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Review Article

Effectiveness of different topical treatments in the healing of pressure injuries: A network meta-analysis

Running title: Treatment for pressure injuries

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Abstract

Objectives: Pressure injuries (PIs) are one of the most common types of complex wounds and impose a huge economic burden to the healthcare system and the patients. A plethora of topical treatments is widely available for PI treatment, yet there is a paucity of evidence with regards to the most effective treatment. The objective of this study was to compare the effect of various topical treatments and identify the best treatment choice(s) for PI healing.

Design: Systematic review and network meta-analysis.

Setting and Participants: All published randomized controlled trials that compared the effectiveness of two or more of the following dressing groups: basic, foam, active, hydroactive, and other wound dressings.

Measures: The outcome was the relative risk (RR) of complete healing following treatment and the generalised pair-wise modelling framework was used to generate mixed treatment effects against hydroactive wound dressing, currently the standard of treatment for PIs. All treatments were then ranked by their point estimates.

Results: 40 studies (1,757 participants) comparing 5 dressing groups were included in the analysis. All dressings groups ranked better than basic (i.e. saline gauze or similar inert dressing). The foam (RR 1.18; 95%CI 0.95-1.48) and active wound dressing (RR 1.16; 95%CI 0.92-1.47) ranked better than hydroactive wound dressing in terms of healing of PIs when the latter was used as the reference group.

Conclusions/Implications: There was substantial uncertainty around the point estimates; however, evidence from our analysis supports the use of hydroactive wound dressings to replace basic dressings. Foam and active wound dressing groups seem promising and therefore need further investigation. High-quality, rigorously conducted research about the clinical effectiveness of the topical treatments in these two groups developed in consultation with health professionals, patients, and their carers is needed to identify if indeed foam and active wound dressings provide advantages over hydroactive dressings.

Introduction

Pressure injuries (PI),[1] also known as pressure ulcers or bed-sores, are wounds involving the skin and sometimes the tissue on bony parts of the body, often occurring over bony prominences such as the sacrum and heel.[2] They are caused by a combination of pressure, shear, and friction that leads to microcirculatory occlusion, resulting in stimulation of inflammatory processes.[2] This in turn can lead to cell death, ulceration, and tissue necrosis.[3] PIs can have a significant impact on those affected, as they can cause pain and infection which can increase patient's hospital length of stay and significantly decrease their health-related quality of life.[4] People at high risk of developing PIs include those with limited mobility such as older people, people with short or long-term medical conditions, and those with spinal injuries.[5] Lack of mobility, reduced sensory perception, poor nutrition, and hydration as well as lack of blood flow can all increase the risk of developing PIs.[5] Development of PI can be rapid and lead to irreversible tissue damage in vulnerable patients after as little as 30 minutes of uninterrupted pressure.[6]

Globally, PIs are one of the most common types of complex wounds. An estimated 2.5 million people are affected annually in the US alone.[7] A large European pilot study estimated the hospital PI point prevalence to be 10.5%.[8] National PI data collected in the UK's National Health Service (NHS) reported a prevalence of 4.2% across community and acute care settings in September 2017,[9] although the study could have underestimated the actual prevalence of PIs in the UK due to the low sensitivity of the tool used to identify the cases.[10,11] Prevalence of PIs can vary according to setting and can be as high as 26% in some settings such as long-term, acute-care, and rehabilitation settings.[12]

Managing PIs can be expensive. Annual health care costs associated with PIs in the UK in 2012/13 were estimated to be in the range GBP 4.5 to 5.1 billion.[13] In the USA in 2014 alone, treatment for PIs were estimated at USD 9.1 to 11.6 billion annually with 2.5 million people affected and approximately 60,000 deaths resulting from PIs.[14] The total costs to the Australian healthcare system for treating PIs have been estimated at AUD 1.8 billion annually or 9% of public

hospital expenditure.[15] Although dated, these cost-estimates provide an insight about the substantial financial burden PIs represent within contemporary health contexts.

In terms of the treatment of PIs, there are two major strategies that are currently being employed: 1) the use of pressure-relieving support surfaces (e.g. alternating pressure air mattresses); and 2) management of ulcers using topical treatments such as wound dressings.[16,17] Other general strategies for treating and healing PIs include optimizing circulation/perfusion, improving nutrition and the treatment of clinical infection.[2,16] Topical treatments are widely used to treat PIs, there are a plethora of options to choose from including alginate, hydrocolloid, protease-modulating dressings, topical agents, and other therapies. Despite this, there is paucity of evidence to facilitate decision-making regarding the type of topical treatments that are the most clinically effective. This is despite many published meta-analyses examining effects of dressings, negative pressure wound therapy and topical agents on healing of PIs in mainly adult populations in care settings.[18-22]

A key issue has been the statistical methods used in previous reviews of topical treatments such as hydrogel,[19] alginate,[18] and foam[22] as well as other therapies such as negative pressure wound therapy[20] which only allowed pairwise comparisons. Results from these reviews consistently reported low to very low certainty of evidence from included studies due to high risk of bias (lack of allocation concealment and blind assessment) and imprecision (small studies and incomplete reporting). More significantly, they were unable to provide clear advice on effectiveness of the topical treatment in healing PIs. While we were undertaking this project, an attempt to address this limitation via a network meta-analysis was published.[21] However, the authors of the study were still unable to determine which topical treatments were the most likely to heal PIs because sparseness of their network led to inconclusive results.[23] Our approach differs from the latter in several ways including in the classification of topical treatments, extent of coverage of studies and methodology used which brings much more clarity to this issue and does away with the issue of sparseness.

Methods

Findings of this systematic review and meta-analysis are presented according to PRISMA reporting guidelines.[24]

Search strategy

The original search strategy was designed in PubMed and converted for use in the following databases using the Systematic Reviews Accelerators Polyglot Search Translation module,[25] with no limitations on year or language: CINAHL, Embase, Web of Science, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL). The initial search was conducted on 15th September 2016 and updated on 1st December 2017. Search terms related to pressure injuries, pressure ulcers, topical treatment types, and outcome measurements (i.e. healing) were included. The full search strategy is shown in the supplementary material (S1). In order to achieve a comprehensive evaluation of the published evidence, the systematic search was supplemented with a forwards and backwards citation search as well as retrieving the first 20 similar articles from PubMed for each of the papers included from the searches. We sought additional papers from the reference lists of relevant meta-analyses and review papers.[16,19-21,26,27]

Titles and abstracts of all papers that were extracted by the search engine were uploaded to the Rayyan platform (http://rayyan.qcri.org/) which is a web application developed by Qatar Computing Research Institute (Data Analytics).[28] Five authors (LFK, RW, BG, SD and LT) independently screened the titles and abstracts on the Rayyan platform. Any disagreements were resolved through author consensus. Additionally, LFK and RW examined the full-text papers for eligibility against the review protocol. Disagreements were resolved through consensus and by involvement of a third author (BG).

