gans, I., K. D. Baldwin, et al. (2013). "Treatment and Management Outcomes of Tibial Eminence Fractures in Pediatric Patients: A Systematic Review." <i>Am J Sports Med</i> .
2062	Garces, S., J. Demengeot, et al. (2013). "The immunogenicity of anti-TNF therapy in immune-mediated inflammatory diseases: a systematic review of the literature with a meta-analysis." <i>Ann Rheum Dis</i> 72(12): 1947–1955.
5938	Suthar, A. B., D. Hoos, et al. (2013). "Integrating antiretroviral therapy into antenatal care and maternal and child health settings: a systematic review and meta-analysis." <i>Bull World Health Organ</i> 91(1): 46–56.
7112	Zhi, X., X. Zhou, et al. (2013). "Practical role of mutation analysis for imatinib treatment in patients with advanced gastrointestinal stromal tumors: a meta-analysis." <i>PLoS One</i> 8(11): e79275.
475	Bauer, S. R., S. E. Hankinson, et al. (2013). "Plasma vitamin D levels, menopause, and risk of breast cancer: dose–response meta-analysis of prospective studies." <i>Medicine (Baltimore)</i> 92(3): 123–131.
591	Bewtra, M., L. M. Kaiser, et al. (2013). "Crohn's disease and ulcerative colitis are associated with elevated standardized mortality ratios: a meta-analysis." <i>Inflamm Bowel Dis</i> 19(3): 599–613.
597	Bhangu, A., D. Nepogodiev, et al. (2013). "Meta-analysis of plasma to red blood cell ratios and mortality in massive blood transfusions for trauma." <i>Injury</i> 44(12): 1693–1699.
675	Bonifazi, M., I. Tramacere, et al. (2013). "Systemic sclerosis (scleroderma) and cancer risk: systematic review and meta-analysis of observational studies." <i>Rheumatology (Oxford)</i> 52(1): 143–154.
701	Bosanquet, D. C., D. A. Harris, et al. (2013). "Systematic review and meta-analysis of intraoperative peritoneal lavage for colorectal cancer staging." <i>Br J Surg</i> 100(7): 853–862.
717	Bougma, K., F. E. Aboud, et al. (2013). "Iodine and mental development of children 5 years old and under: a systematic review and meta-analysis." <i>Nutrients</i> 5(4): 1384–1416.
803	Bryant, A. R., S. B. Wilton, et al. (2013). "Association between QRS duration and outcome with cardiac resynchronization therapy: a systematic review and meta-analysis." <i>J Electrocardiol</i> 46(2): 147–155.
1017	Charidimou, A., P. Kakar, et al. (2013). "Cerebral microbleeds and recurrent stroke risk: systematic review and meta-analysis of prospective ischemic stroke and transient ischemic attack cohorts." <i>Stroke</i> 44(4): 995–1001.
1349	Davies, A., K. P. Singh, et al. (2013). "Treatment outcomes of treatment-naive Hepatitis C patients co-infected with HIV: a systematic review and meta-analysis of observational cohorts." <i>PLoS One</i> 8(2): e55373.
1996	Fumery, M., C. Xiaocang, et al. (2013). "Thromboembolic events and cardiovascular mortality in inflammatory bowel diseases: A meta-analysis of observational studies." <i>J Crohns Colitis</i> .
2066	Garcia, S., Y. Sandoval, et al. (2013). "Outcomes after complete versus incomplete revascularization of patients with multivessel coronary artery disease: a meta-analysis of 89,883 patients enrolled in randomized clinical trials and observational studies." <i>J Am Coll Cardiol</i> 62(16): 1421–1431.
2144	Gielen, C., O. Dekkers, et al. (2013). "The effects of pre- and postoperative fibrinogen levels on blood loss after cardiac surgery: a systematic review and meta-analysis." <i>Interact Cardiovasc Thorac Surg</i> .
2689	Huang, Y., R. Chen, et al. (2013). "Association between point-of-care CRP testing and antibiotic prescribing in respiratory tract infections: a systematic review and meta-analysis of primary care studies." <i>Br J Gen Pract</i> 63(616): 787–794.
2823	James, M. T., S. M. Samuel, et al. (2013). "Contrast-induced acute kidney injury and risk of adverse clinical outcomes after coronary angiography: a systematic review and meta-analysis." <i>Circ Cardiovasc Interv</i> 6(1): 37–43.
3014	Kaptoge, S., S. R. Seshasai, et al. (2013). "Inflammatory cytokines and risk of coronary heart disease: new prospective study and updated meta-analysis." <i>Eur Heart J</i> .
3476	Lemos, E. V., F. P. de la Hoz, et al. (2013). "Carbapenem resistance and mortality in patients with <i>Acinetobacter baumannii</i> infection: systematic review and meta-analysis." <i>Clin Microbiol Infect</i> .
317	Arregui, M., B. Buijsse, et al. (2014). "Adiponectin and Risk of Stroke: Prospective Study and Meta-analysis." <i>Stroke</i> 45(1): 10–17.
367	Baandrup, L., M. T. Faber, et al. (2013). "Nonsteroidal anti-inflammatory drugs and risk of ovarian cancer: systematic review and meta-analysis of observational studies." <i>Acta Obstet Gynecol Scand</i> 92(3): 245–255.

