RESEARCH ARTICLE

Network meta-analysis and random walks

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Network meta-analysis (NMA) is a central tool for evidence synthesis in clinical research. The results of an NMA depend critically on the quality of evidence being pooled. In assessing the validity of an NMA, it is therefore important to know the proportion contributions of each direct treatment comparison to each network treatment effect. The construction of proportion contributions is based on the observation that each row of the hat matrix represents a so-called "evidence flow network" for each treatment comparison. However, the existing algorithm used to calculate these values is associated with ambiguity according to the selection of paths. In this article, we present a novel analogy between NMA and random walks. We use this analogy to derive closed-form expressions for the proportion contributions. A random walk on a graph is a stochastic process that describes a succession of random "hops" between vertices which are connected by an edge. The weight of an edge relates to the probability that the walker moves along that edge. We use the graph representation of NMA to construct the transition matrix for a random walk on the network of evidence. We show that the net number of times a walker crosses each edge of the network is related to the evidence flow network. By then defining a random walk on the directed evidence flow network, we derive analytically the matrix of proportion contributions. The random-walk approach has none of the associated ambiguity of the existing algorithm.

KEYWORDS
electrical networks, evidence flow, network meta-analysis, proportion contribution, random walks, statistical mechanics

1 | INTRODUCTION

Network meta-analysis (NMA) has been established as a central tool of evidence synthesis in clinical research.[1-3] Combining direct and indirect evidence from multiple randomized controlled trials, NMA makes it possible to compare interventions that have not been tested together in any trial.[4-6] The term "network meta-analysis" derives from the fact

that one can mathematically represent the collection of interventions and trials as a graph. A graph consists of a set of nodes and a set of edges connecting pairs of nodes. The nodes of an NMA graph represent the different treatment options, and edges are comparisons made between the treatments in the trials. In line with Rücker[7] we will refer to networks of treatment options and comparisons between treatments as "meta-analytic graphs".

An NMA combines data from multiple trials, each comparing different combinations of treatment options. The accuracy of the conclusions from an NMA depends on potential biases associated with individual trials, and on assumptions such as between-trial homogeneity and consistency between direct and indirect evidence. In this context it is useful to study the so-called "flow of evidence"[8] in the network. This describes the influence different network components have on the estimates of treatment effects. For example, the comparison between two particular treatments may enter as indirect evidence into the estimate of the relative effect of two different nodes in the network. Understanding how exactly evidence flows in the graph then allows one to assess the impact of potential bias originating from different pieces of evidence in the network.[8-10]

Previous literature has, for example, looked at the relative influence of direct evidence compared to indirect evidence.[11,12] Other work has been concerned with measures of network geometry, capturing the frequency with which different comparisons are represented in the trials underpinning an NMA.[13,14] One then asks how the network structure affects NMA estimates of treatment effects, heterogeneity and rank metrics.[13-18] The "hat matrix" in a two-step ("aggregate") NMA model[11] describes how the overall estimates of treatment effects from the network can be expressed in terms of the direct estimates obtained from the trial data. König et al[8] observed that each row of the hat matrix represents an evidence flow network for a particular treatment effect. König et al then visualized the evidence flow on weighted directed acyclic graphs in which nodes represent treatments, and edges indicate the direction and quantity of evidence flow through each direct comparison. Based on this observation, Papakonstantinou et al[9] introduced "streams" of evidence and developed a numerical algorithm to calculate these streams. The streams of evidence are then used to derive the "proportion contribution" of each direct comparison to each treatment effect in the graph. This allows one to quantify how limitations of individual studies impact on the estimates obtained from the network. Indeed, the algorithm in Papakonstantinou et al is implemented in software such as CINeMA (confidence in network meta-analysis)[10] and ROB-MEN (risk-of-bias due to missing evidence in NMA),[19] used in clinical practice for the evaluation of results from an NMA.

More widely, the study of networks plays a key role in a variety of disciplines including ecology, economics, electrical engineering and sociology.[20-22] Through the representation of treatment options and comparisons in trials as a graph, one can therefore take advantage of the extensive literature in network theory, and of ideas developed in the disciplines in which networks are studied. For example one of us[7] used the graph representation of NMA to make the connection between meta-analytic and electrical networks. This allows one to demonstrate that graph theoretical tools routinely applied to electrical networks are also of use in NMA. This approach has since led to advancements in NMA methodology such as frequentist ranking methods[23] and component NMA.[24] It is also the basis for the software package `netmeta`.[25]

In this article, we present a new analogy between random walks and NMA. A random walk on a graph is a stochastic process consisting of a succession of "hops" between vertices connected by edges. Random walks are of interest for a wide range of applications, including statistical physics, biology, ecology, genetics, transport, and economics (for a selection of references see 26-30). Random walks are also a popular tool to study the properties of networks themselves.[31-33]

It is well known that there is a connection between random walks and electrical networks.[34-37] In this context, edges of the electric network are conducting connections (wires). The correspondence between random walks and electrical networks can be established by asserting that the probability that a random walker currently at node a moves to node b in the next step is proportional to the conductance (inverse resistance) of the edge connecting a and b. Quantities in the electrical network such as currents along edges or electric potentials at the nodes then have an interpretation in the random-walk picture. For further details we refer to Doyle and Snell.[37]

Motivated by the connection between electrical networks and NMA on the one hand, and that of electrical networks and random walks on the other, we construct a random walk on the *meta-analytic network*. We show that the random-walk picture we develop can be used to study the flow of evidence in the NMA network. In particular there is a random-walk interpretation of the elements in the hat matrix. Further, we construct a second random-walk model, this time on the *evidence flow network*. From this we derive an analytical expression for proportion contributions which overcomes the limitations of Papakonstantinou et al.[9] In particular, the algorithm in Papakonstantinou et al selects only a subset of paths on the evidence flow network. This means that paths of evidence that potentially contribute risk of bias are missed. Furthermore, the paths identified by the algorithm are not unambiguous and instead depend on the order in which

certain steps are carried out. In contrast, the random-walk approach identifies all possible paths of evidence and delivers an unambiguous analytical result for proportion contributions. In addition, unlike the method in Papakonstantinou et al, the random-walk approach is able to handle networks with multi-arm trials.

The remainder of this article is set out as follows: We present a motivating data set in Section 2. In Section 3 we provide the relevant background information. We describe an aggregate-level frequentist NMA model and show how the associated hat matrix can be interpreted as evidence flow. In Section 4 we introduce the analogies between NMA, electrical networks and random walks. Using the analogies to electrical networks in both the NMA and random-walk literature, we then express the flow of evidence in an NMA in terms of properties of random walks on the aggregate network. In Section 5 we introduce a second random-walk model, now on the directed evidence flow network. We use this to analytically derive the matrix of proportion contributions. In Section 6, we apply our method to the motivating data set and demonstrate that the random-walk approach overcomes the limitations of the numerical algorithm previously proposed by Papakonstantinou et al.[9] We summarize our results in Section 7 and discuss potential future impact of the analogy between NMA and random walks.

2 | MOTIVATING EXAMPLE

We use an NMA of psychological treatments for patients with depressive disorders[38] to motivate our work. The data is described in detail in Rücker and Schwarzer.[39] For convenience we will occasionally refer to this as the "depression data set". The NMA compares $N = 11$ treatments based on $M = 26$ randomized controlled trials. Of these one is a four-arm trial, eight are three-arm trials and 17 contain just two arms. In total, the trials provide $K = 20$ pairs of treatments which are directly compared in at least one trial. The primary outcome of the trials was a binary variable representing patient response after treatment completion. The odds ratio (OR) was used as the measure of relative treatment effect. The graph representing this set of treatments and trials is shown in Figure 1. Vertices in the graph are treatments, and edges represent comparisons between pairs of treatments (two vertices are connected if they have been directly compared in at least one trial). The graph therefore has $N = 11$ vertices and $K = 20$ edges. The thickness of the edges in the figure represent the number of trials making the different comparisons.

NMA aims at estimating treatment effects for all pairs of interventions within this network. One aim of our article is to determine the contribution (as a proportion) of each direct comparison to these estimates.
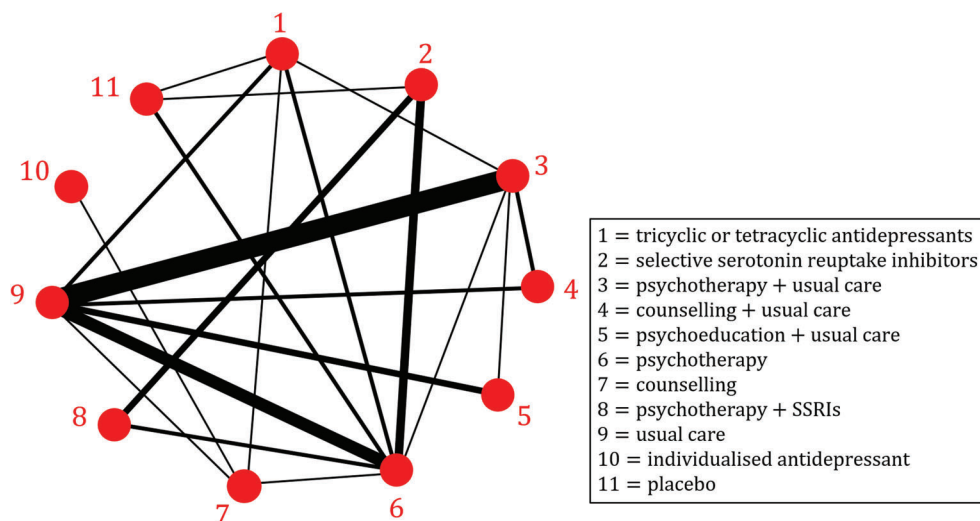

1 = tricyclic or tetracyclic antidepressants
2 = selective serotonin reuptake inhibitors
3 = psychotherapy + usual care
4 = counselling + usual care
5 = psychoeducation + usual care
6 = psychotherapy
7 = counselling
8 = psychotherapy + SSRIs
9 = usual care
10 = individualised antidepressant
11 = placebo

FIGURE 1 A network of psychological treatments for depression (original data from Linde et al;[38] presented in Rücker and Schwarzer[39]). We use numerical labels from 1 to 11, these are the same as in Rücker and Schwarzer.[39] Two treatments are connected by an edge if a direct comparison of the two treatments was made in at least one trial; the edge width indicates the number of trials that make the comparison. The network contains one 4-arm trial (comparing treatments 1-6-7-9), eight 3-arm trials (3-5-9, 2-6-8, 1-6-11, 1-3-9, 2-6-11, 2-6-8, 3-6-9, and 3-4-9) and 17 2-arm trials. Multi-arm trials are not explicitly indicated in the network graph. The data, including the number of trials per comparison, is described in detail in Rücker and Schwarzer[39]

3 | NETWORK META-ANALYSIS MODEL

3.1 | Definitions and notation

Among the multiple equivalent frequentist formulations of NMA[6,11,13,39,40] we choose a so-called "aggregate level" (or two-step) approach[11] to the graph theoretical model developed in Rücker.[7] Rücker's original (one-step) model is implemented in the R package `netmeta`.[25] In Section A of the Supplementary Material we outline how the aggregate-level graph theoretical approach relates to other frequentist NMA models.

