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Citation networks of related trials are often disconnected: implications for bidirectional citation searches

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Abstract

Background and Objectives: Reports of randomized controlled trials (RCTs) should set findings within the context of previous research. The resulting network of citations would also provide an alternative search method for clinicians, researchers, and systematic reviewers seeking to base decisions on all available evidence. We sought to determine the connectedness of citation networks of RCTs by examining direct (referenced trials) and indirect (through references of referenced trials, etc) citation of trials to one another.

Methods: Meta-analyses were used to create citation networks of RCTs addressing the same clinical questions. The primary measure was the proportion of networks where following citation links between RCTs identifies the complete set of RCTs, forming a single connected citation group. Other measures included the number of disconnected groups (islands) within each network, the number of citations in the network relative to the maximum possible, and the maximum number of links in the path between two connected trials (a measure of indirectness of citations).

Results: We included 259 meta-analyses with a total of 2,413 and a median of seven RCTs each. For 46% (118 of 259) of networks, the RCTs formed a single connected citation group—one island. For the other 54% of networks, where at least one RCT group was not cited by others, 39% had two citation islands and 4% (10 of 257) had 10 or more islands. On average, the citation networks had 38% of the possible citations to other trials (if each trial had cited all earlier trials). The number of citation islands and the maximum number of citation links increased with increasing numbers of trials in the network.

Conclusion: Available evidence to answer a clinical question may be identified by using network citations created with a small initial corpus of eligible trials. However, the number of islands means that citation networks cannot be relied on for evidence retrieval.

Keywords: Citation networks; Systematic reviews; Searching; Clinical trials; Meta-analysis; Network analysis

1. Introduction

Medical research, and science more generally, is built step by step on previous work; new trials might replicate, improve, and/or extend earlier research. Although this evolutionary process is not strictly linear, it should be reflected in a citation network—the trial references (direct citation) and the references of these references (indirect citation). However, we know that new trials cite only a small proportion of similar previous trials [1] and rarely set their conclusions in the context of a systematic review of previous work [2]. Instead, new studies are usually highly selective in citing previous research.

The structure and pattern of direct and indirect citations is important to understand whether and how new trials build on previous work and set their new findings in the context of previous research. The network of citations also has implications for those seeking all available evidence, where the references to previous trials may be found from currently identified studies. Citation network–based

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What is new?

Key Finding

- Trials providing evidence about a particular question may be identified by using network citations created with a small initial corpus of relevant trials. However, the number of citation islands means that citation networks cannot be relied on for evidence retrieval.

What this adds to what is known?

- Less than half of RCTs can be identified by searching citation networks. Amongst the other half, there are diminishing returns using citation-based searching because of the asymmetry of islands.

What is the implication, what should change now?

- Our results suggest that one cannot rely solely on the searching of citations lists to identify relevant trials. However, citations may be a useful supplement in comprehensive searching, with a key advantage being that such searching goes beyond the electronic databases searched.

expansion may be part of a solution to providing evidence at the point of care [3]. If trials on a particular topic formed a connected network of citations, it may provide a supplementary search method [4].

We sought to determine how well connected the citation networks were and how often they were divided into separate citation "islands" that failed to cross refer to each other. Citation mapping or network analysis of citations has been used previously to study bibliometric questions such as the relationship of specific documents [5] or citation bias in specific fields or questions [6]. We analyzed citation networks of trials addressing the same question to determine the feasibility of a novel search network.

2. Methods

2.1. Data collection

We used an existing data set of cohorts of randomized controlled trials (RCTs) addressing the same health-care research questions [1]. These data were created by searching the Web of Science for systematic reviews published in 2004 that combined three or more RCTs in a meta-analysis (MA). The data set comprises the RCTs included in the selected MAs, as well as the references those trials cited.

2.2. Network analysis

For each MA, we created a citation network where RCTs are represented as nodes and RCTs citing other RCTs are represented as directed edges. The *size of a network* is the number of RCTs included in the MA. We calculated the *density* of each citation network—defined as the number of citations in the network as a proportion of the total possible number of citations. The total possible number of citations is calculated assuming a standard definition of chronology—RCTs could only cite other RCTs that have already been published.