Selection criteria

Eligible studies were published and unpublished randomized controlled trials (RCTs) that enrolled patients with stage 2-4 PIs and compared the effectiveness of two or more of the following

13 narrow topical treatment categories: antimicrobial, basic (i.e. gauze with normal saline), collagenase, collagen, combined treatment (i.e. when multiple active components were included), film, foam (i.e. lyofoam, polyurethane), growth factors, hydrocolloid, hydrogel, moisture retentive (i.e. calcium alginate), negative pressure, and radiant heat. These dressings were selected because they were either:1) identified in the literature as wound care products used for the treatment of PIs; 2) available to clinicians for use in routine practice; 3) recommended by international clinical guidelines;[2] or 4) under investigation as an experimental or alternative dressing for the treatment of PIs. Dressings were grouped according to their dominant element. The network using these 13 narrowly defined topical treatment categories initially selected was noted to be sparse. The key issue with this is that networks that are not well connected may provide unreliable estimates and rank treatment options incorrectly and/or may lead to inconsistent ranking of the dressing when the reference category changes.

For these reasons a parallel analysis using a broader classification based on mechanisms of action provided by Horn[29] was conducted. This classification defined five dressing groups as follows: Basic wound dressing (i.e. inert materials like saline gauze), hydroactive wound dressing (i.e. hydrocolloid, hydrogel, moisture retentive dressings), foam dressing, active wound dressing (i.e. collagen, growth factors), and other wound dressing (i.e. antimicrobial, collagenase, film, negative pressure, radiant heat) to achieve a network that was not sparse. These two classifications are given in table 1.

Studies were also excluded if they assessed effectiveness more than one year post-treatment or included other types of wounds (e.g. chronic wound and venous leg ulcers). Because we used a pair-wise modelling approach (described below), if studies compared an odd number of eligible treatments, we selected a pair (or multiple pairs) of treatments for inclusion in meta-analysis. In such cases, we prioritised the inclusion of treatments with the lowest dose and that are currently in widespread use for PI healing over novel treatments.

Data extraction

Data extraction was performed by LFK and RW. We extracted the year and country of study; study population topical treatment names, types and schedules; sample size; number of people "healed" and "not healed" after treatment; and follow-up time. If a study compared the same intervention in both arms, it was assumed that the effect of such an intervention cancelled itself from both arms (e.g. a RCT compared hydrocolloid + hydrogel against hydrocolloid + collagen, it was considered as hydrogel compared to collagen) and dressings were classified accordingly to the remaining active ingredients.

Quality assessment

Quality of included studies was assessed using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials.[30] This scale assessed studies for risk of bias using items related to random sequence generation, allocation concealment, selective reporting, blinding, incomplete data, and attrition rate (supplementary material S2).

Statistical analysis

We aimed to examine healing rate; that is the proportion of treated individuals whose PIs healed completely based on the cure criteria, where reported in each study. The outcome calculated for each study was the relative risk (RR) of cure following topical treatment. We used an automated generalised pair-wise modelling (GPM) framework[31] to generate mixed treatment effects against basic dressings, currently the simplest standard treatment. This framework requires no additional assumptions other than that of transitivity, and uses an automated process to extend the previously reported Bucher method[32] for single three-treatment loops. The method involves: (1) pooling effect sizes for direct comparisons between each combination of two treatments using meta-analysis; (2) performing indirect comparisons by automated generation of all possible closed loops of three treatments such that one is common to two studies; and (3) pooling all direct and indirect effects

using meta-analysis to give a final effect size comparing each treatment to the common comparator. To pool estimates, we used the inverse variance heterogeneity model, which uses a quasi-likelihood based variance structure without distributional assumptions and has been shown to perform better when compared to the random effects method.[33] For comparison, all analyses were re-run using the random effects model within a multivariate frequentist framework.[34]

We assessed statistical heterogeneity across pooled direct effects using Cochran's *Q* and the *H* index. The *H* index is the square root of H^2, the estimated residual variance from the regression of the standardized treatment effect estimates against the inverse standard error in each direct meta-analysis. *H* was computed as follows:

$$H = \sqrt{\frac{\max\left[\max(1,n-1),Q\right]}{\max(1,n-1)}},$$

where *n* is the number of study estimates and Q represents the Chi squared from Cochran's *Q*. Transitivity across the network was assessed by examining inconsistency across the network using the weighted pooled *H* index ($\bar{H}$), which was computed from Cochran's *Q* as follows:

$$\bar{H} = \sqrt{\frac{\sum_{j=1}^{k} \max\left[\max(1,n-1),Q\right]}{(\sum_{j=1}^{k} n)-k+s}},$$

where *n* is the number of estimates pooled across each comparison and *s* is the number comparisons (out of *k*) where *n*=1. The minimum value *H* or $\bar{H}$ can take is 1. $\bar{H} < 3$ was taken to be minimal inconsistency based on our simulations in homogenous direct meta-analyses.

Sensitivity analyses were performed based on restricting the network to studies that examined efficacy within 6-12 weeks and to assess the impact of the risk of bias on the results (using a quality effects model[35]).

Publication bias was assessed using 'comparison-adjusted' funnel plots, that plots the difference of each study's observed *ln(RR)* versus the comparison's mean *ln(RR)* obtained from meta-analysis on the horizontal axis. In the absence of small-study effects, studies are expected to form an inverted funnel centred at zero.[36]

All analyses involved in the generalised pair-wise modelling (GPM) framework were conducted using MetaXL version 5.3 (EpiGear Int Pty Ltd.; Brisbane, Australia) developed by one of us (SD). Funnel and network plots were created in Stata version 14.1 (College Station, TX, USA).

Role of funding sources

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Results

Identified studies

Database searches, forwards and backwards citation search, and retrieving the first 20 similar articles from PubMed identified 2496 studies that were initially screened by title and abstract, from which 172 potentially relevant papers were selected. Of these, 44 met the inclusion criteria for the systematic review and were included in the network meta-analysis (Figure 1).

Characteristics of included studies

The 44 included studies were published between 1983 and 2015. Studies were conducted in Asia (2 countries [Korea and Iran], 2 studies), North America (1 country [USA]; 21 studies), and Europe (10 countries [Denmark, Finland, France, Germany, Italy, Netherlands, Poland, Spain, Sweden, and UK]; 21 studies).

Twenty studies had a comparison to basic dressing, and 31 studies to a hydroactive dressing; representing the two most common topical treatments. The remaining studies had a variety of topical treatment types. Complete healing was assessed at a median follow-up of 8 weeks (IQR 6.5 – 13 weeks) with a range of 1.5 – 52 weeks (Table 2).

Included topical treatments

A total of 13 topical treatment categories and 5 dressing wound groups were included in the network meta-analyses. Topical treatments within the same category were deemed exchangeable (Table 2). Figure 2A and 2B depict the network plot showing the comparison groups for each study.

Quantitative synthesis

Based on 44 studies examining treatment of PIs, when basic dressing was used as the reference treatment category, all topical treatment categories were found to have a better rank than basic dressing being negative pressure, film, and combined treatment the ones with the biggest effect size. Combined treatment (RR 1.88; 95%CI 1.08-3.25) was found to be the only dressing

category to have statistically significant improvement in healing when compared to basic dressings (Figure 3A). When hydrocolloid was used as the reference category in the analysis, the ranking of the dressing categories dramatically changed (Figure 3B). It is clear from the results that the network with 13 dressing categories was sparse, the point estimates were not reliable, and the ranking of the treatments was not stable. This analysis was not informative and therefore we proceeded with the next analysis.