We consider a network of N treatments, denoted $a = 1, \ldots, N$, and M studies, $i = 1, \ldots, M$. Throughout this article we will use the lower case letters a, b, c and d to refer to treatment nodes. Occasionally we also use x and y as dummy indices referring to nodes in sums or products. Study i compares a subset of n_i treatments (ie, n_i is the number of treatments in trial i). We use a random-effects model where we focus on relative, rather than absolute effects. To this end, we write $Y_{i,ab}$ for the observed effect of treatment b in trial i relative to treatment a. We denote the variance associated with this observation by $\sigma_{i,ab}^2$. The heterogeneity, τ^2, in the network can be estimated, for example, using the method-of-moments approach.[41] The estimated heterogeneity is added to the within-trial variance estimate from each study to make the total variance $\sigma_{i,ab}^2 + \tau^2$.

Trial i contributes $q_i = n_i(n_i - 1)/2$ observed relative treatment effects and associated variances. For a trial with $n_i = 2$, comparing treatments a and b, the weight assigned is given by the inverse variance, $w_{i,ab} = 1/(\sigma_{i,ab}^2 + \tau^2)$. In order to account for correlations induced by multi-arm trials ($n_i \geq 3$), we use an adjustment method described in detail in References 7,39,42. The method involves adjusting the variances associated with each pairwise comparison in a multi-arm trial. For multi-arm trial i this results in $q_i \geq 3$ weights, $w_{i,ab}$, where a and b run through all treatments compared in that trial. This defines a complete subgraph of q_i two-arm trials which is equivalent to the multi-arm trial.

3.2 | Aggregate-level description

The set of adjusted weights $\{w_{i,ab}\}$ for all trials $i = 1, \ldots, M$ defines a network of $\sum_{i=1}^{M} q_i$ two-arm trials. This network is equivalent to the original network of M (potentially multi-arm) trials in that the resulting relative treatment effect estimates from the network of two-arm trials described by $\{w_{i,ab}\}$ are the same as those obtained from the original network.[39]

We write M_{ab} for the set of trials $i \in \{1, \ldots, M\}$ comparing treatments a and b. Using the weights $\{w_{i,ab}\}$, we perform a pairwise meta-analysis across each of the K edges in the network. For the edge connecting nodes a and b, the direct estimate is calculated as the weighted mean,

$$\hat{\theta}_{ab}^{\mathrm{dir}} = \frac{\sum_{i \in M_{ab}} w_{i,ab} Y_{i,ab}}{\sum_{i \in M_{ab}} w_{i,ab}}. \tag{1}$$

This results in K *direct* estimates of the relative treatment effects, $\hat{\theta}_{ab}^{\mathrm{dir}}$, which we collect in the vector $\hat{\boldsymbol{\theta}}^{\mathrm{dir}}$. The weight associated with the direct estimate $\hat{\theta}_{ab}^{\mathrm{dir}}$ (and to be used in the subsequent analysis) is given by

$$w_{ab} = \sum_{i \in M_{ab}} w_{i,ab}. \tag{2}$$

The direct estimates of the relative treatment effects have been termed "aggregate" data.[8,43] Therefore, Equations (1) and (2) describe the observations and inverse-variance weights for an aggregate-level model.

The aggregate model can be represented by an "aggregate network" where w_{ab} is the weight associated with the edge ab. We collect the aggregate edge weights in a $K \times K$ diagonal matrix, $\boldsymbol{W} = \mathrm{diag}(w_{ab})$. Figure 2A shows a fictional example of an aggregate network with five treatments $a = 1, 2, 3, 4, 5$. The aggregate weight matrix for this example is $\boldsymbol{W} = \mathrm{diag}(1, 3, 4, 6, 5, 2, 7)$. We write $\boldsymbol{B}$ for the $K \times N$ edge-incidence matrix of the aggregate network. Each column of $\boldsymbol{B}$
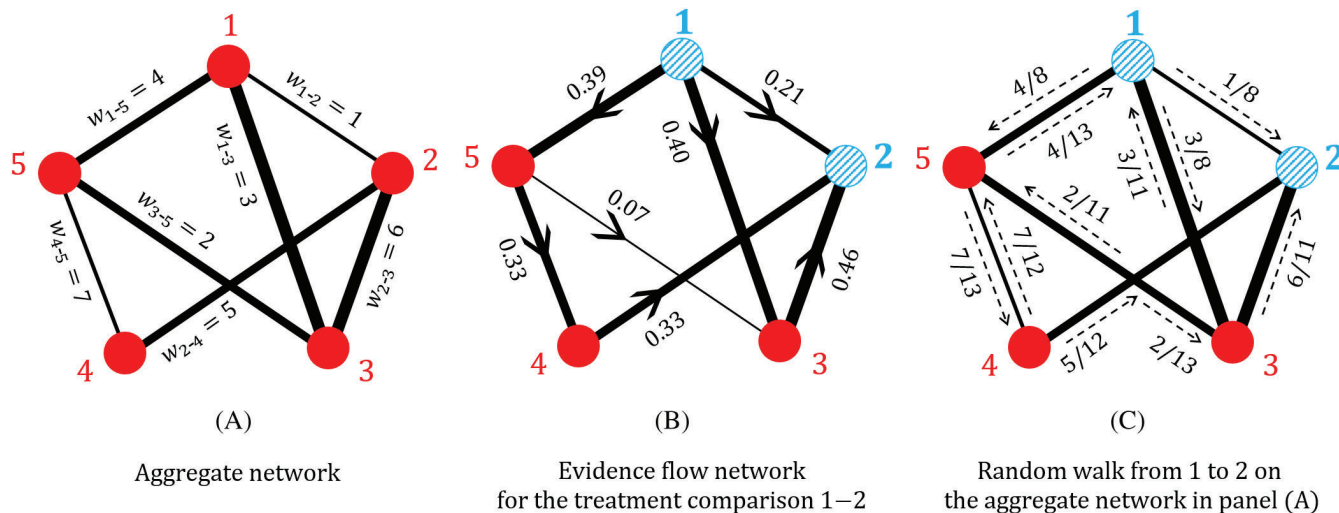
FIGURE 2 (A) A fictional example of an aggregate meta-analytic network with edges weighted and labeled by their respective (inverse-variance) weights. (B) The resulting evidence flow network for the comparison 1-2 from the aggregate network in (A); the comparison 1-2 is indicated by shading these nodes with blue stripes. Edges are directed according to the sign of the corresponding element of the hat matrix, and are weighted by the absolute value of the hat matrix element. (C) The random walk on the aggregate network in (A) for a walker starting at node 1 and finishing at node 2; edges are labeled by the associated transition probabilities

corresponds to a treatment in the network and each row corresponds to an edge. To construct the matrix, one of the two treatments in each edge is designated as the "baseline treatment" for this edge without loss of generality. Entries are +1 in the column corresponding to the "baseline" treatment of the comparison represented by that row, and −1 in the column corresponding to the treatment compared to that baseline. For the example in Figure 2A the edge incidence matrix can be chosen as

$$
\boldsymbol{B} = \begin{pmatrix}
1 & -1 & 0 & 0 & 0 \\
1 & 0 & -1 & 0 & 0 \\
1 & 0 & 0 & 0 & -1 \\
0 & 1 & -1 & 0 & 0 \\
0 & 1 & 0 & -1 & 0 \\
0 & 0 & 1 & 0 & -1 \\
0 & 0 & 0 & 1 & -1
\end{pmatrix},
\tag{3}
$$

where the columns represent treatments 1, 2, 3, 4, and 5, and the rows represent the edges (direct comparisons) 1-2, 1-3, 1-5, 2-3, 2-4, 3-5, and 4-5. In the following we will use this hyphenated notation when we refer to specific comparisons (eg, 1-2 for the comparison between treatments 1 and 2). When we refer to a comparison between unspecified treatments a and b, we will then use the notation ab, to avoid confusion with "a minus b".

3.3 | Hat matrix and network estimates

The *network* estimates of the relative treatment effects $\hat{\theta}_{ab}^{\text{net}}$ are obtained via

$$
\hat{\theta}^{\text{net}} = \boldsymbol{H}\hat{\theta}^{\text{dir}},
\tag{4}
$$

where the hat matrix associated with the aggregate model is[39]

$$
\boldsymbol{H} = \boldsymbol{B}(\boldsymbol{B}^{\mathsf{T}}\boldsymbol{W}\boldsymbol{B})^{+}\boldsymbol{B}^{\mathsf{T}}\boldsymbol{W}.
\tag{5}
$$

The hat matrix has dimension $K \times K$ where each row and each column correspond to one edge. We denote the element in the ab row and cd column by $H_{cd}^{(ab)}$. The matrix $\boldsymbol{L} = \boldsymbol{B}^{\top}\boldsymbol{W}\boldsymbol{B}$, with dimensions $N \times N$ and rank $N - 1$, is the Laplacian of the aggregate network. The matrix $\boldsymbol{L}^{+} = (\boldsymbol{B}^{\top}\boldsymbol{W}\boldsymbol{B})^{+}$ is its pseudo-inverse.[7,42] The hat matrix describes how the direct evidence combines to give the network estimates. Each network estimate is a weighted linear combination of direct and indirect evidence. The coefficients of the estimates $\hat{\theta}^{\text{dir}}$ for each network treatment effect are found in the corresponding row of $\boldsymbol{H}$. The diagonal elements of $\boldsymbol{H}$ give the coefficients for the direct evidence while the off-diagonal elements indicate the contribution of indirect evidence. The larger the diagonal elements, the more weight is given to direct evidence.[8] For the example in Figure 2 we calculate $\boldsymbol{H}$ using Equation (5), $\boldsymbol{W} = \text{diag}(1, 3, 4, 6, 5, 2, 7)$ and $\boldsymbol{B}$ given in Equation (3). The resulting hat matrix is quoted in Equation (B5) in the Supplementary Material.

3.4 | Evidence flow

König et al[8] noted that each row in the hat matrix can be interpreted as a flow network. Focusing on one row of the hat matrix, the magnitude of the flow of evidence between two nodes is given by the absolute value of the element in the corresponding column of $\boldsymbol{H}$. The direction is determined by the sign of the element of the hat matrix. For the ab-row of the hat matrix one defines evidence flows $f_{cd}^{(ab)}$ (from c to d) and $f_{dc}^{(ab)}$ (from d to c) as follows:[8]

$$
\begin{aligned}
\text{if } H_{cd}^{(ab)} > 0 : \qquad & f_{cd}^{(ab)} = H_{cd}^{(ab)}, \qquad f_{dc}^{(ab)} = 0, \\
\text{if } H_{cd}^{(ab)} < 0 : \qquad & f_{cd}^{(ab)} = 0, \qquad f_{dc}^{(ab)} = |H_{cd}^{(ab)}|.
\end{aligned}
\tag{6}
$$

Flows are non-negative, and only one of $f_{cd}^{(ab)}$ and $f_{dc}^{(ab)}$ is non-zero. We note that setting one of the coefficients for each pair of nodes to zero is a choice. Alternatively, one could have chosen conventions such that $f_{cd}^{(ab)} = -f_{dc}^{(ab)}$ for all pairs c and d. This is an equivalent reparameterization, but is less convenient for our subsequent workings. We comment further on this in Section C of Supplementary Material.

It is important to note that each comparison ab gives rise to a separate network of flows. We refer to these graphs as "evidence flow networks". The edges of these graphs are directional and point in the direction of positive flow. Due to the properties of the hat matrix each of these evidence flow networks is acyclic. Specifically, in the network corresponding to the comparison ab, node a only has outgoing edges, and node b only incoming edges. The flow network then has the following properties:

1. The total outflow from a is equal to one, $\sum_x f_{ax}^{(ab)} = 1$;
2. the sum of inflows to node b is also one, $\sum_x f_{xb}^{(ab)} = 1$;
3. and at every intermediate node, $c \neq a, b$, the sum of outflows equals the sum of inflows, $\sum_x f_{cx}^{(ab)} = \sum_x f_{xc}^{(ab)}$.