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- 1865 Fillion, K. B., D. Chateau, et al. (2013). "Proton pump inhibitors and the risk of hospitalisation for community-acquired pneumonia: replicated cohort studies with meta-analysis." *Gut*.

Reason for exclusion:

There is no comparison group ($n = 22$)

Study ID Reference of included citation

- 239 Andrews, P. L., J. R. Shiber, et al. (2013). "Early application of airway pressure release ventilation may reduce mortality in high-risk trauma patients: a systematic review of observational trauma ARDS literature." *J Trauma Acute Care Surg*75(4): 635–641.

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Reason for exclusion:

Not a meta-analysis/No statistical pooling of the results ($n = 16$)

Study ID	Reference of included citation
175	Almekhlafi, M. A., B. K. Menon, et al. (2013). "A meta-analysis of observational intra-arterial stroke therapy studies using the Merci device, Penumbra system, and retrievable stents." <i>AJNR Am J Neuroradiol</i> 34(1): 140–145.
1103	Chiappini, E., L. Galli, et al. (2013). "Use of combination neonatal prophylaxis for the prevention of mother-to-child transmission of HIV infection in European high-risk infants." <i>AIDS</i> 27(6): 991–1000.
1505	Dienstknrecht, T., K. Horst, et al. (2013). "A meta-analysis of operative versus nonoperative treatment in 463 scapular neck fractures." <i>Scand J Surg</i> 102(2): 69–76.
2431	Hasan, S., L. Liu, et al. (2013). "The role of postoperative radiation and chemoradiation in merkel cell carcinoma: a systematic review of the literature." <i>Front Oncol</i> 3: 276.

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- 1559 Domecq, J. P., G. Prutsky, et al. (2013). "Adverse effects of the common treatments for polycystic ovary syndrome: a systematic review and meta-analysis." *J Clin Endocrinol Metab*98(12): 4646–4654.

Reason for exclusion:

Meta-Analysis does not include results from observational studies ($n = 12$)

- | Study ID | Reference of included citation |
|----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 87 | Ahmed, F., M. C. Lindley, et al. (2014). "Effect of influenza vaccination of healthcare personnel on morbidity and mortality among patients: systematic review and grading of evidence." <i>Clin Infect Dis</i> 58(1): 50–57. |
| 125 | Albanna, A. S., B. M. Smith, et al. (2013). "Fixed-dose combination antituberculosis therapy: a systematic review and meta-analysis." <i>Eur Respir J</i> 42(3): 721–732. |
| 1982 | Fu, R., S. Selph, et al. (2013). "Effectiveness and harms of recombinant human bone morphogenetic protein-2 in spine fusion: a systematic review and meta-analysis." <i>Ann Intern Med</i> 158(12): 890–902. |
| 3004 | Kansagara, D., E. Dyer, et al. (2013). "Treatment of anemia in patients with heart disease: a systematic review." <i>Ann Intern Med</i> 159(11): 746–757. |
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| 6034 | Taylor, P. N., O. E. Okosieme, et al. (2014). "Therapy of Endocrine Disease: Impact of iodine supplementation in mild-to-moderate iodine deficiency: systematic review and meta-analysis." <i>Eur J Endocrinol</i> 170(1): R1-R15. |
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| 3012 | Kapadia, S., S. Hapani, et al. (2013). "Risk of liver toxicity with the angiogenesis inhibitor pazopanib in cancer patients." <i>Acta Oncol</i> 52(6): 1202–1212. |
| 5089 | Reichenpader, U., G. Gartlehner, et al. (2013). "Sexual Dysfunction associated with Second-Generation Antidepressants in Patients with Major Depressive Disorder: Results from a Systematic Review with Network Meta-Analysis." <i>Drug Saf</i> . |
| 1936 | Fortmann, S. P., B. U. Burda, et al. (2013). "Vitamin and Mineral Supplements in the Primary Prevention of Cardiovascular Disease and Cancer: An Updated Systematic Evidence Review for the U.S. Preventive Services Task Force." <i>Ann Intern Med</i> . |