When the analysis was carried-out using the 5 wound dressing groups as defined by Horn;[29] 40 studies were included, 4 studies[37-40] were excluded because they compared wound dressings within the same group. The basic wound dressings was used as the reference group, all dressings groups were better in rank than basic dressings. In ascending order of efficacy based on the point estimate, the ranking was other, hydroactive, active, and foam dressings and only the latter being statistically significantly better (Figure 4A). The ranking of dressing groups remained unchanged when the hydroactive dressings was used as the reference (Figure 4B and supplementary material S3) revealing a stable (non-sparse) network with reliable results.

Analysis using a conventional approach (i.e. multivariate frequentist framework) did not alter the ranking nor the pooled estimates significantly, but differed in terms of error estimation (confidence intervals) (supplementary material S4).

Sensitivity analysis and assessment of bias

Sensitivity analysis restricting the network to studies that assessed healing between 6-12 weeks after treatment (n=28), showed that the results remain robust to these changes in the selection criteria revealing that foam, active wound dressing, and hydroactive wound dressing are the only treatment options (supplementary material S5).

The most common deficiencies in safe-guarding against bias were: participants and personnel not blind to study group allocation (6 studies) or not clearly stated (354 studies); allocation concealment not properly conducted (4 studies) or not stated (32 studies); and outcome

assessors not blind to study group allocation (6 studies), or not stated (26 studies) (supplementary material S2). Results after application of the quality effects model[35] were not different to the main results (supplementary material S6).

Comparison-adjusted funnel plots (supplementary material S7) demonstrated little evidence of asymmetry. There was minimal inconsistency across treatment networks, with $\bar{H}$ = 1.20. There was little inconsistency across direct and indirect effects (H<3.0) for each of the treatment comparison pairs, including when the network was restricted in sensitivity analyses.

Discussion

The results of the network meta-analysis that included 40 RCTs involving 1,757 participants, comparing five dressing groups revealed that foam and active dressings are the most effective treatments for healing PIs. While the effect size of all dressing groups was higher than basic wound dressings, the uncertainty was also high, which means that these results need confirmation.

A major issue in the recent network meta-analysis may have been the approach the researchers used to grouping PI topical treatments leading to a sparse network,[23] and we avoided this by creating groups of tentatively similar mechanisms of action. Another key strength of the current study is the use of the GPM framework which does not require assumptions that are not stated explicitly or cannot be verified when the method is applied. In comparison, the multivariate frequentist framework commonly used in other network meta-analyses[21] assumes that if there is no common comparator in the network, this then has to be handled by augmenting the dataset using fictional arms with high variance. This requires a decision as to what constitutes a sufficiently high variance and therefore may not always be impartial.[41] Additionally, the GPM framework has fewer assumption (i.e. transitivity and independence of treatment effects between studies) than the multivariate frequentist framework that also requires distributional assumptions as well as augmented datasets (using fictional study arms of high variance) when studies lack the reference treatment.[34]

The absence of robust research in this area and the extensive heterogeneity of dressings makes it difficult for researchers to provide clear advice to clinicians and decision-makers about safe and effective PI treatment options for patients. While the findings from our analysis contribute to decision-making related to choice of therapy, topical treatments, they should be considered carefully. Given the huge variety of treatment options now available within the health industry, clinicians should also consider contextual factors such as wound characteristics, patient preference and cost. However, the results of this study do indicate that basic dressings should be abandoned in favor of the better options in terms of wound healing.

Despite the methodological strengths of our study, we acknowledge some limitations. Firstly, the topical treatments included in the designated categories may have been developed by different manufacturers, had slightly different compositions, and had variation in duration of interventions between studies. Additionally, the assumption of exchangeability within category was an empirical judgement and should be considered a limitation of this network meta-analysis. Secondly, the network meta-analysis only focused on complete wound healing. Other outcomes such as time to complete healing, reduction in ulcer size, adverse events, cost, and patient quality of life should also be considered in future analyses.

Conclusion

Findings from this systematic review and network meta-analysis demonstrate evidence for the discontinuation of use of basic dressings. Hydroactive dressings are the mainstay practice, but our analysis suggests that the use of foam or active wound dressings may be more effective strategies for healing PIs. This should not be considered conclusive and more high-quality, rigorous research about the effectiveness of the dressings within these two groups is needed to confirm if these are indeed better than the current standard of hydroactive dressings.

Contributors' statement

RW, BG, SD, and LT conceived and designed the review protocol. JC built the search strategies and performed the database search. LFK and RW screened the articles. LFK, RW, BG, and SD assisted with the data extraction and quality assessment. LFK, RW, SD, and LT conducted the statistical analysis and/or drafted the initial version of the manuscript. All authors contributed to editing and revising the manuscript. All authors approved the final version of the manuscript.

Declaration of interests

The authors declare no competing interests.

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Figures titles

Figure 1. PRISMA flow diagram of study selection for quantitative synthesis

Figure 2. Network plot showing the A) 13 topical treatment categories and B) 5 wound dressing groups. The circle size is proportional to the number of arms while the width of the lines is proportional to the number of pairs.

Figure 3. Network forest plot baseds on 44 studies ranking comparisons based on their relative risk for wound healing using A) basic and B) hydrocolloid as the reference topical treatment category. When the reference treatment category changes, the ranking changes as well due to sparseness in the network making these results unreliable.

Figure 4. Network forest plots based on 40 studies ranking comparisons based on their relative risk for wound healing using A) basic and B) hydroactive as the reference dressing group. This network is non-sparse and stable, thus rankings remain reliable when the reference dressing group changes.

524 **Table 1.** Classification of the dressings

Topical treatment categories		Wound dressing groups		Description
BAS	Basic (e.g. saline gauze, placebo)	BWD	Basic	Inactive dressings can pick up secretions from the wound, but do not create a specific microenvironment that promotes wound healing.
HCD	Hydrocolloid (e.g. DuoDerm, Comfeel Plus, Tegaderm)	HWD	Hydroactive	Hydroactive wound dressings accelerate wound healing by altering the microclimate of the wound and imitating the physiological process to form a moist wound environment.
HGD	Hydrogel (e.g. Askina Transorbent, BioFilm hydrogel, Acemannan hydrogel)			
MRD	Moisture retentive (e.g. UrgoSorb, Aquacel)			
FOA	Foam (e.g. Epi-Lock dressing, Allevyn hydrocellular foam, Spyrosorb)	FOA	Foam	Foam dressings absorb wound exudate, insulate the wound and provide a moist wound healing environment.
COL	Collagen (e.g. Promogran, Medifil Collagen Particles)	AWD	Active	Active dressings have a defined mechanism of action through which they intervene in the patho-physiological processes in the wound by substitution / suppression or alteration of factors.
GRF	Growth factor (e.g. Dermagraft, Transforming growth factor beta-3, Recombinant platelet-derived growth factor-BB)			
AMD	Antimicrobial (e.g. Cadexomer iodine, povidine soaked wet gauze, Dakin's solution)	OWD	Other	Wound dressings with other mechanisms of action.
CLD	Collagenase (e.g. Iruxol mono ointment)			
FIL	Film (e.g. 3M Tegaderm Absorbent Clear Acrylic Dressing)			
NPD	Negative pressure (e.g. V.A.C. therapy system)			
RHD	Radiant heat (e.g. Augustine Medical warm-up)			
COM	Combined – multiple active compoenents	Classified in a dressing group depending on the type of combination of the active ingredients.		