These properties were stated in König et al,[8] and an algebraic proof for the first and the second property was given in Papakonstantinou et al.[9] We provide a heuristic argument for all three properties in Section D of the Supplement. These three properties make an interpretation as a "flow" natural. We adopt the term "flow of evidence" used in previous literature,[8,9] noting that it is perhaps not immediately clear what precisely "evidence" is mathematically, and how it can flow from one node to another. The random-walk picture we develop later in this article offers a possible interpretation, which we will discuss in Section 4.3 and in the Supplementary Material (Section C).

Figure 2B shows the evidence flow network for the comparison 1-2 for the aggregate network in Figure 2A. The values of flow shown in Figure 2B correspond to the first row of the matrix $\boldsymbol{H}$ given in Equation (B5) in Supplementary Material.

4 | NMA, ELECTRICAL NETWORKS AND RANDOM WALKS

In this section we set up the analogies between NMA, electrical networks and random walks. A summary of these analogies can be found in Table 1.

TABLE 1 Summary of the analogy between NMA, electrical networks and random walks (RW) on the aggregate network

NMA	Electric circuit	RW on the aggregate network
Treatments $1, 2, \ldots, N$	Nodes $1, 2, \ldots, N$	Nodes $1, 2, \ldots, N$
Direct treatment comparisons	Edges (conducting wires)	Edges (along which a random walker can travel in both directions)
w_{ab} inverse-variance weight associated with edge ab on the aggregate network	$C_{ab} = R_{ab}^{-1}$ conductance (inverse resistance) across edge ab	$T_{ab} = C_{ab}/\sum_{c \neq a} C_{ac} = w_{ab}/\sum_{c \neq a} w_{ac}$ probability that a walker at node a hops to node b in the next step
The aggregate hat matrix element $H_{cd}^{(ab)}$ that defines the flow of evidence through the direct comparison cd for the network treatment effect ab	Flow of current through edge cd when a battery is attached across nodes a and b such that a unit current flows into a and out of b	Expected net number of times a walker starting at a and ending at b crosses the edge from c to d

4.1 | NMA and electrical networks

The connection between meta-analytic and electrical networks was first introduced by one of us.[7] In the meta-analytic network, treatments are nodes connected by edges representing pairwise comparisons. On the other hand, edges in an electrical network represent resistors that connect at the nodes. If two (or more) nodes of an electric network are connected to the poles of a battery then an electric potential (a real-valued scalar quantity) can be associated with each node in the network. The potential in turn results in voltages (differences in electric potential) across all edges. The potential difference between two nodes connected by a path on the graph is the sum of the voltages along each edge of the path. If there are multiple paths connecting two nodes then the sum of voltages is independent of the path. Voltages along a cycle on the network sum to zero.

The voltages in turn induce currents across the edges (current = voltage divided by resistance). Currents may also flow into or out of a node from or to the external battery (often referred to simply as the "exterior"). The sum of currents entering each node equals the sum of currents leaving that node (Kirchhoff's current law, see for example Urbano[44]).

The analogy between NMA and electric networks is based on the observation that resistances in parallel and sequential electrical circuits combine in the same way as variances of treatment effects in an NMA. Variance therefore corresponds to resistance. One can show that relative treatment effects are the analog of voltages measured across edges, and weighted treatment effects the analog of electrical current (see Rücker[7] for details). This allows one to use graph theoretical tools, routinely applied to electrical networks, to address questions in NMA.

In Rücker[7] no voltages or external currents are applied directly to the electric circuit representing the NMA network (ie, there is no external battery). Instead, the starting point is given by measurements of treatment effects (voltages) across the edges of the network. These are understood to be the true treatment effects subject to some random additive error. It is then shown in Rücker[7] that finding the NMA estimates of treatment effects corresponds to finding the set of consistent voltages across all edges that minimizes the (Euclidian) distance to these observed treatment effects.

Here, we extend this analogy and show that the elements of the hat matrix have an interpretation in the electric-circuit picture. More precisely, the elements of the row in the hat matrix corresponding to the comparison between treatments a and b can be obtained as follows: Connect a battery to nodes a and b in the electric circuit so that one unit of current flows from the exterior into node a, and out of the network (to the exterior) from node b. The external currents into/out of all other nodes are maintained at zero. This reflects the properties 1-3 of the coefficients $f_{cd}^{(ab)}$ in Section 3.4. These derive from the properties of the hat matrix via Equation (6), which in turn are a consequence of the function of the hat matrix to project onto the space of consistent relative treatment effects (see Rücker[7]). This set-up induces currents across the edges in the network. Our main result is then the following: The current along edge cd is identical to the hat matrix element $H_{cd}^{(ab)}$. A detailed mathematical proof can be found in Section E of Supplementary Material.

We illustrate this with a simple network of four nodes in Figure 3. Panel (A) shows a generic electrical circuit resulting from a meta-analytic graph with four treatment options and with direct comparisons between all pairs of treatments except treatments 1 and 4. We focus on the row in the hat matrix corresponding to the comparison between treatments 1 and 2. Using Equation (4) we have for this example

$$\hat{\theta}_{1\text{-}2}^{\text{net}} = H_{1\text{-}2}^{(1\text{-}2)}\hat{\theta}_{1\text{-}2}^{\text{dir}} + H_{1\text{-}3}^{(1\text{-}2)}\hat{\theta}_{1\text{-}3}^{\text{dir}} + H_{2\text{-}3}^{(1\text{-}2)}\hat{\theta}_{2\text{-}3}^{\text{dir}} + H_{2\text{-}4}^{(1\text{-}2)}\hat{\theta}_{2\text{-}4}^{\text{dir}} + H_{3\text{-}4}^{(1\text{-}2)}\hat{\theta}_{3\text{-}4}^{\text{dir}}. \tag{7}$$

Our result indicates that the coefficients $H_{cd}^{(1\text{-}2)}$ can be obtained from the setup shown in Figure 3. A battery is attached to nodes 1 and 2 and the voltage of the battery is chosen such that one unit of current flows into node 1 (from the battery) and out of node 2 (into the battery). This induces currents in the five edges (resistors) of the electric circuit. These currents are the hat matrix elements in Equation (7). Via Equation (6) these then determine the flow of evidence.

4.2 | Electrical networks and random walks

4.2.1 | Definitions and notation

As illustrated in Figure 4, a random walk on a graph is a stochastic process consisting of a succession of "hops" between neighboring nodes (nodes connected by an edge). We use the word "path" to describe the sequence of nodes visited by the walker, including repeat visits to individual nodes. We always assume that time is discrete. The walk is then a Markov process described by an $N \times N$ transition matrix, $\boldsymbol{T}$, where N is the number of nodes in the network. The element T_{ab} of this matrix is the probability that a walker, currently at node a, moves to node b in the next time step. These probabilities only depend on the current position of the walker, and not on the path taken to reach that position. One has $\sum_b T_{ab} = 1$ for all a, that is, $\boldsymbol{T}$ is a stochastic matrix.

The connection between random walks and electrical networks has been recognized for some time[34-36] and is described extensively in Doyle and Snell.[37] Here we will only summarize the concepts and known results that are most relevant for our work.
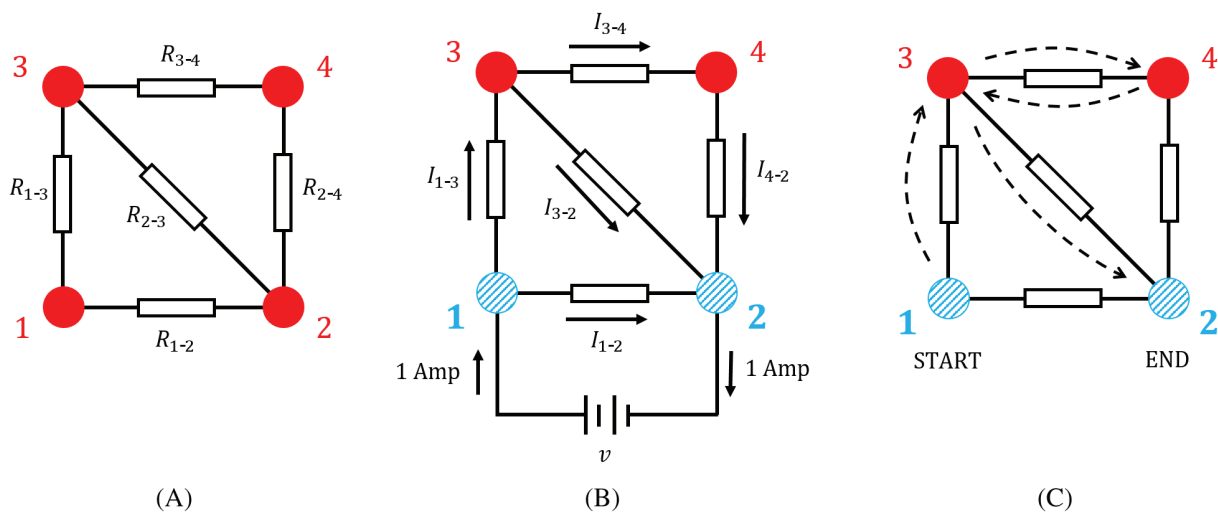

FIGURE 3 An illustration of the interpretation of current. (A) An electrical network with associated edge resistances. (B) The same network with a battery attached across the edge 1-2 such that a unit current flows into 1 and out of 2. The current in edge cd is labeled I_{cd}. Current is measured in ampéres, hence the unit current is labeled as "1 Amp". The direction of the current induced in the edges is shown. (C) A possible path taken by a random walker starting at node 1 and stopping at node 2. The sequence of nodes visited is $1 \to 3 \to 4 \to 3 \to 2$. For this particular realization of the random walk, the net number of times the walker crosses edges 1-3 and 3-2 is one, while all other edges are crossed net zero times. The expected net number of times the walker crosses an edge is given by the currents shown in (B) for that edge.[37] The focus on the comparison of nodes 1 and 2 in panels (B) and (C) is indicated by the blue striped pattern of these nodes
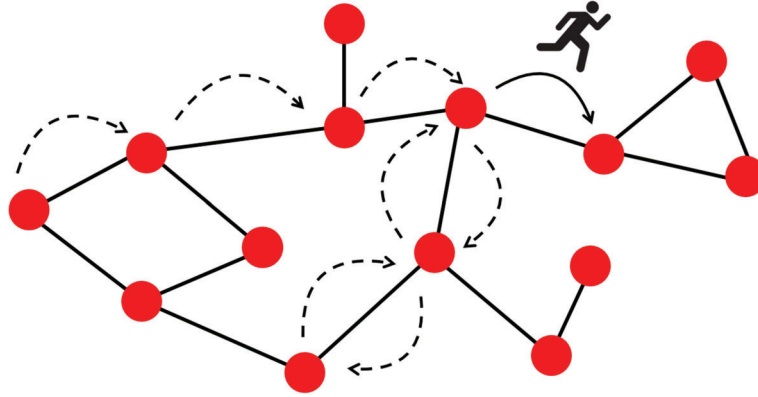
FIGURE 4 An illustration of a random walker moving on a network graph. The walker starts its journey from the far left node. The arrows show the path taken by the walker for one realization of the random walk. The figure indicates the "current" position of the walker as it hops between two nodes. The solid arrow indicates this transition. The dotted arrows indicate the previous transitions made between nodes by the walker

Starting from an electrical network with given resistances R_{ab} a random walk process can be constructed by defining the transition probabilities ($a \neq b$)

$$T_{ab} = \frac{R_{ab}^{-1}}{\sum_{c \neq a} R_{ac}^{-1}}. \tag{8}$$

This definition indicates that transitions from one node to another occur in proportion to the inverse resistance of the direct connection between the two nodes (if there is no direct connection, then no hop can occur between the two nodes). We set $T_{aa} = 0$ for all a. The denominator in Equation (8) ensures normalization ($\sum_b T_{ab} = 1$).