In each network, we counted the *number of citation islands*—where an island is defined as a set of one or more RCTs that are linked to at least one other node in the set, thus linking (directly or indirectly) all RCTs in the set. The *size of an island* is the number of RCTs in the island. Thus, in networks that consist of only one island, the size of the island is equal to the number of RCTs in the network.

We examined the topology of the citation networks of RCTs using a bidirectional citation search. This enumerated every possible path between all pairs of RCTs in an MA. The *maximum path length* is the maximum number of citation steps between two connected RCTs. This metric indicates the maximum depth of the search required to find all RCTs in an island. As a consequence, this metric is most appropriate for networks comprising only one island as the path length between RCTs on separate islands is infinite.

The *expected coverage* is the average proportion of RCTs that can be reached by each RCT in the network. This metric indicates the ability to identify RCTs via citations. The value was calculated by traversing the network from every RCT to every other reachable RCT along citation paths. The proportion of RCTs that can be reached from each RCT in turn gives the reach of each RCT, and the average reach is then the expected coverage in the network.

3. Results

Our data set included 259 MAs with a total of 2,413 RCTs and a median network size of seven RCTs (range, 3–59). The journals of publication for the MAs represented a variety of disciplines: oncology (12%), general medicine (16%), and cardiology (19%) were the disciplines with the largest proportion of MAs. Fig. 1 illustrates 4 of these 259 citation networks, showing different patterns of connectedness.

The citation networks constructed for each of the MAs exhibited differences in fragmentation, which were illustrated by the *number of citation islands* in the networks. For 46% (118 of 259) of networks, the RCTs formed a single connected citation group—a single island (as in Fig. 1A). For these networks, every RCT could be reached from every other RCT by following a chain of citations. Of the 54% of networks that did not form a single connected network, 39% had only two islands (Fig. 2). However, 4% (10 of 257) of networks had 10 or more separate citation islands.

The four MAs in Fig. 1 illustrate citation networks with 1, 2, 8, and 23 islands, respectively. The trials of