- Topical treatment categories: AMD antimicrobial; BAS basic; CLD collagenase; COL collagen; COM combined treatment; FIL film; FOA foam; GRF growth factor; HCD hydrocolloid; HGD hydrogel; MRD moisture retentive; NPD negative pressure; RHD radiant heat.
- Wound dressing groups: AWD active; BWD basic; FOA foam; HWD hydroactive; OWD other wound dressing.

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Table 2. Characteristics of the included studies

Serial number	First author and year of publication	Study location	Follow-up duration	Topical treatments	Topical treatment category	Wound dressing group	Number of participants (healed/ treated)	Criteria for complete healing
1	Alm (1989)[42]	Sweden	6 weeks	- Hydrocolloid - Saline gauze	HCD BAS	HWD BWD	17/31 4/25	Area of the PI equal to zero
2	Anguilo-Sanchez (2001)[43]	Spain	7 weeks	- Alginate and hydrocolloid - Saline gauze	COM BAS	HWD BWD	20/35 10/35	Not reported
3	Ashby (2012)[44]	UK	26 weeks	- Hydrocolloid, alginate - Negative pressure dressing	COM NPD	HWD OWD	0/6 1/6	Epithelialisation and cessation of treatment to achieve healing
4	Bale (1997)[45]	UK	4 weeks	- Polyurethane foams - Hydrocolloid	FOA HCD	FOA HWD	7/29 5/31	Not reported
5	Banks (1994a)[46]	UK	6 weeks	- Semi-permeable polyurethane dressing - Hydrocolloid	FOA HCD	FOA HWD	11/13 10/16	Not reported
6	Banks (1994b)[47]	UK	12 weeks	- Polyurethane dressing - Hydrocolloid	FOA HCD	FOA HWD	12/20 10/20	Not reported
7	Belmin (2002)[48]*	France	8 weeks	- Hydrocolloid - Calcium alginate and hydrocolloid	BAS MRD	BWD HWD	31/53 43/57	Surface area reduction ≥40%
8	Brod (1990)[37†]	USA	8 weeks	- Polyhema dissolved in polyethylene glycol - Hydrocolloid	HGD HCD	HWD HWD	14/27 10/16	Not reported
9	Brown-Etris (1996)[38†]	USA	10 weeks	- Hydrogel - Hydrocolloid	HGD HCD	HWD HWD	39/77 37/77	Not reported
10	Brown-Etris (2008)[49]	USA	8 weeks	- Hydrocolloid - Transparent absorbent acrylic	HCD FIL	HWD OWD	22/37 21/35	Closed PI wounds
11	Burgos (2000)[50]	Spain	12 weeks	- Hydrocolloid - Collagenase ointment	HCD CLD	HWD OWD	3/19 3/18	PI with final surface area of zero
12	Colwell (1993)[51]	USA	12 weeks	- Hydrocolloid wafer dressing - Saline gauze	HCD BAS	HWD BWD	11/33 1/37	PI completely covered with epithelial tissue
13	Darkovich (1990)[39†]	USA	8.5 weeks	- Hydrocolloid - Biofilm hydrogel	HCD HGD	HWD HWD	9/36 12/35	PI wound closure
14	Ford (2002)[52]	USA	6 weeks	- Vaccum assisted closure - Healthpoint system	NPD COM	OWD HWD	2/20 2/15	Not reported
15	Gorse (1987)[53]	USA	11 weeks	- Hydrocolloid - Wet-to-dry dressing with Dakin solution	HCD AMD	HWD OWD	54/76 26/52	Not reported
16	Graumlich (2003)[54]	USA	8 weeks	- Hydrocolloid - Collagen	HCD COL	HWD AWD	15/30 18/35	Not reported
17	Hirshberg (2001)[55#]	USA	16 weeks	- TGF-b3 1 ug/cm^2 - TGF-b3 2.5 ug/cm^2 [excluded arm] - Placebo gel	GRF - BAS	AWD - BWD	0/4 - 0/5	Not reported

18	Hollisaz (2004)[56¶]	Iran	8 weeks	- Hydrocolloid - Saline gauze - Phenytoin cream [excluded arm]	HCD BAS -	HWD BWD -	12/18 3/19 -	Intact dermis and epidermis, no abrasion or ulceration.
19	Kim (1996)[57]	Korea	7.6 weeks	- Hydrocolloid - Wet-to-dry dressing with povidone iodine	HCD AMD	HWD OWD	21/26 14/18	When no further dressing was required
20	Kraft (1993)[58]	USA	24 weeks	- Saline gauze - Epi-lock dressing	BAS FOA	BWS HWS	3/14 10/24	Not reported
21	Kuflik (2001)[59&]	USA	6 weeks	- ResurfixR - Petrolatum jelly	COM BAS	AWD BWD	2/5 0/3	Not reported
22	Landi (2003)[60]	Italy	6 weeks	- Topical nerve growth factor - Balanced salt solution	GRF BAS	AWD BWD	8/18 1/18	Not reported
23	Matzen (1999)[61]	Denmark	12 weeks	- Saline gauze - Hydrocolloid	BAS HCD	BWD HWD	0/15 5/17	Not reported
24	Moberg (1983)[40†]	Sweden	8 weeks	- Saline, enzyme debriding, or nonadhesive dressing - Cadexomer iodine	COM AMD	OWD OWD	1/18 6/16	Not reported
25	Muller (2001)[62]	Netherlands	14 weeks	- Collagenase ointment - Hydrocolloid	CLD HCD	OWD HWD	11/12 7/11	Total epithelialization of PIs
26	Mustoe (1994)[63^]	USA	26 weeks	- rPDGF-BB 100 ug/ml - rPDGF-BB 300 ug/ml [excluded arm] - Placebo - Growth factor excluded	GRF - BAS	AWD - BWD	2/15 - 1/14	Area of opening being equal to zero
27	Neill (1989)[64]	USA	8 weeks	- Hydrocolloid - Saline gauze	HCD BAS	HWD BWD	13/42 10/45	Not reported
28	Nisi (2005)[65]	Italy	26 weeks	- Povidone iodine plus paraffin - Protease modulating matrix	AMD COL	OWD AWD	28/40 36/40	Not reported
29	Oleske (1986)[66]	USA	1.5 weeks	- Polyurethane self-adhesive foam dressing - Saline gauze	FOA BAS	HWD BWD	0/5 0/5	Not reported
30	Payne (2001)[67¥]	USA	52 weeks	- GM-CSF - Placebo - bFGF [excluded arm] - Sequential GM-CSF and bFGF [excluded arm]	GRF BAS - -	AWD BWD - -	12/15 10/15 - -	Wound closure ≥85%
31	Payne (2004)[68]	USA	24 weeks	- Saline gauze - Dermagraft	BAS GRF	HWD AWD	2/16 2/18	Full epithelialization and the absence of drainage
32	Payne (2009)[69]	USA	4 weeks	- Self-adhesive polyurethane foam dressing - Saline gauze	FOA BAS	HWD BWD	10/20 6/16	Not reported
33	Piatkowski (2012)[70§]	Germany	3 weeks	- Polyurethane foam dressing + Collagen - Polyurethane foam dressing	COL BAS	AWD BWD	5/5 4/5	Not reported
34	Price (2000)[71]	UK	6 weeks	- Alginates - Radiant heat dressing	MRD RHD	HWD OWD	2/25 3/25	Not reported
35	Ramos-Torrecillas (2015)[72£]	Spain	5 weeks	- Saline gauze - PRGF - 2 doses of PRGF [excluded arm] - PRGR + hyaluronic acid [excluded arm]	BAS GRF - -	HWD AWD - -	0/25 3/34 - -	Total closure of the PI