We always assume the network does not divide into multiple disconnected components. As a result, the transition matrix defined in Equation (8) is such that a walker starting at any node a will eventually reach any other node $b \neq a$ with finite probability.

4.2.2 | Interpretation of electrical current

Electrical current can be interpreted in the random-walk picture as follows:[37] When a voltage is applied between two nodes a and b such that the total current flowing into a and out of b from the exterior is 1, the current induced in each edge, cd, is equal to the expected *net* number of times a random walker, starting at a and walking until it reaches b, moves along the edge from c to d. The net number of times the walker moves from c to d is the number of crossings in the direction from c to d minus the number of crossings in the opposite direction.

To describe this mathematically we need to ensure that no more hops occur when the walker reaches the designated end point b. In other words, this node must become absorbing. This is achieved by setting the elements T_{bc} to zero for all c. For later convenience we denote the resulting modified transition matrix by $\boldsymbol{T}^{(ab)}$, recognizing that the modifications made only depend on the choice of b, and not on a. Mathematically, we have $T_{bc}^{(ab)} = 0$ for all $c \neq b$, and $T_{cd}^{(ab)} = T_{cd}$ for $c \neq b$ and all d. We set $T_{bb}^{(ab)}$ to unity.

Now consider random walks starting at node a and then following the process defined by the transition matrix $\boldsymbol{T}^{(ab)}$. All walks therefore end at node b. The probability that a walker takes a particular path π connecting a and b can be written as

$$P^{(ab)}(\pi) = \prod_{\{xy \in \pi\}} T_{xy}^{(ab)}, \tag{9}$$

where the notation $\{xy \in \pi\}$ indicates the set of pairs of successive nodes in the path π. We note that $P^{(ab)}(\pi)$ is non-zero if and only if the path π starts at a and ends when b is reached for the first time.

The average number of net crossings from node c to node d along paths starting at a and ending at b can therefore be obtained as

$$\overline{N_{cd}^{(ab)}} = \sum_{\pi} P^{(ab)}(\pi) N_{cd}(\pi), \tag{10}$$

where $N_{cd}(\pi)$ is the net number of crossings from c to d along path π. We note that this quantity can be negative; this occurs if the walker makes more transitions from d to c than from c to d. The sum in Equation (10) extends over all paths connecting a and b.

To develop some intuition, consider again the electrical network in Figure 3A. Assume that we are interested in the scenario where the external current flows into node 1 and out of node 2, but not into or out of any of the other nodes. We then start the random-walk process at node 1, and use transition probabilities as defined in Equation (8) until the walker reaches node 2. In the first step, the walker either hops to node 2 (this occurs with probability $T_{1\text{-}2}$) or to node 3 (with probability $T_{1\text{-}3}$). If the walker hops to node 2, the walk stops and the path taken by the walker is $1 \rightarrow 2$. Otherwise, the walker is at node 3 and in the next step it can transition to 2, 4 or back to 1 with respective probabilities $T_{3\text{-}2}$, $T_{3\text{-}4}$ and $T_{3\text{-}1}$. This process continues until the walker eventually reaches node 2. The current through the edge cd is then given by the expected net number of times such a walker crosses the edge from c to d before it arrives at node 2. A crossing in the direction from d to c contributes negatively to this value.

Since the random walker can move in both directions along the network edges, there are infinitely many paths the walker can take as it travels from node 1 to node 2 in this example. Figure 3C shows one possible path, $1 \rightarrow 3 \rightarrow 4 \rightarrow 3 \rightarrow 2$. The probability the random walker takes this path is given by the product of the individual transition probabilities along the path, that is

$$P^{(1\text{-}2)}(1 \rightarrow 3 \rightarrow 4 \rightarrow 3 \rightarrow 2) = T_{1\text{-}3} T_{3\text{-}4} T_{4\text{-}3} T_{3\text{-}2}. \tag{11}$$

Although $P^{(ab)}(\pi)$ can be obtained relatively easily for each path π, carrying out the sum in Equation (10) by exhaustive enumeration of all relevant paths is not practicable. This is because there are generally infinitely many paths starting and ending at the designated nodes (due to the possibility to hop back to nodes visited earlier).

The analogy between electrical circuits and random walks[37] however can be used to calculate the expected number of net crossings through an edge analytically. This is detailed in Sections F and G of the Supplement, see in particular Equation (G45).

The expected number of net crossings can also be obtained from simulations of the random-walk process. An ensemble of walkers is released at the starting point a. Each walker then independently hops from node to node on the network with transition rates as in Equation (8) until it hits the designated endpoint (node b). The process then stops. For each walker the net number of crossings from c to d can be recorded, and this is then averaged over the ensemble of walkers.

4.3 | Random walk on a meta-analytic network

As described above, conductance (inverse resistance) in an electrical network has an analog in terms of both NMA, and random walks. Exploiting these analogies, we now define a random-walk process on a meta-analytic network via the transition rates

$$T_{ab} = \frac{w_{ab}}{\sum_{c \neq a} w_{ac}}, \tag{12}$$

with weights w_{ab} associated with the edges as discussed in Section 3.2, see in particular Equation (2).

In order to study walks starting at node a and ending at b we use the matrix $T^{(ab)}$ as defined in Section 4.2.2. This enforces absorption of the walker at node b when this node is reached. For the example aggregate network in Figure 2A, the transition matrix for a random walk starting at node 1 and ending at node 2 is

$$T^{(1\text{-}2)} = \begin{pmatrix} 0 & 1/8 & 3/8 & 0 & 4/8 \\ 0 & 1 & 0 & 0 & 0 \\ 3/11 & 6/11 & 0 & 0 & 2/11 \\ 0 & 5/12 & 0 & 0 & 7/12 \\ 4/13 & 0 & 2/13 & 7/13 & 0 \end{pmatrix}. \tag{13}$$

Each row and column of $T^{(1\text{-}2)}$ represents a treatment in the network, $a = 1, 2, 3, 4, 5$. Given that we focus on the comparison between treatments 1 and 2, node 1 is the start point of the walk, and node 2 is absorbing. Therefore, the row corresponding to treatment 2 contains only zeroes except for the diagonal element which is equal to one (when the walker reaches node 2 it stays there indefinitely). The entries in each row of the matrix in Equation (13) sum to one. The diagonal elements of $T^{(1\text{-}2)}$ (except for the element relating to node 2) are zero. This indicates that, with the exception of the absorbing state, the random walker cannot stay at the same place at any step. Figure 2C illustrates the dynamics of the random walk from node 1 to node 2 for this example.

In Section 4.1 we made the connection between the flow of electric current and the flow of evidence in an NMA. Using the interpretation of current as a random walk we can now establish the following analogy: For the comparison of treatments a and b, the hat matrix element $H_{cd}^{(ab)}$ that defines the flow of evidence through the direct comparison cd is equal to the expected *net* number of times a random walker starting at node a on the aggregate NMA network moves along the edge from c to d before it reaches node b. In other words, we equate

$$H_{cd}^{(ab)} = \overline{N_{cd}^{(ab)}}, \tag{14}$$

and define the flow of evidence $f_{cd}^{(ab)}$ in terms of $H_{cd}^{(ab)}$ via Equation (6).

The random-walk picture that we have developed provides a possible interpretation for the concept of "flow of evidence". Namely, it is random walkers starting at a and ending at b that "flow" along the network based on the rules defined by the transition rates T_{cd}. A more detailed discussion of this interpretation can be found in Section C of the Supplementary Material.

In summary, we have used existing analogies between electric circuits and random walks on the one hand, and network meta-analysis and electric circuits on the other to introduce an interpretation of the flow of evidence in network meta-analysis in terms of random walks. The analogies between all three areas are highlighted in Table 1.

5 | PROPORTION CONTRIBUTION

In this section we present a random-walk interpretation and construction of the so-called "proportion contribution matrix".[9] As explained in more detail below, the definition of these proportion contributions originates from the fact that we can interpret each row of the hat matrix as a flow network.[8,9] For this task, therefore, the random walk now no longer takes place on the meta-analytic network. Instead, walkers move on the evidence flow network. The entries of the proportion contribution matrix in NMA can then be obtained from this random walk.

We show that the random-walk approach overcomes the limitations of the algorithm proposed for the evaluation of proportion contributions in Papakonstantinou et al.[9] In particular, it provides an analytical expression for proportion contributions that removes ambiguity associated with the selection of paths. Furthermore, unlike the numerical algorithm of Papakonstantinou et al,[9] the random-walk approach identifies all paths of evidence so that all potential sources of bias are taken into account. In Section 5.1 we introduce the concept of proportion contributions. In Section 5.2 we describe the algorithm in Papakonstantinou et al[9] and its limitations. We then present and discuss the random-walk approach in Section 5.3.

5.1 | Background and definition

In NMA it is important to assess the influence of individual study bias on the estimates obtained from the network. To this end, the CINeMA framework and software[10,45] provides a user friendly system to assess confidence in the results

from an NMA. One function of the software is to display the relative influence of evidence that comes from studies with high, moderate and low risk of bias on each network treatment effect. This assessment involves calculating the matrix of so-called "proportion contributions".[9] This matrix describes how much each direct treatment effect contributes to each network treatment effect as a relative *proportion*. The idea of the proportion contribution matrix is based on the hat matrix. The elements of the hat matrix are the coefficients of the linear relation between network estimates and direct estimates in the NMA as described in Equation (4). These coefficients can be positive or negative. The proportion contribution matrix uses the properties of the hat matrix and translates the elements of $\boldsymbol{H}$ to positive proportion contributions, where the total contribution is normalized to one. We now explain this in more detail using the work of Papakonstantinou et al.[9]

Consider the example network in Figure 5A. This relates to an NMA of the four topical antibiotics given in the figure caption for the treatment of chronically discharging ears.[46] To keep the text concise we label the treatments 1, 2, 3, and 4. In accordance with Equation (4), the network estimate of comparison 1-2 is given by the linear Equation (7), which we repeat here for clarity,

$$\hat{\theta}_{1\text{-}2}^{\text{net}} = H_{1\text{-}2}^{(1\text{-}2)}\hat{\theta}_{1\text{-}2}^{\text{dir}} + H_{1\text{-}3}^{(1\text{-}2)}\hat{\theta}_{1\text{-}3}^{\text{dir}} + H_{2\text{-}3}^{(1\text{-}2)}\hat{\theta}_{2\text{-}3}^{\text{dir}} + H_{2\text{-}4}^{(1\text{-}2)}\hat{\theta}_{2\text{-}4}^{\text{dir}} + H_{3\text{-}4}^{(1\text{-}2)}\hat{\theta}_{3\text{-}4}^{\text{dir}}. \tag{15}$$