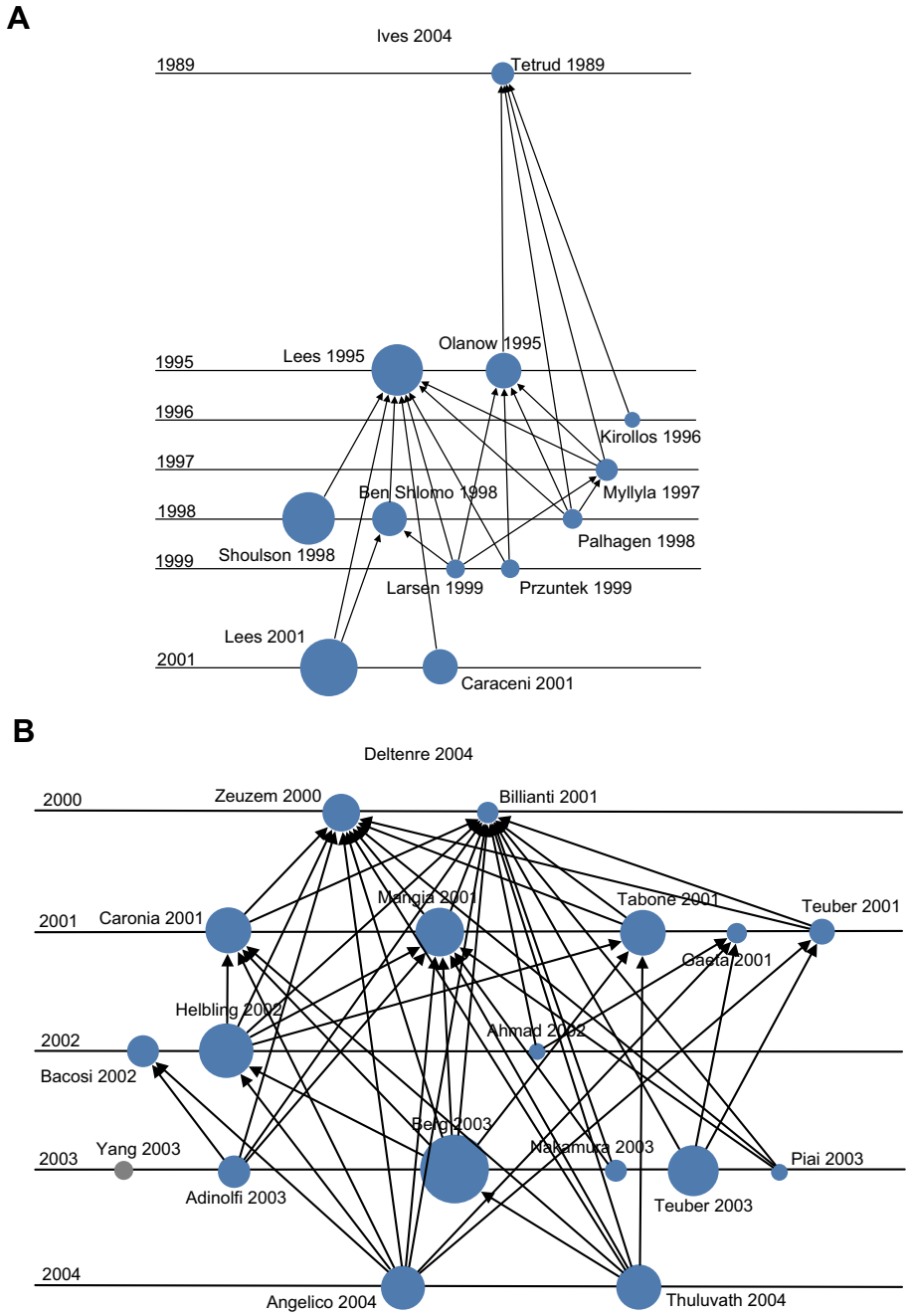
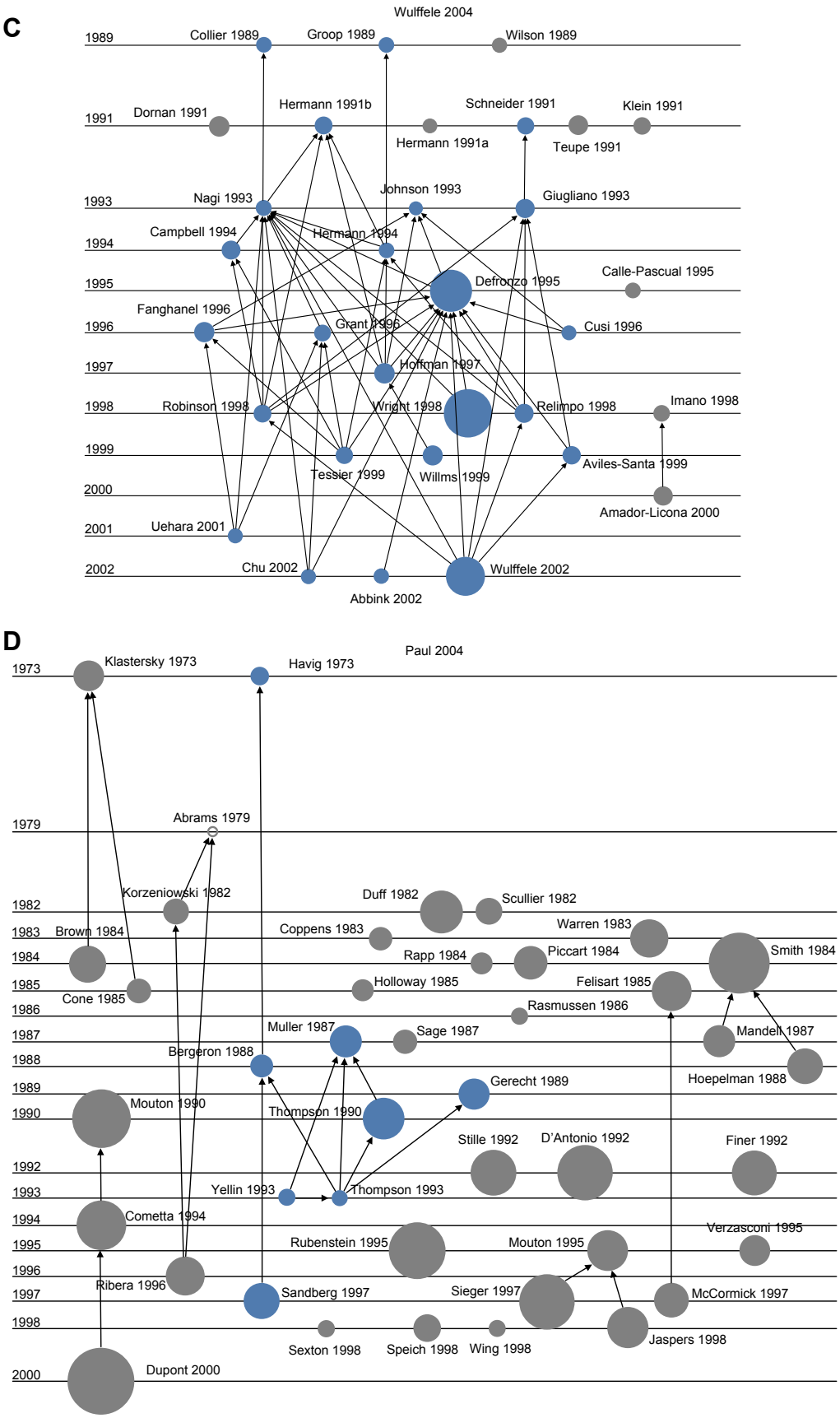