36	Rees (1999)[73‡]	USA	16 weeks	- Saline gauze - Becaplermin gel 100 ug/g only - Becaplermin gel 100 ug/g alternated with placebo [excluded arm] - Becaplermin gel 300 ug/g alternated with placebo [excluded arm]	BAS GRF - -	BWD AWD - -	0/31 7/31 - -	100% healed PIs
37	Scevola (2010)[74]	Italy	14 weeks	- Allogenic platelet gel - Standard treatment	GRF COM	AWD HWD	0/8 0/8	Not reported
38	Sebern (1986)[75]	USA	8 weeks	- Moisture vapour permeable dressing - Wet-to-dry gauze	FIL BAS	OWD BWD	14/22 0/12	Not reported
39	Seeley (1999)[76]	USA	8 weeks	- Hydrocolloid - Hydrocellular foam	HCD FOA	HWD FOA	8/19 8/20	Closed PI
40	Sipponen (2008)[77]	Finland	26 weeks	- Sodium carboxymethylcellulose hydrocolloid polymer - Resin salve of the Norway spruce	MRD AMD	HWD OWD	4/9 12/13	Not reported
41	Sopata (2002)[78]	Poland	8 weeks	- Lyofoam - Hydrogel	FOA HGD	FOA HWD	15/18 15/20	Closed PI wounds
42	Thomas (1998)[79]	UK	10 weeks	- Acermannan hydrogel - Saline gauze	HGD BAS	HWD BWD	10/16 9/14	Not reported
43	Thomas (2005)[80]	UK	12 weeks	- Hydrocolloid - Radiant heat dressing	HCD RHD	HWD OWD	7/20 8/21	Not reported
44	Xakellis (1992)[81]	USA	10 weeks	- Hydrocolloid - Saline gauze	HCD BAS	HWD BWD	16/18 18/21	PI had epithelial covering

* Belmin (2002): Both intervention arms received hydrocolloid, the effect of hydrocolloid cancels and the comparison will be saline (BAS) versus calcium alginate (MRD).
[#] Hirshberg (2001): Contains three internvention arms (2 active [GRF] and 1 control [BAS]), the active arm with the lowest dose and the control were included in the analysis.
[¶] Hollisaz (2004): Contains three intervention arms, phenytoin cream was excluded from the analysis as it does not fit in any of the pre-specified dressing categories.
[&] Kuflik (2001): Both intervention arms contain petrolatum, the effect of petrolatum jelly cancels and the comparison will be saline (BAS) versus combine treatment (COM).
^ Mustoe (1994): Contains three internvention arms (2 active [GRF] and 1 control [BAS]), the active arm with the lowest dose and the control were included in the analysis.
[¥] Payne (2001): Contains four internvention arms (3 active [GRF] and 1 control [BAS]), the active arm with the GM-CSF and the control were included in the analysis.
[§] Piatkowski (2012): Both intervention arms recevied foam dressing, the effect of foam dressing cancels and the comparison will be saline (BAS) versus collagen (COL).
[£] Ramos-Torrecilla (2015): Contains four internvention arms (3 active [GRF] and 1 control [BAS]), the active arm with the lowest dose and the control were included in the analysis.
[‡] Rees (1999): Contains four internvention arms (3 active [GRF] and 1 control [BAS]), the active arm with the lowest dose and the control were included in the analysis.

[†] Brod (1990), Brown-Etris (1996), Darkovich (1990), Moberg (1983) excluded from the analysis using the 5 dressing groups.

- Topical treatment categories: *AMD* antimicrobial; *BAS* basic; *CLD* collagenase; *COL* collagen; *COM* combined treatment; FIL film; *FOA* foam; *GRF* growth factor; *HCD* hydrocolloid; *HGD* hydrogel; *MRD* moisture retentive; *NPD* negative pressure; *RHD* radiant heat.
- Dressing wound groups: *AWD* active; *BWD* basic; *FOA* foam; *HWD* hydroactive; *OWD* other wound dressing.

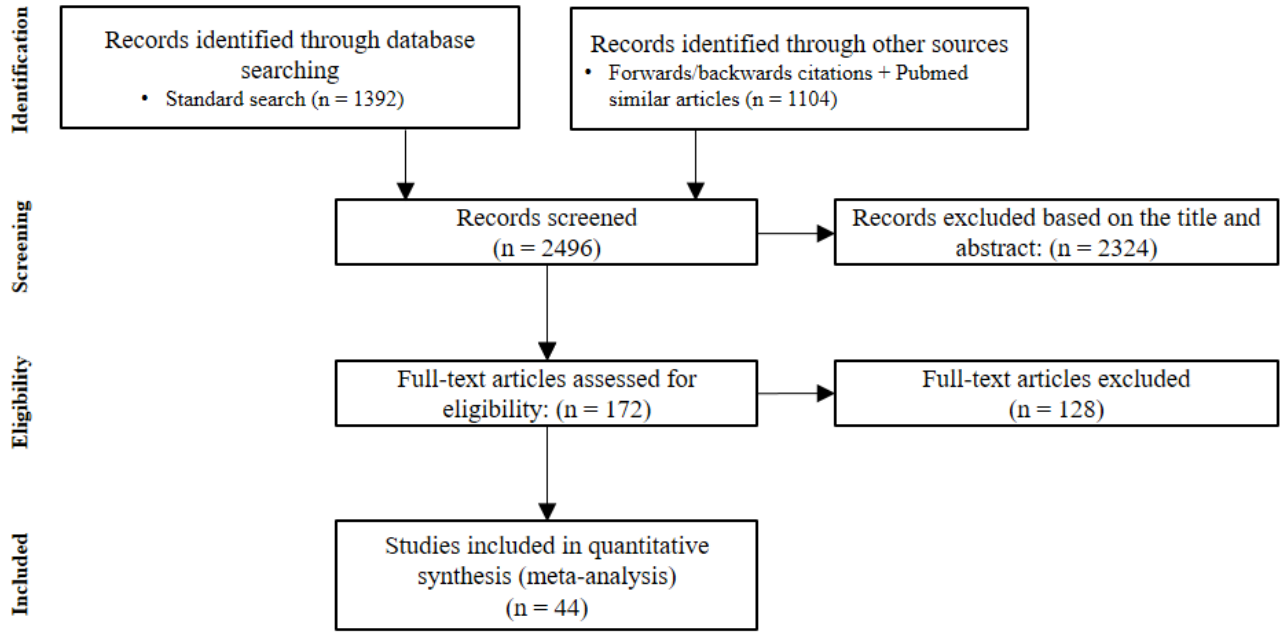


Figure 1. PRISMA flow diagram of study selection for quantitative synthesis.