We can think of the expression on the right-hand side as a combination of different direct and indirect estimates of $\theta_{1\text{-}2}$. The direct estimate is simply $\hat{\theta}_{1\text{-}2}^{\text{dir}}$. We obtain one indirect estimate using node 3 and the consistency equation,

$$\hat{\theta}_{1\text{-}2}^{\text{ind}(1)} = \hat{\theta}_{1\text{-}3}^{\text{dir}} - \hat{\theta}_{2\text{-}3}^{\text{dir}}. \tag{16}$$

A second indirect estimate is found via nodes 3 and 4,

$$\hat{\theta}_{1\text{-}2}^{\text{ind}(2)} = \hat{\theta}_{1\text{-}3}^{\text{dir}} - (\hat{\theta}_{2\text{-}4}^{\text{dir}} - \hat{\theta}_{3\text{-}4}^{\text{dir}}). \tag{17}$$

These three ways of estimating $\theta_{1\text{-}2}$ correspond to so-called "paths of evidence" on the evidence flow network.[9] We label these paths π_i $(i = 1, 2, 3)$. As illustrated in Figure 5B, these are $\pi_1 = 1{\to}2$, $\pi_2 = 1{\to}3{\to}2$, and $\pi_3 = 1{\to}3{\to}4{\to}2$. We can now write the network estimate $\hat{\theta}_{1\text{-}2}^{\text{net}}$ as a linear combination of the estimates $\hat{\theta}_{1\text{-}2}^{\text{dir}}$, $\hat{\theta}_{1\text{-}2}^{\text{ind}(1)}$, and $\hat{\theta}_{1\text{-}2}^{\text{ind}(2)}$. That is,

$$\begin{aligned} \hat{\theta}_{1\text{-}2}^{\text{net}} &= \phi_1\hat{\theta}_{1\text{-}2}^{\text{dir}} + \phi_2\hat{\theta}_{1\text{-}2}^{\text{ind}(1)} + \phi_3\hat{\theta}_{1\text{-}2}^{\text{ind}(2)} \\ &= \phi_1\hat{\theta}_{1\text{-}2}^{\text{dir}} + \phi_2(\hat{\theta}_{1\text{-}3}^{\text{dir}} - \hat{\theta}_{2\text{-}3}^{\text{dir}}) + \phi_3(\hat{\theta}_{1\text{-}3}^{\text{dir}} - \hat{\theta}_{2\text{-}4}^{\text{dir}} + \hat{\theta}_{3\text{-}4}^{\text{dir}}). \end{aligned} \tag{18}$$

The coefficients, ϕ_i, define the flow of evidence through each path π_i, see Papakonstantinou et al.[9]

Figure 5B shows how the flows in each edge, described by the hat matrix coefficients, are deconstructed into the flows through each path of evidence, described by the coefficients ϕ_i. In this example, only the edge 1-3 is used for more than one path. When calculating the flow through each path, the flow in edge 1-3 is "split" between the paths $\pi_2 = 1{\to}3{\to}2$, and $\pi_3 = 1{\to}3{\to}4{\to}2$ according to the flow in the subsequent edges along those two paths.

A so-called "stream" of evidence[9] is a pair consisting of a path and the flow associated with this path, $S_i = (\pi_i, \phi_i)$. The proportion contribution of each direct comparison cd to the network estimate of each comparison ab, is then defined as[9]

$$p_{cd}^{(ab)} = \sum_{i:\ cd \in \pi_i} \frac{\phi_i}{|\pi_i|}, \tag{19}$$

where $|\pi_i|$ is the number of edges that make up the path. The sum extends over all paths in the evidence flow network for the comparison ab that contain the edge cd. We note that all such paths start at a and end at b, and, because the evidence flow network is acyclic, multiple visits to the same node do not occur.

(A)

Evidence flow network
for comparison 1−2

(B)

Evidence streams for comparison 1−2
(paths taken by a random walker)

(C)

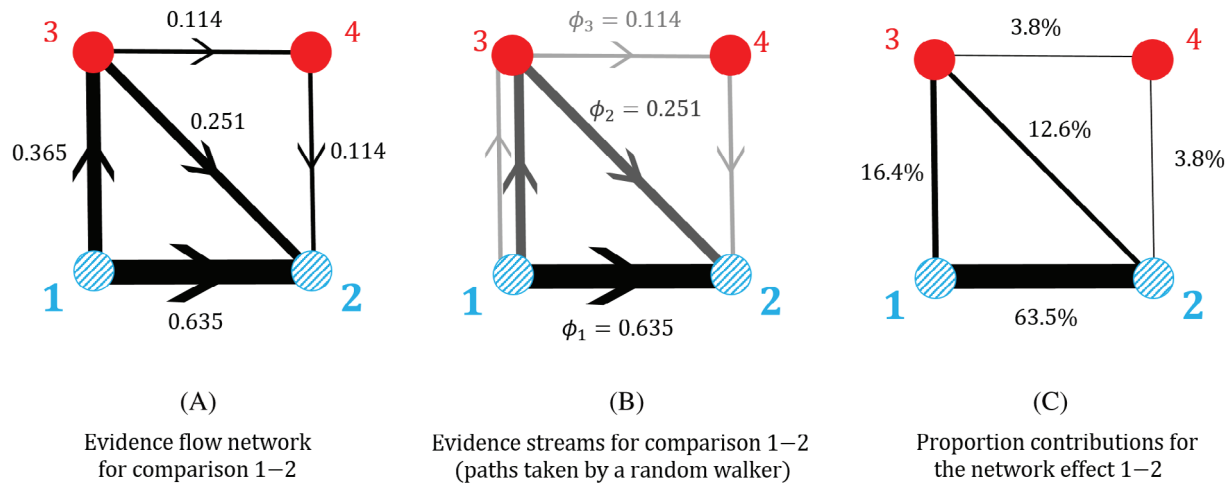Proportion contributions for
the network effect 1−2

FIGURE 5 Illustration of evidence flow, streams of evidence and proportion contributions for a network of topical antibiotics without steroids for chronically discharging ears presented in Macfadyen.[46] Node 1 is no treatment; 2 is quinolone antibiotic; 3 is antiseptic; and 4 is non-quinolone antibiotic. (A) The evidence flow network for comparison 1-2, based on Figure 1, panel (b) in Papakonstantinou et al.[9] The edge labels are the entries of the 1-2 row of the hat matrix, their signs are associated with the direction of the arrows. (B) The decomposition of edge flows into flow through paths of evidence as estimated by the algorithm in Papakonstantinou et al. The paths of evidence shown are equivalent to the possible paths taken by a random walker on the evidence flow network. (C) The proportion contributions (expressed as percentages) of each direct treatment effect to the network estimate of the 1-2 relative treatment effect

For simple examples, such as the one in Figure 5, one can obtain the path flows ϕ_i by directly comparing coefficients in Equations (15) and (18). Using the properties of the hat matrix in Section 3.4 one can then also see that $\phi_i \geq 0$ for all i, and that $\sum_i \phi_i = 1$. This means that the proportion contributions in Equation (19) are also non-negative, and sum to one. Figure 5C shows the proportion contributions, expressed as percentages, for the example in Figure 5A.

For larger, more connected networks it is not immediately clear how to obtain the ϕ_i. In particular, when there are more paths than edges, expressing the ϕ_i in terms of the coefficients of the hat matrix is non-trivial. Papakonstantinou et al[9] present an iterative algorithm to identify streams for a general evidence flow network. The starting point for this algorithm is the hat matrix. In the initial implementation of the algorithm, Papakonstantinou et al[9] used a hat matrix that did not account for correlations due to multi-arm trials (it treated each comparison in a multi-arm trial as an independent two-arm study). In this work, we instead implement the algorithm using the hat matrix of the aggregate model defined in Equation (5). We will now briefly describe the algorithm.

5.2 | Existing iterative numerical algorithm to determine streams of evidence

Broadly speaking, each iteration of the algorithm consists of the following steps: (i) A path in the evidence flow network is selected. (ii) The minimum flow through the edges making up the path is identified. This is assigned as the flow associated with the path. (iii) The flow of the path is subtracted from the values of flow in the edges that make up that path. This means that the edge corresponding to the minimum flow in that path is removed from the graph. (iv) A new path is then selected from the remaining graph. The process repeats until all the evidence flow in the edges has been assigned to a path.

Different methods for selecting the paths in step (i) give rise to multiple variants of the algorithm. For example, paths may be selected at random or in order from shortest to longest. We refer to these approaches as "Random" and "Shortest", respectively. The Shortest algorithm is implemented in the software `netmeta` using a breadth first search algorithm.[47] Each time the Random algorithm is run it selects the paths in a different order and, potentially, gives a different outcome. For reasons of reproducibility, this version of the algorithm is not implemented in current software. For simple networks such as the example in Figure 5, the order of selection does not affect the outcome. However, for more

complicated networks this is not the case. In some graphs, the flow of evidence is fully exhausted before every possible path has been selected. The remaining paths can then not be associated with any flow. Critically, this approach means that many paths of evidence are not identified and their contribution (along with any potential bias) is not accounted for. The set of paths that are missed in this way can depend on the order in which paths are selected by the algorithm. Examples of this behavior are presented in Supplementary File 3 in Papakonstantinou et al[9] and in Section 6.2 of this article.

One potential remedy consists of averaging results from the Random algorithm by Papakonstantinou et al[9] over a large number of realizations. We call this method "Average". Provided enough realizations are generated, the Average algorithm will eventually identify every evidence path. However, because of the nature of the algorithm, the number of times a particular path is sampled by this method can depend on features of the network not directly related to the path. In step (iii) of the algorithm the edge associated with the smallest flow in a particular path is removed from the network. This means that any other path containing this edge can no longer be selected. As a result, paths that do not share edges with any other paths will be selected in every run of the algorithm, whereas paths which do share edges with other paths will be sampled less often. It is therefore not clear how to interpret average proportion contributions determined in this way. Furthermore, this approach is computationally intensive as it relies on repeating the (already iterative) algorithm many times. For this reason, this version of the algorithm is not implemented in current software.

To overcome these limitations, we develop a random-walk approach for deriving the streams of evidence. We will now describe this.

5.3 | Random walk on the evidence flow network

To obtain the evidence streams we define a random walk on the evidence flow network for comparison ab. We denote the transition matrix for this model by $\boldsymbol{U}^{(ab)}$ to distinguish it from the random-walk on the aggregate NMA network defined in Section 4.3. We note that there is a different evidence flow network for each treatment comparison ab. We indicate this by the superscript (ab). Since the evidence flow network has directed edges the walker can only move in one direction along each edge (in the direction of evidence flow). Node a in the evidence flow network for comparison ab has only outgoing edges, and node b only incoming edges. We also note that the evidence flow network is acyclic.[8] This means that a walker can never visit any node more than once.

It is important to distinguish carefully between the random-walk model on the aggregate network and that on the evidence flow network. In Section 4.3 we defined a transition matrix for a random walker moving from node a to node b on the aggregate meta-analytic network. The walker was allowed to move in both directions along the edges of the network. We labeled this transition matrix $\boldsymbol{T}^{(ab)}$ where the superscript indicates the start and end nodes of the walk, that is, the treatment comparison we are interested in. By analyzing the average movement of the walker, we obtained the evidence flow. In this section we focus instead on a random walk on the evidence flow network, and our aim is to construct streams of evidence. The two approaches are summarized in Table 2.