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Reason for exclusion:

Full text not available ($n = 10$)

Study ID	Reference of included citation
3702	Liu, Y., P. Su, et al. (2013). "Endoscopic sphincterotomy plus balloon dilation versus endoscopic sphincterotomy for choledocholithiasis: A meta-analysis." <i>J Gastroenterol Hepatol</i> 28(6): 937–945.
3704	Liu, Y., W. Tang, et al. (2013). "Association between statin use and colorectal cancer risk: a meta-analysis of 42 studies." <i>Cancer Causes Control</i> .
4701	Pasipanodya, J. G. and T. Gumbo (2013). "A meta-analysis of self-administered vs directly observed therapy effect on microbiologic failure, relapse, and acquired drug resistance in tuberculosis patients." <i>Clin Infect Dis</i> 57(1): 21–31.
5285	Saheb, K. J., B. Q. Deng, et al. (2013). "Triple antithrombotic therapy versus double antiplatelet therapy after percutaneous coronary intervention with stent implantation in patients requiring chronic oral anticoagulation: a meta-analysis." <i>Chin Med J (Engl)</i> 126(13): 2536–2542.
5922	Sun, Z. J., W. J. Li, et al. (2013). "Comparing minimally invasive and open transforaminal lumbar interbody fusion for treatment of degenerative lumbar disease: a meta-analysis." <i>Chin Med J (Engl)</i> 126(20): 3962–3971.
6783	Wu, Y. C., J. F. Zhang, et al. (2013). "Transcatheter aortic valve implantation versus surgical aortic valve replacement for severe aortic stenosis: a meta analysis." <i>Chin Med J (Engl)</i> 126(6): 1171–1177.
7106	Zheng, Z., L. Sheng, et al. (2013). "Statins and amyotrophic lateral sclerosis: a systematic review and meta-analysis." <i>Amyotroph Lateral Scler Frontotemporal Degener</i> 14(4): 241–245.
3598	Lin, G. H., H. L. Chan, et al. (2013). "The Effect of Flapless Surgery on Implant Survival and Marginal Bone Level: A Systematic Review and Meta-analysis." <i>J Periodontol</i> .
4225	More, K., G. Athalye-Jape, et al. (2013). "Association of inhibitors of gastric acid secretion and higher incidence of necrotizing enterocolitis in preterm very low-birth-weight infants." <i>Am J Perinatol</i> 30(10): 849–856.
4175	Moen, C. A., A. Burrell, et al. (2013). "Does tranexamic acid stop haemoptysis?" <i>Interact Cardiovasc Thorac Surg</i> 17(6): 991–994.

Reason for exclusion:

Meta-analysis not main objective ($n = 6$)

Study ID	Reference of included citation
1469	D'Errigo, P., F. Biancari, et al. (2013). "Thirty-day mortality after coronary artery bypass surgery in patients aged <50 years: results of a multicenter study and meta-analysis of the literature." <i>J Card Surg</i> 28(3): 207–211.
1735	Etminan, M., S. T. Bird, et al. (2013). "Isotretinoin and risk for inflammatory bowel disease: a nested case-control study and meta-analysis of published and unpublished data." <i>JAMA Dermatol</i> 149(2): 216–220.
1753	Faggioli, G., R. Pini, et al. (2013). "Contralateral carotid occlusion in endovascular and surgical carotid revascularization: a single centre experience with literature review and meta-analysis." <i>Eur J Vasc Endovasc Surg</i> 46(1): 10–20.
3067	Kennedy, N. A., E. Rhatigan, et al. (2013). "A trial of mercaptopurine is a safe strategy in patients with inflammatory bowel disease intolerant to azathioprine: an observational study, systematic review and meta-analysis." <i>Aliment Pharmacol Ther</i> 38(10): 1255–1266.
3624	Linehan, M. F., U. Nurmatov, et al. (2013). "Does BCG vaccination protect against childhood asthma? Final results from the Manchester Community Asthma Study retrospective cohort study and updated systematic review and meta-analysis." <i>J Allergy Clin Immunol</i> .
4455	Nouri, K., M. Demmel, et al. (2013). "Prospective cohort study and meta-analysis of cyclic bleeding after laparoscopic supracervical hysterectomy." <i>Int J Gynaecol Obstet</i> 122(2): 124–127.