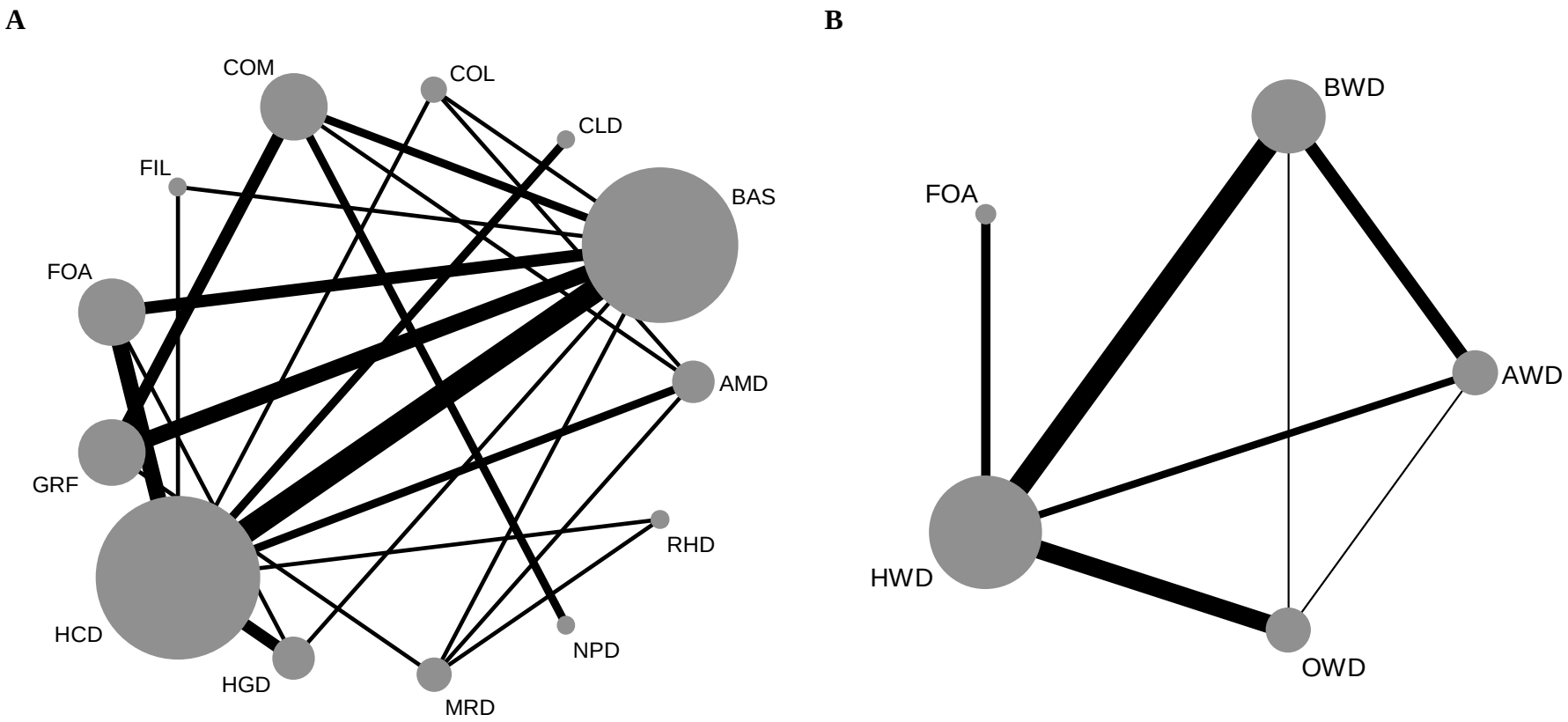


Figure 2. Network plot showing the A) 13 topical treatment categories and B) 5 wound dressing groups. The circle size is proportional to the number of arms while the width of the lines is proportional to the number of pairs.

AMD antimicrobial; *BAS* basic; *CLD* collagenase; *COL* collagen; *COM* combined treatment; FIL film; *FOA* foam; *GRF* growth factor; *HCD* hydrocolloid; *HGD* hydrogel; *MRD* moisture retentive; *NPD* negative pressure; *RHD* radiant heat.
AWD active; *BWD* basic; *FOA* foam; *HWD* hydroactive; *OWD* other wound dressing.

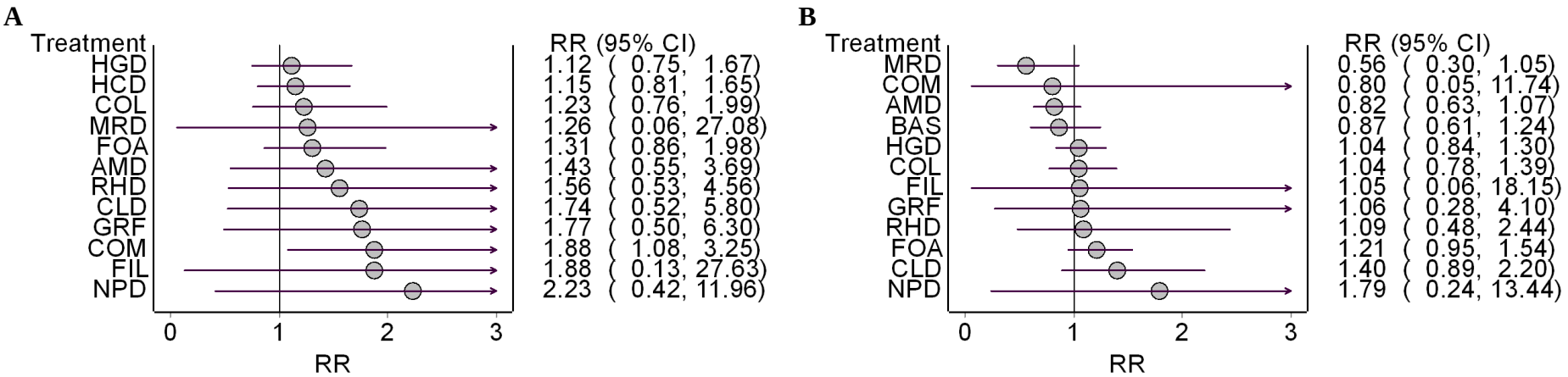


Figure 3. Network forest plot baseds on 44 studies ranking comparisons based on their relative risk for wound healing using A) basic and B) hydrocolloid as the reference topical treatment category. When the reference treatment category changes, the ranking changes as well due to sparseness in the network making these results unreliable.