To illustrate this, we consider the evidence flow network for comparison 1-2 in Figure 5A. We now construct a transition matrix for a random walk on this directed acyclic graph assuming that the walker starts at node 1. In contrast to random walks on the undirected meta-analytic graphs in Section 4.3, the walker can only move in one direction across each edge as indicated by the direction of evidence flow. If the flow $f_{cd}^{(ab)} = 0$ (because the associated hat matrix element $H_{cd}^{(ab)} \leq 0$), then no hop from c to d can occur. Each possible transition occurs with probabilities proportional to the evidence flows indicated in Figure 5A. More generally, for the evidence flow network of comparison ab, the elements of the transition matrix $\boldsymbol{U}^{(ab)}$ are given by

$$U_{cd}^{(ab)} = \frac{f_{cd}^{(ab)}}{\sum_{x \neq c} f_{cx}^{(ab)}} = \begin{cases} \frac{H_{cd}^{(ab)}}{\sum_{x \neq c} H_{cx}^{(ab)}} & \text{if } H_{cd}^{(ab)} > 0, \\ \\ 0 & \text{if } H_{cd}^{(ab)} < 0. \end{cases} \tag{20}$$

TABLE 2 Summary of the two random-walk approaches to NMA

Section	Network	Transition probabilities	Measured quantity	Outcome
4.3	Aggregate	$T_{cd} = \dfrac{w_{cd}}{\sum\limits_{x \neq c} w_{cx}}$	Expected net number of times a walker crosses an edge while traveling from a to b	Flow of evidence through the edge (elements of the hat matrix in the row corresponding to comparison ab)
5.3	Evidence flow	$U_{cd}^{(ab)} = \begin{cases} \dfrac{H_{cd}^{(ab)}}{\sum_{x \neq c} H_{cx}^{(ab)}} & \text{if } H_{cd}^{(ab)} > 0 \\ 0 & \text{if } H_{cd}^{(ab)} < 0 \end{cases}$	Proportion of walkers taking a particular path while traveling from a to b	Evidence streams for the comparison between a and b

Note: In one approach ("aggregate") the walker moves on the undirected aggregate network. In the second ("evidence flow"), the walker moves on the directed acyclic evidence flow network for a particular comparison of treatments. The transition matrices are denoted by T and $U^{(ab)}$ respectively. Except for the imposition of a suitable absorbing state (see text) the transition probabilities on the aggregate network do not depend on the particular comparison that is studied. In contrast, there are separate evidence flow networks (and hence random-walk models) for each comparison ab, hence the superscript in $U^{(ab)}$. The first column in the table indicates the sections in the text containing further definitions and details.

For the comparison ab, the walker remains at b indefinitely once it gets there, that is, we have $U_{bb}^{(ab)} = 1$, and the probability of transitioning from b to any other node $c \neq b$ is $U_{bc}^{(ab)} = 0$. All other elements of the matrix $U^{(ab)}$ are given by Equation (20).

For the example in Figure 5A, the transition matrix for a random walk on this graph is

$$U^{(1\text{-}2)} = \begin{pmatrix} 0 & 0.635 & 0.365 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & \frac{0.251}{0.251+0.114} & 0 & \frac{0.114}{0.251+0.114} \\ 0 & 1 & 0 & 0 \end{pmatrix} = \begin{pmatrix} 0 & 0.635 & 0.365 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0.688 & 0 & 0.312 \\ 0 & 1 & 0 & 0 \end{pmatrix}. \tag{21}$$

The third row of $U^{(1\text{-}2)}$ corresponds to transitions from node 3. From Equation (20) and the edge flows shown in Figure 5A, we find that if the walker is at node 3, then it moves to either node 2 or node 4 with probabilities $0.251/(0.251 + 0.114)$ and $0.114/(0.251 + 0.114)$ respectively. Similar calculations are done to find the elements in the other rows. Once arrived at 2 the walker remains there indefinitely. This behavior is described by the second row of $U^{(1\text{-}2)}$.

The walker can take one of three paths from 1 to 2: $\pi_1 = 1 \rightarrow 2$, $\pi_2 = 1 \rightarrow 3 \rightarrow 2$, or $\pi_3 = 1 \rightarrow 3 \rightarrow 4 \rightarrow 2$. These are the same as the paths of evidence defined in Section 5.1 and are illustrated in Figure 5B. The probability of a walker taking a certain path is given by the product of the individual transition probabilities associated with each edge along that path (Equation (9)). For example, the probability that a random walker takes the path $1 \rightarrow 3 \rightarrow 2$ is $P^{(1\text{-}2)}(\pi_2) = U_{1\text{-}3}^{(1\text{-}2)} U_{3\text{-}2}^{(1\text{-}2)} = 0.365 \times 0.688$.

The probability that a walker takes a given path can also be measured from simulations of the random-walk process on the evidence flow network. To do this one simulates a large ensemble of independent walkers, and measures the proportions of walkers taking each path. We can think of this as flows of walkers through the different paths. We use this interpretation to provide a general analytical definition of the flow of evidence through a particular path: for the evidence flow network for comparison ab, we define

$$\phi_i = P^{(ab)}(\pi_i) = \prod_{cd \in \pi_i} U_{cd}^{(ab)}. \tag{22}$$

With this definition we can construct decompositions such as the one in Equation (18) for all networks. From the ϕ_i the proportion contributions can then be calculated via Equation (19).

For the example in Figure 5A, Equation (22) leads to the streams,

$$S_1 = (\pi_1, \phi_1): \qquad \pi_1 = 1 \rightarrow 2 \qquad \phi_1 = U_{1\text{-}2}^{(1\text{-}2)} = 0.635, \tag{23}$$

$$S_2 = (\pi_2, \phi_2): \qquad \pi_2 = 1 \rightarrow 3 \rightarrow 2 \qquad \phi_2 = U_{1\text{-}3}^{(1\text{-}2)} U_{3\text{-}2}^{(1\text{-}2)} = 0.365 \times \frac{0.251}{0.251 + 0.114} = 0.251, \tag{24}$$

$$S_3 = (\pi_3, \phi_3): \qquad \pi_3 = 1 \rightarrow 3 \rightarrow 4 \rightarrow 2 \qquad \phi_3 = U_{1\text{-}3}^{(1\text{-}2)} U_{3\text{-}4}^{(1\text{-}2)} U_{4\text{-}2}^{(1\text{-}2)} = 0.365 \times \frac{0.114}{0.251 + 0.114} \times 1 = 0.114. \tag{25}$$

For this simple example the random-walk approach results in the same evidence streams (and therefore proportion contributions) as the algorithm by Papakonstantinou et al, see Figure 5B.

The random-walk approach provides an analytical construction of the proportion contributions. Unlike the iterative algorithm, the outcome is unambiguous. In the following section we demonstrate how the random-walk approach can be used for the more intricate network from Section 2.

6 | APPLICATION TO REAL DATA SET

We now apply the random-walk approach to the data set described in Section 2. Following Rücker and Schwarzer,[39] we choose a fixed-effect model ($\tau^2 = 0$). The edge weights in the aggregate network were obtained using the methods described in Section 3 and are shown in Figure 6.

6.1 | Evidence flows

First, we use the random-walk approach described in Section 4.3 to obtain the evidence flows for a certain comparison. We focus on the comparison of treatments 1 (tricyclic or tetracyclic antidepressants) and 3 (psychotherapy + usual care). To this end, we define the transition matrix for a random walker on the *aggregate network* (Figure 6) starting at node 1 and ending at node 3. Using Equation (12) we find
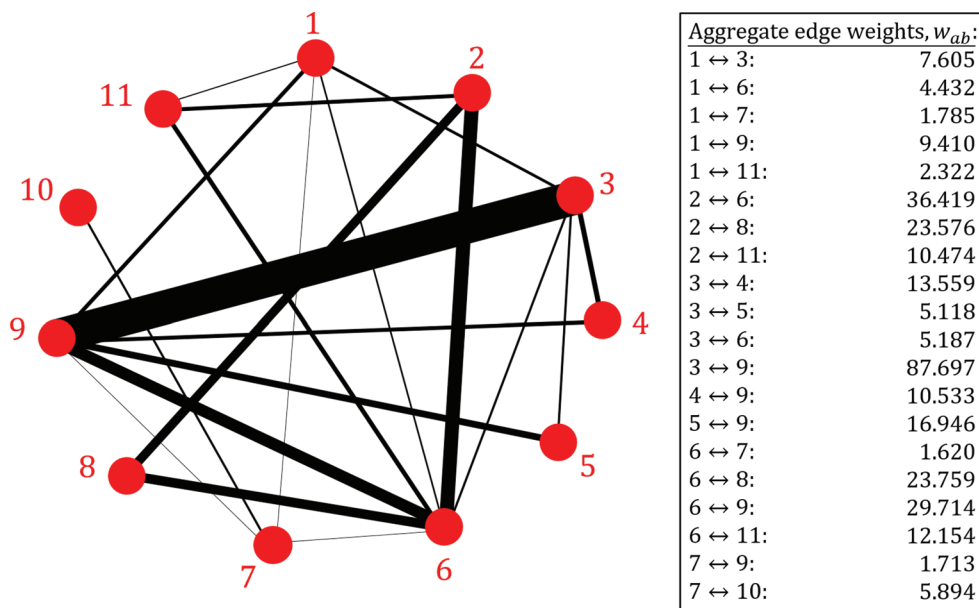

Aggregate edge weights, w_{ab}:	
1 ↔ 3:	7.605
1 ↔ 6:	4.432
1 ↔ 7:	1.785
1 ↔ 9:	9.410
1 ↔ 11:	2.322
2 ↔ 6:	36.419
2 ↔ 8:	23.576
2 ↔ 11:	10.474
3 ↔ 4:	13.559
3 ↔ 5:	5.118
3 ↔ 6:	5.187
3 ↔ 9:	87.697
4 ↔ 9:	10.533
5 ↔ 9:	16.946
6 ↔ 7:	1.620
6 ↔ 8:	23.759
6 ↔ 9:	29.714
6 ↔ 11:	12.154
7 ↔ 9:	1.713
7 ↔ 10:	5.894

FIGURE 6   The aggregate network for the depression data set in Section 2. Treatments 1 to 11 are defined in Figure 1. Here the thickness of each edge *ab* represents the associated weight, w_{ab}. The aggregate weights, as presented in the box, were calculated using the methods described in Section 3. The values are quoted to 3 decimal places

$$
T^{(1\text{-}3)} = \begin{array}{c}
 \\
1 \\
2 \\
3 \\
4 \\
5 \\
6 \\
7 \\
8 \\
9 \\
10 \\
11
\end{array}
\begin{array}{ccccccccccc}
1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 & 9 & 10 & 11 \\
0 & 0 & 0.298 & 0 & 0 & 0.173 & 0.070 & 0 & 0.368 & 0 & 0.091 \\
0 & 0 & 0 & 0 & 0 & 0.517 & 0 & 0.335 & 0 & 0 & 0.149 \\
0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0.563 & 0 & 0 & 0 & 0 & 0 & 0.437 & 0 & 0 \\
0 & 0 & 0.232 & 0 & 0 & 0 & 0 & 0 & 0.768 & 0 & 0 \\
0.039 & 0.321 & 0.046 & 0 & 0 & 0 & 0.014 & 0.210 & 0.262 & 0 & 0.107 \\
0.162 & 0 & 0 & 0 & 0 & 0.147 & 0 & 0 & 0.156 & 0.535 & 0 \\
0 & 0.498 & 0 & 0 & 0 & 0.502 & 0 & 0 & 0 & 0 & 0 \\
0.060 & 0 & 0.562 & 0.068 & 0.109 & 0.190 & 0.011 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\
0.093 & 0.420 & 0 & 0 & 0 & 0.487 & 0 & 0 & 0 & 0 & 0
\end{array}
\qquad (26)
$$

We have labeled the rows and columns according to the treatments they represent and we quote the values of the entries in the matrix to 3 decimal places. The third row of $T^{(1\text{-}3)}$ is constructed such that once the walker reaches node 3 (the end node) it remains there indefinitely.