Fig. 1. Citation networks for four meta-analyses, with increasing levels of disconnectedness. Trials are ordered by year, connected by citations, and the areas of the nodes represent their weight (size) in the meta-analysis. The networks are (A) Ives [22]: a weakly connected network; (B) Deltenre [23]: a weakly connected network with a single disconnection; (C) Wulffelé [24]: a weakly connected core and a periphery of islands that are not connected to the core and mostly not connected to each other; and (D) Paul [25]: an archipelago structure without an obvious weakly connected core.

Monoamine Oxidase Inhibitors for Parkinson's disease (Fig. 1A) formed a single connected network with the first trial cited by four subsequent trials but with two later larger trials (one from the United States and one from the United Kingdom) then becoming the dominantly cited studies (one with eight citations). The 20 trials for amantadine for hepatitis C (Fig. 1B) formed a well-connected network, except for one isolated Taiwanese trial that neither cited any of the previous nine trials nor was cited by the later 10 trials. The network for the effect of metformin on cardiovascular risk factors (Fig. 1C) was more fragmented with eight separate citation islands: one large island of 23 trials, one of two trials, and six isolated trials. This fragmentation may be partly explained by the different end points of the studies—blood pressure and lipids. The two earliest studies (1989) examined lipids,



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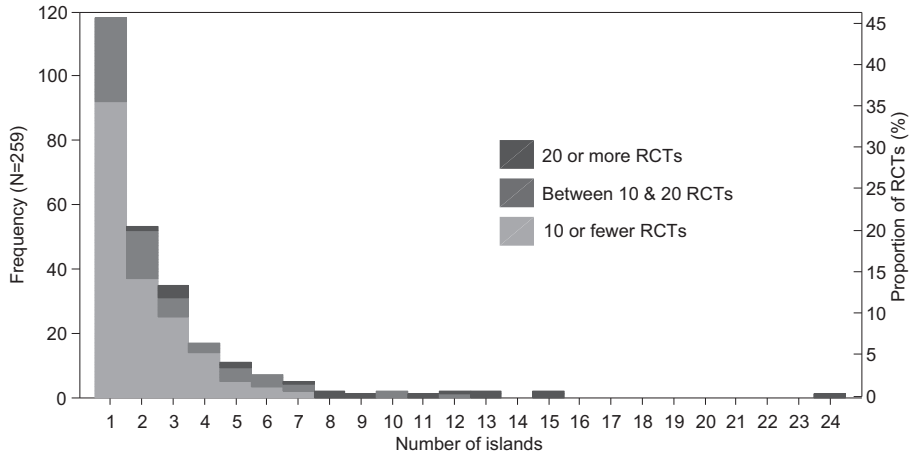

Fig. 2. The distribution of the number of islands represented among the 259 meta-analyses shows that most meta-analyses are represented by one or two islands. In the histogram, meta-analyses are shaded by the number of trials; meta-analyses with a large number of islands also tend to include a larger number of trials. RCT, randomized controlled trial.

whereas some of the trials from 1991 examined only blood pressure. This difference may help to explain the noncitation of the earlier trials, but it does not explain why they were not cited in subsequent studies. The most fragmented network was a review of trials of antibiotics in sepsis that examined the addition of beta-lactam to aminoglycoside alone (Fig. 1D). Given the number of possible combinations of these two classes of antibiotics, some degree of lower citation is perhaps understandable, but that all trials refer to either none or only one other trial was somewhat surprising.