AMD antimicrobial; *BAS* basic; *CLD* collagenase; *COL* collagen; *COM* combined treatment; FIL film; *FOA* foam; *GRF* growth factor; *HCD* hydrocolloid; *HGD* hydrogel; *MRD* moisture retentive; *NPD* negative pressure; *RHD* radiant heat

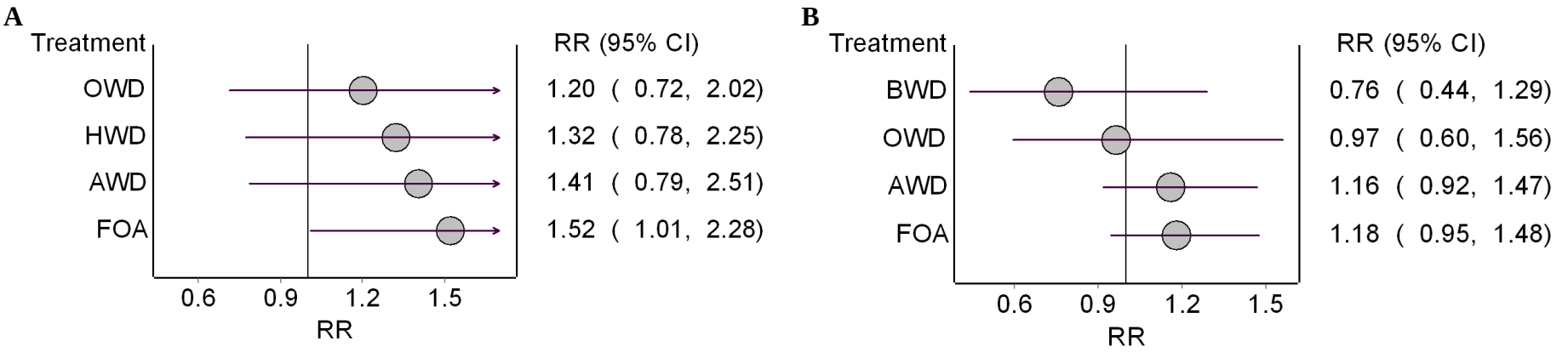


Figure 4. Network forest plots based on 40 studies ranking comparisons based on their relative risk for wound healing using A) basic and B) hydroactive as the reference dressing group. This network is non-sparse and stable, thus rankings remain reliable when the reference dressing group changes.

AWD active; *BWD* basic; *FOA* foam; *HWD* hydroactive; *OWD* other wound dressing

Figure 1

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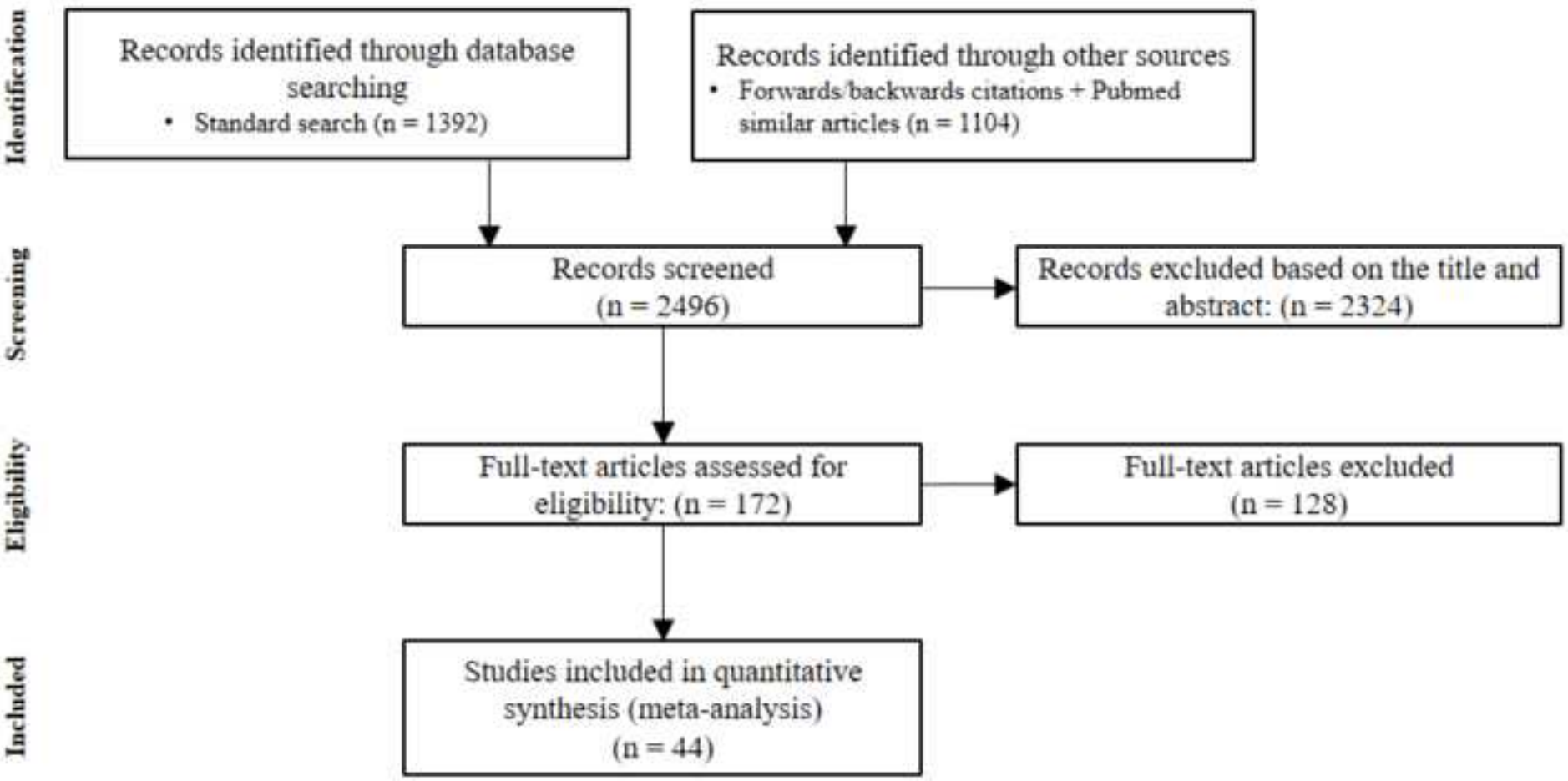