As described in Section 4.3, the evidence flow through each direct comparison for the network comparison 1-3 is obtained from the expected net number of times a walker crosses each edge as it travels from node 1 to node 3 on the aggregate network (Figure 6). The expected net number of times a walker crosses each edge can be estimated by simulating a large ensemble of random walkers, each moving independently as described by the transition matrix $T^{(1\text{-}3)}$. For each walker we count the net number of times it crosses the designated edge, and we then subsequently average over all walkers. The more walkers we simulate, the more accurate our estimation.

Alternatively, we can use the analogy to electrical networks described in Section 4.2 to obtain an analytical result for this value in terms of electric current. These methods are described in more detail in Section G of the Supplement.
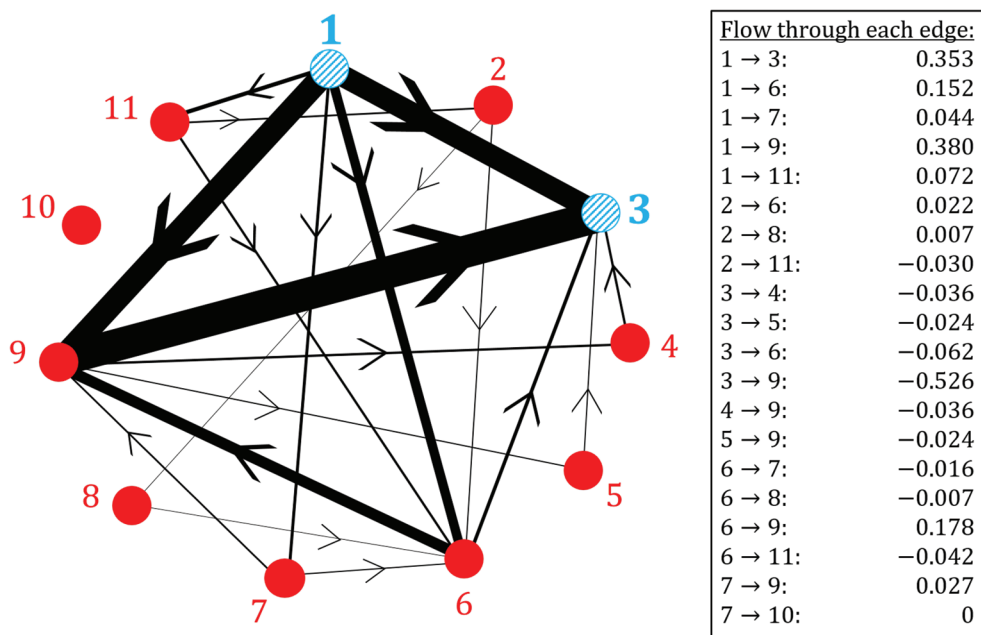

Flow through each edge:

Edge	Flow
$1 \to 3$:	0.353
$1 \to 6$:	0.152
$1 \to 7$:	0.044
$1 \to 9$:	0.380
$1 \to 11$:	0.072
$2 \to 6$:	0.022
$2 \to 8$:	0.007
$2 \to 11$:	−0.030
$3 \to 4$:	−0.036
$3 \to 5$:	−0.024
$3 \to 6$:	−0.062
$3 \to 9$:	−0.526
$4 \to 9$:	−0.036
$5 \to 9$:	−0.024
$6 \to 7$:	−0.016
$6 \to 8$:	−0.007
$6 \to 9$:	0.178
$6 \to 11$:	−0.042
$7 \to 9$:	0.027
$7 \to 10$:	0

FIGURE 7   The evidence flow network for the comparison of treatments 1 and 3 in the depression data set in Section 2. The thickness of each edge corresponds to the expected net number of times a random walker crosses each edge of the aggregate network in Figure 6 as it travels from node 1 to node 3. The direction of flow is indicated by the arrow. These values are summarized in the box and quoted to 3 decimal places

We choose the analytical approach which results in the evidence flow network shown in Figure 7. We find that for the comparison of treatments 1 and 3, most of the evidence flows directly from 1 to 3 or indirectly via treatment 9. Comparing Figures 6 and 7 we observe that the pairwise comparison of treatments 7 and 10 is the only piece of direct evidence that has no influence on the network comparison 1-3.

The hat matrix of the aggregate model for this data is given in Section H.1 of the Supplement. The flow network obtained from the row of the hat matrix corresponding to the comparison of treatments 1 and 3 is identical to the network in Figure 7.

6.2 | Proportion contributions

Next, we calculate the proportion contributions for the network comparison 1-3. To do this we first define the transition matrix for a random walker moving from node 1 to node 3 on the *evidence flow network* (Figure 7). From Equation (20) we find

$$
U^{(1\text{-}3)} = \begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \\ 5 \\ 6 \\ 7 \\ 8 \\ 9 \\ 10 \\ 11 \end{array}
\begin{array}{c}
\begin{array}{cccccccccccc}
1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 & 9 & 10 & 11
\end{array} \\
\left(\begin{array}{ccccccccccc}
0 & 0 & 0.353 & 0 & 0 & 0.152 & 0.044 & 0 & 0.380 & 0 & 0.072 \\
0 & 0 & 0 & 0 & 0 & 0.755 & 0 & 0.245 & 0 & 0 & 0 \\
0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0.259 & 0 & 0 & 0 & 0 & 0 & 0.741 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0.371 & 0 & 0 & 0.629 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0.899 & 0.061 & 0.040 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\
0 & 0.415 & 0 & 0 & 0 & 0.585 & 0 & 0 & 0 & 0 & 0
\end{array}\right)
\end{array}, \tag{27}
$$

where we have again labeled the rows and columns. Matrix entries are quoted to 3 decimal places. The third row indicates that once a walker reaches node 3 it remains there indefinitely. Since treatment 10 is disconnected from all other nodes in the evidence flow network (Figure 7), the probability of transitioning to this node from any other is zero. Similarly, if the walker starts at node 10, it remains there forever ($U_{10\text{-}10}^{(1\text{-}3)} = 1$).

The set of all possible paths that a random walker can take on the evidence flow network can be found using a recursive algorithm.[48] The probability with which the walker takes a particular path is calculated from Equation (22). This is the flow of evidence through that path. For the comparison of treatments 1 and 3 in the depression data set, we find 27 distinct paths. These paths and their associated flow ϕ_i make up the evidence streams presented in Table 3. We find $\phi_i \geq 0$ and $\sum_i \phi_i = 1$. Using these values we can construct the network estimate $\hat{\theta}_{1\text{-}3}^{\text{net}}$ as a linear combination of direct and indirect estimates following each evidence path listed in Table 3. This leads to the same odds ratios as those quoted in Rücker and Schwarzer[39] up to the precision provided.

Table 3 also contains the streams identified by the algorithm in Papakonstantinou et al[9] (see Section 5.1). We present the results for three versions of the algorithm, Shortest, Random and Average. The results for the Random algorithm are obtained from one single run. Each result in the column labeled "Average" is an average over 10^8 runs of the Random algorithm. From Table 3, it is clear that the streams identified by the iterative algorithm depend on the order in which paths are selected. For this example, fewer than half of the possible paths are identified by the Shortest and Random algorithms (paths not detected are indicated by the symbol "−"). Therefore, these versions of the algorithm fail to take into account multiple evidence paths that contribute to the NMA (and potentially have a high risk of bias).

Compared to the Shortest and Random versions of the algorithm, the Average algorithm produces results which are more similar to flows obtained from the random-walk approach. However, as described in Section 5.1, the frequency

TABLE 3 Evidence streams (paths and their associated flow) for the network comparison of treatments 1 and 3 in the depression data set in Section 2

Stream, S_i	Path, π_i	RW approach (analytical)	Algorithm Shortest	Random	Average
$S_1 = (\pi_1, \phi_1)$	1→3	0.3526	0.3526	0.3526	0.3526
$S_2 = (\pi_2, \phi_2)$	1→6→3	0.0394	0.0622	0.0549	0.0303
$S_3 = (\pi_3, \phi_3)$	1→6→9→3	0.1015	0.0901	0.0974	0.1091
$S_4 = (\pi_4, \phi_4)$	1→6→9→4→3	0.0069	-	-	0.0082
$S_5 = (\pi_5, \phi_5)$	1→6→9→5→3	0.0045	-	-	0.0048
$S_6 = (\pi_6, \phi_6)$	1→7→6→3	0.0042	-	-	0.0055
$S_7 = (\pi_7, \phi_7)$	1→7→6→9→3	0.0108	0.0162	-	0.0061
$S_8 = (\pi_8, \phi_8)$	1→7→6→9→4→3	0.0007	-	0.0162	0.0024
$S_9 = (\pi_9, \phi_9)$	1→7→6→9→5→3	0.0005	-	-	0.0021
$S_{10} = (\pi_{10}, \phi_{10})$	1→7→9→3	0.0246	0.0274	0.0274	0.0171
$S_{11} = (\pi_{11}, \phi_{11})$	1→7→9→4→3	0.0017	-	-	0.0060
$S_{12} = (\pi_{12}, \phi_{12})$	1→7→9→5→3	0.0011	-	-	0.0043
$S_{13} = (\pi_{13}, \phi_{13})$	1→9→3	0.3414	0.3798	0.3604	0.3656
$S_{14} = (\pi_{14}, \phi_{14})$	1→9→4→3	0.0231	-	0.0194	0.0090
$S_{15} = (\pi_{15}, \phi_{15})$	1→9→5→3	0.0153	-	-	0.0052
$S_{16} = (\pi_{16}, \phi_{16})$	1→11→2→6→3	0.0058	-	-	0.0076
$S_{17} = (\pi_{17}, \phi_{17})$	1→11→2→6→9→3	0.0150	-	-	0.0085
$S_{18} = (\pi_{18}, \phi_{18})$	1→11→2→6→9→4→3	0.0010	0.0062	-	0.0034
$S_{19} = (\pi_{19}, \phi_{19})$	1→11→2→6→9→5→3	0.0007	0.0163	0.0225	0.0030
$S_{20} = (\pi_{20}, \phi_{20})$	1→11→2→8→6→3	0.0019	-	0.0073	0.0024
$S_{21} = (\pi_{21}, \phi_{21})$	1→11→2→8→6→9→3	0.0049	-	-	0.0027
$S_{22} = (\pi_{22}, \phi_{22})$	1→11→2→8→6→9→4→3	0.0003	-	-	0.0012
$S_{23} = (\pi_{23}, \phi_{23})$	1→11→2→8→6→9→5→3	0.0002	0.0073	-	0.0010
$S_{24} = (\pi_{24}, \phi_{24})$	1→11→6→3	0.0109	-	-	0.0163
$S_{25} = (\pi_{25}, \phi_{25})$	1→11→6→9→3	0.0280	0.0126	0.0409	0.0170
$S_{26} = (\pi_{26}, \phi_{26})$	1→11→6→9→4→3	0.0019	0.0294	-	0.0054
$S_{27} = (\pi_{27}, \phi_{27})$	1→11→6→9→5→3	0.0013	-	0.0011	0.0033

Note: Results obtained from the random-walk (RW) approach are presented along with the results from three versions of the algorithm in Papakonstantinou et al.[9] "Shortest" refers to the algorithm where paths are selected from shortest to longest. "Random" describes the variant in which paths are selected at random, and "Average" is the average over 10^8 iterations of the Random algorithm. Values are rounded to 4 decimal places. The Shortest and Random algorithms fail to identify all possible paths, as indicated by the symbol "−".