Reason for exclusion:

No observational studies ($n = 4$)

Study ID	Reference of included citation
946	Cates, C. J. and B. H. Rowe (2013). "Vaccines for preventing influenza in people with asthma." <i>Cochrane Database Syst Rev</i> 2: CD000364.
2240	Gouya, G., J. Arrich, et al. (2013). "Antiplatelet Treatment for Prevention of Cerebrovascular Events in Patients With Vascular Diseases: A Systematic Review and Meta-Analysis." <i>Stroke</i> .
6484	Wang, C. H., C. H. Huang, et al. (2013). "Biphasic versus monophasic defibrillation in out-of-hospital cardiac arrest: a systematic review and meta-analysis." <i>Am J Emerg Med</i> 31(10): 1472–1478.
4859	Pineda, A. M., F. O. Nascimento, et al. (2013). "A meta-analysis of transcatheter closure of patent foramen ovale versus medical therapy for prevention of recurrent thromboembolic events in patients with cryptogenic cerebrovascular events." <i>Catheter Cardiovasc Interv</i> .

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Reason for exclusion:

Not published in 2013 ($n = 4$)

Study ID	Reference of included citation
179	Almenawer, S. A., F. Farrokhyar, et al. (2013). "Chronic Subdural Hematoma Management: A Systematic Review and Meta-analysis of 34829 Patients." <i>Ann Surg</i> .
3159	Klatte, T., S. F. Shariat, et al. (2013). "Systematic review and meta-analysis of perioperative and oncological outcomes of laparoscopic cryoablation versus laparoscopic partial nephrectomy for the treatment of small renal tumors." <i>J Urol</i> .
5708	Sligl, W. I., L. Asadi, et al. (2013). "Macrolides and Mortality in Critically Ill Patients With Community-Acquired Pneumonia: A Systematic Review and Meta-Analysis." <i>Crit Care Med</i> .
6482	Wang, C. H., W. H. Hsieh, et al. (2013). "Liberal Versus Restricted Fluid Resuscitation Strategies in Trauma Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials and Observational Studies." <i>Crit Care Med</i> .

Reason for exclusion:

Individual Patient Data meta-analysis ($n = 2$)

Study ID	Reference of included citation
5616	Simmonds, M. C., J. V. Brown, et al. (2013). "Safety and effectiveness of recombinant human bone morphogenetic protein-2 for spinal fusion: a meta-analysis of individual-participant data." <i>Ann Intern Med</i> 158(12): 877–889.
485	Bazelier, M. T., F. de Vries, et al. (2013). "Risk of fracture with thiazolidinediones: an individual patient data meta-analysis." <i>Front Endocrinol (Lausanne)</i> 4: 11.

Abbreviations

CER: comparative effectiveness research; NRSI: non-randomized studies of interventions; RCT: randomized controlled trial; RoB Tool: Risk of Bias tool.

Competing interests

The authors declare that they have no competing interests.

Authors' contribution

TF was involved in the study conception, study selection, data extraction, interpretation of results, and drafting the manuscript. PR was involved in the study conception, interpretation of the results, and drafting the manuscript. CR was involved in data extraction. EP was involved in data analysis. AD was involved in the study conception, interpretation of the results, and drafting the manuscript. All authors read and approved the final manuscript.

Acknowledgements

Philippe Ravaud is director of the French EQUATOR Centre and a member of the EQUATOR Network Steering Group.

Sources of funding

The researchers did not receive external sources of funding.

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Received: 14 October 2015 Accepted: 15 March 2016

Published online: 22 March 2016

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