Trials do not cite all possible previous trials. The *average density* of the citation networks was 0.38 (Table 1). The networks on average have three-eighths of the possible citations to other trials (if each trial cited all previous trials). As illustrated by Fig. 1B and C, when there is more than one island in the network, the typical network topology is that of a larger core and a periphery of disconnected islands.

For the 46% (118 of 256) of MAs with a single connected citation group or island, the *expected coverage* was, by definition, 100%—that is, all trials in the MA are connected through a chain of citations. For the remaining 141 MAs, the expected coverage ranged between 7.4% and 92%. The expected coverages across these 141 MAs were uniformly distributed within this range. The degree of fragmentation and the *maximum path length* increased with increasing numbers of trials in the MA (Fig. 3A and B). This was consistent with the lower citation density as the number of trials increases (Fig. 3C).

4. Discussion

Our findings confirm and extend previous work suggesting that most trials do not cite prior relevant trials [1,2]. This is known for direct citation, but we found this is also true of indirect citation: fewer than 50% of the cohorts of trials formed a single completely connected network of citations. Although the citation pattern even within connected networks appears suboptimal, more problematic is the lack of any cross-citation between sets of related trials in around half the MAs. The number and sizes of islands constrain the ability for a citation-based search to identify relevant RCTs and indicate the presence of potential disconnections between old and new studies attempting to answer the same clinical questions.

Strengths of this work include the large number of MAs (networks) and the diversity of health-care questions, disciplines, and sources. There are some limitations. First, we used the Web of Science to identify the MAs and the RCTs included in those MAs. Some networks are thus not

Table 1. Network metrics for four selected meta-analyses and across all 259 meta-analyses

Meta-analysis	Size	Density (%)	Islands	Largest island (%)	Maximum (noninfinite) path length	Expected coverage (%)
Ives [22]	12	30	1	100	5	100
Deltenre [23]	18	30	2	94	4	90
Wulffelé [24]	32	10	8	75	6	57
Paul [25]	42	2	24	19	4	7
All MAs						
Median	7	33	2	80	3	86
IQR	5–11	18–54	1–3	67–100	3–4	50–100

Abbreviations: MA, meta-analysis; IQR, interquartile range.