TABLE 4 Proportion contributions, expressed as percentages, for the network comparison of treatments 1 and 3 in the depression data set

| | Proportion contribution, $p_{ab}^{(1-3)}$ | | | |
| | | Algorithm | | |
Direct evidence, ab	RW approach	Shortest	Random	Average
1-3	35.3%	35.3%	35.3%	35.3%
1-6	5.6 %	6.1 %	6.0%	5.5%
1-7	1.3 %	1.3%	1.2%	1.3%
1-9	18.3 %	19.0%	18.7%	18.8%
1-11	1.7%	1.4%	1.6%	1.7%
2-6	0.5%	0.4%	0.4%	0.5%
2-8	0.1%	0.1%	0.1%	0.1%
2-11	0.6%	0.5%	0.5%	0.6%
3-4	1.1%	0.7%	1.0%	0.9%
3-5	0.7%	0.4%	0.4%	0.6%
3-6	2.7%	3.1%	2.9%	2.5%
3-9	22.6%	23.6%	23.2%	23.3%
4-9	1.1%	0.7%	1.0%	0.9%
5-9	0.7%	0.4%	0.4%	0.6%
6-7	0.4%	0.4%	0.3%	0.4%
6-8	0.1 %	0.1%	0.1%	0.1%
6-9	5.1%	4.8%	5.0%	5.2%
6-11	1.1%	0.9%	1.0%	1.1%
7-9	0.9%	0.9%	0.9%	0.8%
7-10	0%	0%	0%	0%

Note: Results obtained from the random walk (RW) approach are presented along with the results from three versions of the algorithm in Papakonstantinou et al.[9] Shortest refers to the algorithm where paths are selected from shortest to longest. Random is when paths are selected at random. Average is the average over 10^8 iterations of the Random algorithm. Values are rounded to 1 decimal place.

with which a path is selected across different runs depends on whether it shares edges with other paths in the network. Therefore, the results of the Average algorithm do not necessarily converge to the results from the random-walk approach even as the number of iterations becomes large.

Using Table 3 and Equation (19), we calculate the proportion contribution of each direct estimate to the network comparison of treatments 1 and 3 from the random-walk approach. These contributions are presented as percentages in the second column of Table 4. The direct evidence from trials comparing treatments 1 and 3 has the largest contribution followed by indirect evidence from trials comparing 3 and 9, and 1 and 9. Table 4 also contains the proportion contributions obtained from the three versions of the algorithm (Shortest, Random, and Average). As before, these results depend on the order in which paths are selected.

7 | SUMMARY AND DISCUSSION

7.1 | The analogy between random walks and evidence flow, and the role of the graph theoretical model

In this article, we have presented a novel analogy between NMA and random walks. Edge weights from the aggregate graph theoretical NMA model define a transition matrix for a random walk on the network of evidence. The walker

moves around on the aggregate network along edges corresponding to direct evidence. The movement of the random walker contains information about the propagation of evidence through the network. In particular, we have shown that the expected net number of times a walker crosses an edge can be interpreted as the evidence flow through the direct comparison represented by that edge. Therefore, we can obtain the elements of the hat matrix of the aggregate model from the random-walk process on the aggregate network.

The flow of evidence defined by König et al[8] is based on a two-step version of the standard frequentist NMA model (see Section A of the Supplement). In the first step, the direct estimates are obtained by pooling evidence from trials making the same comparisons. For two-arm trials, a pairwise meta-analysis is performed. For multi-arm trials that compare a particular subset of treatments, an NMA is performed on the sub-graph described by the multi-arm trial design. The direct estimates are therefore separated into evidence that comes from two-arm trials and evidence from multi-arm trials. This is reflected in the hat matrix of this model. Consequently, in König et al's evidence flow networks, the flow through multi-arm trials is displayed separately. This is an interesting feature but, as the authors note, it is only feasible for simple networks.[8]

In our definition of evidence flow, we have instead used a two-step version of the so-called *graph theoretical* model.[7] We make use of the fact that the adjusted weights describe a network of two-arm trials which is equivalent to the network of multi-arm trials. The direct estimates are then obtained from pairwise meta-analyses using the adjusted edge weights. The elements in the row of the hat matrix for a particular comparison then assign a single value of flow to each direct treatment comparison in the network. The flow through an edge therefore represents the combined contribution from all studies, two-arm and multi-arm, that make that comparison. While this means that the specific contribution of multi-arm studies is not displayed, our approach makes it easier to display evidence flow networks for graphs with a large number nodes, edges and multi-arm trials of varying designs. In addition, it is this property of the aggregate level graph theoretical approach that means we are able to make the analogy to random walks in the general case (ie, networks including multi-armed trials).

As explained in Section A of the Supplementary Materials, the standard NMA model, the graph theoretical model and the aggregate level versions of both these models, all yield the same network treatment effect estimates.[8,39] For networks containing exclusively two-arm trials, the hat matrices of the two aggregate level models are the same. Therefore, for these networks, the evidence flow networks we define are the same as those in König et al.

The graph theoretical approach provides a straightforward visualization of the flow of evidence for each treatment comparison. Random effects models and networks with multi-arm trials can be accounted for with no extra complications. For networks with both of these characteristics, heterogeneity needs to be combined with the original observed variances (ie, one needs to use $\sigma_{i,ab}^2 + \tau^2$ instead of $\sigma_{i,ab}^2$) before adjusting the weights to deal with multi-arm trials.[39,42]

7.2 | The random walk derivation of evidence streams overcomes the limitations of previous algorithms

We have shown that the random-walk analogy for NMA leads to an analytical derivation of evidence streams. In doing so, we defined a second transition matrix, this time for a random walker moving on the evidence flow network. For each comparison of treatments *ab* there is one separate evidence flow network. The network is directed and it has no cycles. Walkers can only move in one direction along each edge, according to the direction of flow. All paths on this graph start at *a* and end at *b*. As the walker travels from *a* to *b* it moves along paths of direct and indirect evidence. Imagining a large number of independent random walkers undergoing this process, we interpret the proportion of walkers flowing through a particular path as the flow of evidence through that path, that is, the flow of evidence through a path is the probability of a walker taking that path. This can be expressed analytically as the product of the transition probabilities along the edges that make up the path.

The analytical definition of evidence streams leads directly to an analytical derivation of the so-called proportion contributions defined in Papakonstantinou et al.[9] The result is unambiguous in contrast with previously proposed algorithms whose output depends on the order in which paths are selected. Furthermore, individual runs of the algorithm in Papakonstantinou et al can fail to identify all paths of evidence on the evidence flow network. This means that in the calculation of proportion contributions, multiple paths of evidence and their potential bias are not taken into account. Running the algorithm many times and subsequently performing an average, we are eventually able to identify every path of evidence. However, the frequency with which a given path is selected depends strongly on the number of other paths with which it shares edges. As a result, the average flow obtained in this way does not accurately reflect the contribution

of each path. The random-walk approach overcomes these limitations. All possible paths of evidence are identified and they are each assigned a value of flow that reflects the properties of the hat matrix. Therefore, all possible sources of bias are taken into account in the calculation of the proportion contributions.

In our application to real data, we observe that the differences between the proportion contributions obtained from the random walk approach and those obtained via the Average algorithm are relatively small. We would expect larger differences between the two approaches when the network contains fewer independent paths, that is, when many pairs of paths have shared edges. This increases the bias in path selection in the Average algorithm. Potential characteristics that may lead to this scenario include networks that are highly connected, and networks that contain "central" nodes or edges.

For multi-arm trials, the method presented in Papakonstantinou et al[9] naïvely treats each pairwise comparison in a multi-arm trial as an independent two-arm study. This does not account for correlations due to multi-arm trials. By instead using the adjusted weights from the graph theoretical model, we are able to define a network of two-arm trials that is equivalent to the original network of multi-arm trials. Therefore, an additional advantage of the methods presented in this article, is that networks with multi-arm trials are handled more appropriately.

The CINeMA software currently relies on the algorithm in Papakonstantinou et al to calculate the relative contribution of studies with high, moderate and low risk of bias to each network treatment effect. Similarly, ROB-MEN (risk of bias due to missing evidence in network meta-analysis[19]) also uses the contribution matrix. Due to the advantages of the random-walk approach in deriving evidence streams we expect that applications such as these would benefit in terms of accuracy from the implementation of the method described in this article. The recently updated PRISMA guidelines[49] require systematic reviewers to assess their body of evidence for risk of bias. The results of our article mean that existing software tools to help researchers make this assessment can now be made more reliable. To this end, we have implemented the aggregate hat matrix in `netmeta`,[25] along with the random-walk approach to proportion contributions, see Section I in the Supplementary Material for details.

7.3 | Potential future impact

We believe that the analogy between NMA and random walks is interesting and that it provides new insight into NMA methodology. In our work we have explored the applications of only a small subset of the random-walk literature; there is, therefore, scope for the impact of this analogy to be investigated further. We hope that by presenting this analogy, more ideas will be shared between the two disciplines and additional practical applications of the random walk-approach will be developed in the future.

For example, we have looked at the interpretation of the number of times a walker crosses each edge in the network. However, there is potentially also interest in investigating the number of times the walker visits each node. The random walk transition probabilities are proportional to the respective edge weights. Therefore, a walker is more likely to travel across an edge corresponding to a more precise treatment effect estimate. The expected number of times a walker visits a certain node will depend on how many connections the node has, and the weight (ie, the inverse variance) associated with each of these connections. A node corresponding to a treatment that is involved in many direct comparisons will be visited more often than a node corresponding to a treatment with comparatively few connections. Furthermore, the larger the weight associated with the edges connected to a certain node, the more often the random walker will visit that node. Potentially, this value provides a measure of vertex centrality that accounts for both connectivity and the precision of treatment effect estimates. There may also be interest in measuring random walk variation. The variability in the paths traversed by a walker moving on the evidence flow network may indicate inconsistency between paths of indirect evidence. Finally, we may also be able to use the random-walk analogy in the methodology for planning future studies based on an NMA. By considering a random walk on the network with the addition of the proposed study, it may be possible to work out how much the addition of that study will contribute to the overall results.

In summary, by using the analogy to electrical networks as an intermediate step, we have made a novel connection between NMA and random walks. The interdisciplinary analogy provides new insight into NMA methodology. In particular, the analogy leads to an analytical derivation of the proportion contribution matrix without the ambiguity of existing numerical algorithms. Our approach can therefore be used to reliably quantify the contribution of individual study limitations to the resulting network treatment effects. We hope that this article will provide

a starting point for future developments of NMA methodology that can benefit from ideas in the random-walk literature.

DATA AVAILABILITY STATEMENT

The data, results and associated codes used in this work can be found in the GitHub repository here https://github.com/AnnieDavies/NMA_and_RW. For further details please contact the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.