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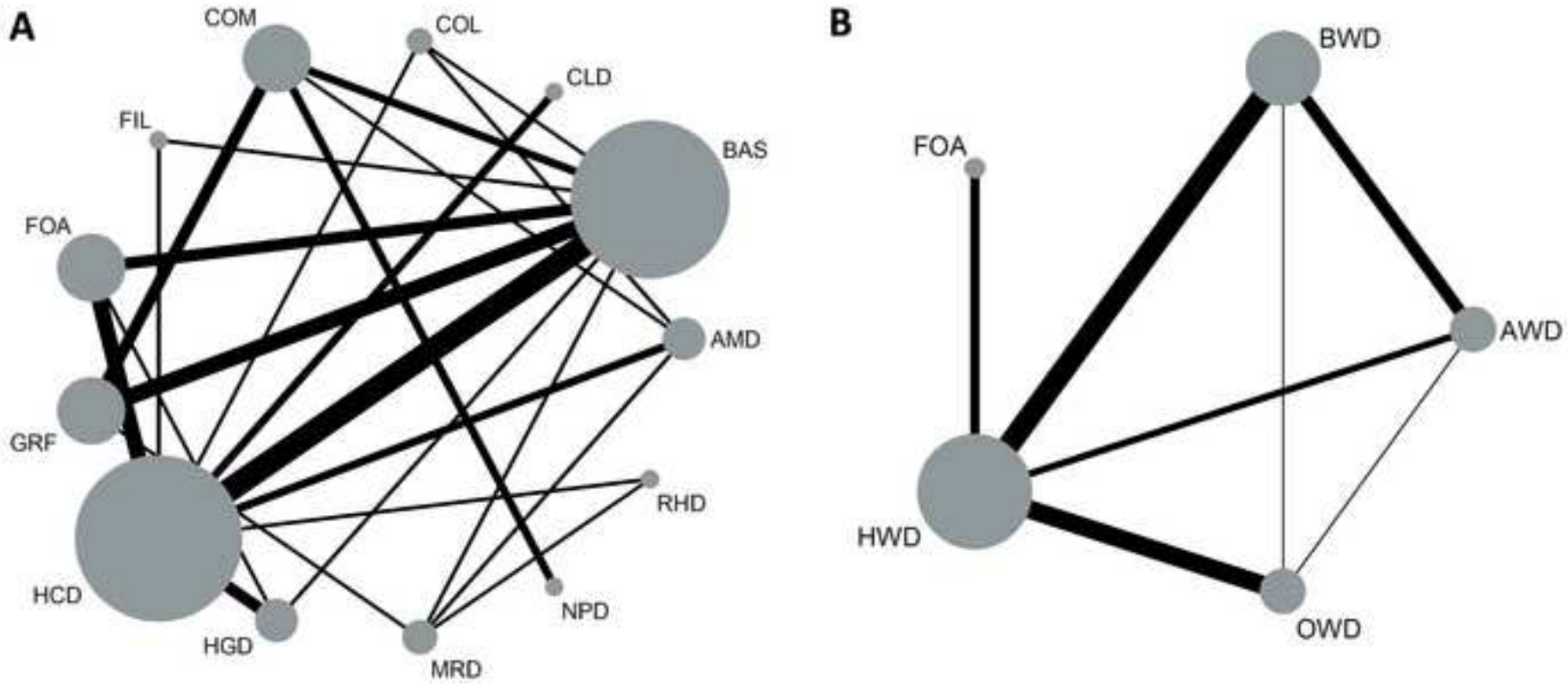


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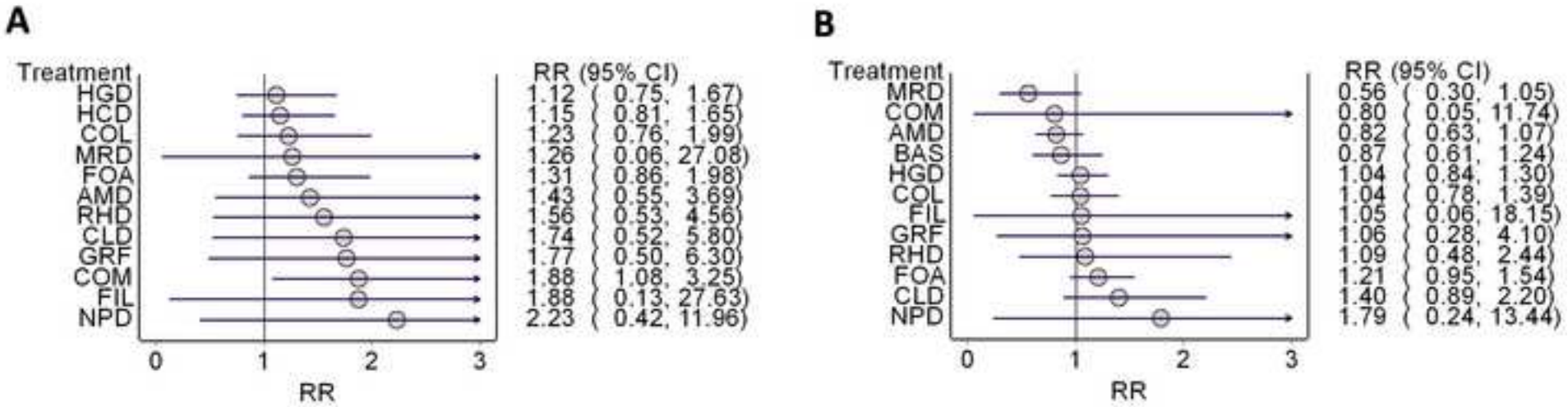
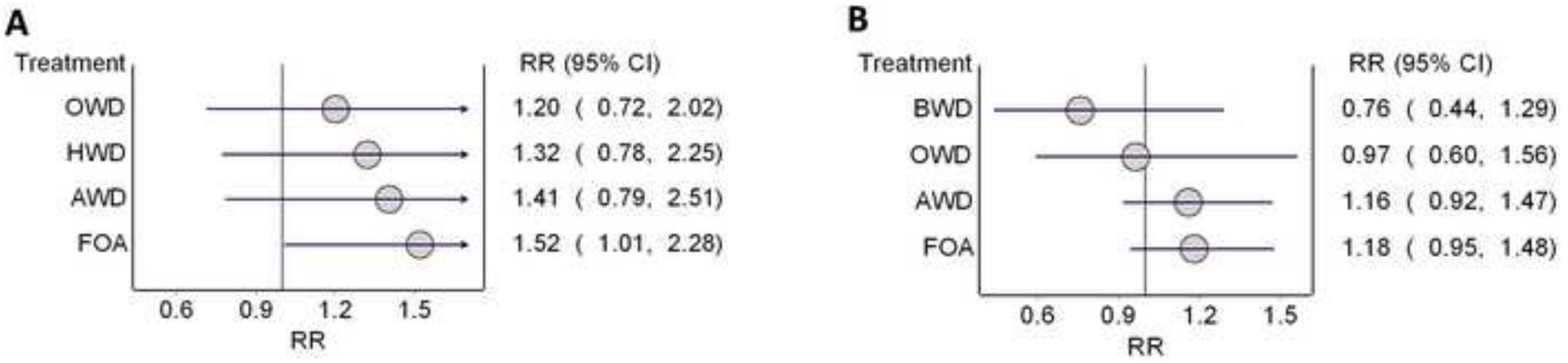


Figure 4

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Supplementary Material

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