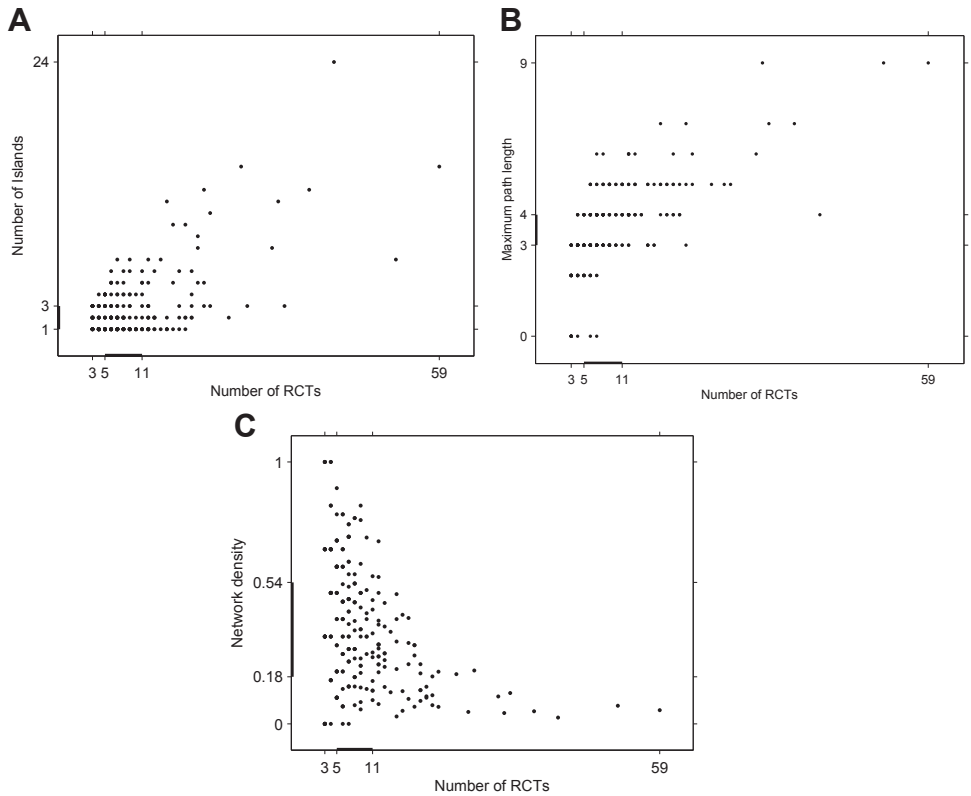

Fig. 3. Three scatter plots indicate the relationship between the number of trials in a meta-analysis and (A) the increasing number of islands as an indicator of disconnectedness, (B) the increasing maximum path length as a measure of information turnover and chronology, and (C) the increasingly constrained network density. RCT, randomized controlled trial.

complete as one or more of the RCTs from the MA are not included in our data set. Given the relatively small number of RCTs missing per network, it is not likely that these missing RCTs would substantively change our results. Another limitation is that a trial could have cited systematic reviews rather than individual prior trials. We did not check this as other studies have suggested few trials cite up-to-date systematic reviews [2].

A previous analysis of this set of MAs suggested that authors cite less than a quarter of citable relevant trials and that the median number of prior cited trials was two, with no increase as the number of citable trials increased [1]. Similarly, using a different metric, we found that the networks of RCTs had on average three-eighths of the possible citations to other trials.

The few trials that are selected to cite are likely selected in a biased manner. Trials are more likely to be cited if they report statistically significant results [7–9], if the authors are from the same country [10], and other reasons unrelated to the strength of evidence available from the prior trial [11–16].

Despite limited citation of prior trials, checking references of eligible studies does lead to the identification of additional relevant studies for systematic reviews. A Cochrane review of 12 studies found that reference checking yielded between 3% and 43% additional references beyond the standard search methods [4]. Greenhalgh and Peacock [17] assessed the relative contributions of sources for studies to a non–health-care systematic review. Forward citation tracking identified 7% of the articles included in the systematic review, whereas scanning reference lists of included articles provided the highest yield, identifying 44% of the articles ultimately included in the review. One study of health-related reviews examined sensitivity and precision of types of extended search methods in identifying RCTs for two systematic reviews [18,19]. For both the reviews examined, scanning reference lists of eligible articles retrieved about a third of the trials subsequently deemed eligible for inclusion.

Our results suggest that one cannot rely solely on the searching of citation lists to identify relevant trials. As noted earlier, citations may be a useful supplement, with a key advantage being that such searching goes beyond the electronic databases searched. However, our results suggest that there is a need to complete more than one cycle forward and backward in citation searching. The number of cycles depends on the path length in the network of related trials, something not known at the time of searching. In general, per findings in Table 1, four steps in any direction may be needed. The feasibility and the number of cycles typically required for this process is an interesting future research question. We recommend that the cycle of forward and

backward citation searching be repeated as long much as possible or until no more eligible studies are identified. This research, along with related work such as examining techniques to estimate search completeness [20,21], has the potential to make the increasingly burdensome task of conducting searches for systematic reviews more efficient.

Future research is needed to identify possible predictors of connectedness. In this and the prior work by Robinson and Goodman [1], the size of the trial seems to influence citation with bigger trials being cited more. However, this does not explain the variation across the MAs we examined. Other variables to be explored include elements of the research question—in particular the complexity of the interventions and comparisons, the weight or direction of effects, and the statistical significance of results.

5. Conclusions

Trials providing evidence about a particular question may be identified by using network citations created with a small initial corpus of relevant trials. However, the number of citation islands means that citation networks cannot be relied on for evidence retrieval.

Less than half of RCTs can be identified by searching citation networks. Among the other half, there are diminishing returns using citation-based searching because of the asymmetry of islands. For users of the health literature, it seems clear that the reports of trials are not set in the context of all relevant studies [1,2]. To paraphrase Clarke et al., reports of (many) trials seem to indeed be orphans or broken branches in the family tree of evidence.

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