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GOSH – a graphical display of study heterogeneity

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Estimates from individual studies included in a meta-analysis often are not in agreement, giving rise to statistical heterogeneity. In such cases, exploration of the causes of heterogeneity can advance knowledge by formulating novel hypotheses. We present a new method for visualizing between-study heterogeneity using combinatorial meta-analysis. The method is based on performing separate meta-analyses on all possible subsets of studies in a meta-analysis. We use the summary effect sizes and other statistics produced by the all-subsets meta-analyses to generate graphs that can be used to investigate heterogeneity, identify influential studies, and explore subgroup effects. This graphical approach complements alternative graphical explorations of data. We apply the method to numerous biomedical examples, to allow readers to develop intuition on the interpretation of the all-subsets graphical display. The proposed graphical approach may be useful for exploratory data analysis in systematic reviews. Copyright © 2012 John Wiley & Sons, Ltd.

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1. All-subsets combinatorial meta-analysis to explore heterogeneity: A graphical approach

Meta-analysis is most often used to summarize findings across studies into a single overall estimate. More often than not, estimates from individual studies are not in agreement, giving rise to statistical heterogeneity. In such cases, simply 'summing up' studies is often inadequate, and the summary estimate may be misleading (Lau *et al*., 1998); further exploration may advance knowledge by formulating novel hypotheses (Thompson and Higgins, 2002) or alerting on the presence of bias (Egger and Smith, 1998). From this point of view, statistical between-study heterogeneity is an opportunity to be taken advantage of, rather than an obstacle. Heterogeneity can be a manifestation of genuine differences in the populations, comparisons, outcomes, design, and conduct of studies; the result of biases; or the play of chance. It is therefore important to develop a variety of tools to provide methods of detection and visualization of heterogeneity.

Detecting statistical heterogeneity turns out to be quite a challenging task. In most meta-analyses, the assessment of heterogeneity is based on performing statistical tests against the null hypothesis of no heterogeneity. A variety of tests or metrics have been constructed (for a discussion see (Cooper *et al*., 2009)), the most commonly used being Cochran's Q statistic or its transform, the I^2 index (Cochran, 1954; Higgins and Thompson, 2002). Most procedures rely on quantifying the between-study variance (τ^2) of the true effects, an unobserved quantity that has to be deduced (estimated) from the findings of the studies themselves. Although it is important to quantify the between-study variance in a meta-analysis, there are several problems with the use of heterogeneity tests and metrics: their power to detect statistical heterogeneity is low when the number of studies is small (the norm in medical meta-analysis), and typically, there is large uncertainty around Q or I^2 estimates. In the presence of very large studies, both Q and I^2 will indicate large heterogeneity, even if differences among studies are not clinically important. Furthermore, the Q statistic relies on the assumption of normality, which may not be appropriate for some datasets.

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More generally, global tests of heterogeneity may fail to capture variability related to specific study characteristics. For these reasons, undue emphasis on a single statistic or metric for assessing statistical heterogeneity in a meta-analysis is hardly a satisfactory approach. Herein, we approach the challenge from a different angle. We study graphs arising from analysis of all possible combinations of studies in a meta-analysis and show how these visualizations can help assess heterogeneity, identify outlying or influential studies, and aid exploratory analysis of modifier effects.

2. Graphical assessment of heterogeneity using combinatorial meta-analysis

We present a new method for visualizing between-study heterogeneity. We call this method GOSH: a graphical display of study heterogeneity. The key idea is to perform a meta-analysis on all possible subsets of the k studies in a meta-analysis. If the studies are homogeneous, we expect to obtain similar results regardless of the subset chosen. On the other hand, if there is heterogeneity, some subsets may show different results than others. For example, say that two influential studies, A and B, have different estimates. Then, all subsets that include A, but not B, would yield different results compared with subsets that include B, but not A. A statistical test for heterogeneity may be inadequate for demonstrating the effect of these studies. The proposed method can identify influential discordant studies or subgroups of studies and can complement typically used methodologies. More specifically, for a meta-analysis of $k \geq 2$ studies, there are 2^k-1 potential subsets of studies that exhaust all combinations of 1, 2, . . ., k studies. The number of possible subsets grows rapidly with k; it is 1023 for $k = 10$ and 1 048 575 for $k = 20$. Within each subset, we calculate a summary estimate of the effect size of interest, using standard inverse variance fixed effect meta-analysis methods (Cooper *et al*., 2009). The same method can be used with any type of weighting. We use fixed effect models because we are interested in the average effect in each subgroup and not in how each subgroup generalizes to external studies (Cooper *et al*., 2009; Higgins *et al*., 2009). The metric of choice can be any of the popular metrics used in meta-analysis, such as the log-odds ratio, Peto log-odds ratio, risk difference, log-risk ratio, or the (standardized) mean difference.

Once all-subsets meta-analyses are completed, various exploratory graphs can be generated, such as a frequency distribution of the summary effect sizes and two-way scatterplots of the Q statistic or I^2 index values over the corresponding summary effect sizes. The intent is to provide a visualization that may shed light on the existence of heterogeneity and to suggest its potential sources.

Multiple examples will help familiarize the researcher with the proposed method. As examples, we selected 24 meta-analyses with binary outcomes from the Cochrane Database of Systematic Reviews (Issue 4, 2005), of these 12 are 'small', in the sense that they include only five to ten primary studies, and 12 are 'large', in that these include 11–20 primary studies. In each group, six meta-analyses were designated as homogeneous ($I^2 \leq 25\%$), and six were designated as heterogeneous ($I^2 \geq 75\%$).

In addition, we analyzed two well-known meta-analysis examples, namely, the use of thrombolytics (Lau *et al*., 1992) and magnesium (Yusuf and Flather, 1995) for the treatment of acute myocardial infarction. For each dataset, we performed all-subsets meta-analysis using the log-odds ratio as a metric and generated the aforementioned graphs.

2.1. Examples of all-subsets meta-analyses from homogeneous datasets

To familiarize readers with the proposed visualizations, we first display histograms of summary log-odds ratios from homogeneous and heterogeneous meta-analyses. Figure 1(a) shows histograms from large meta-analyses in which heterogeneity was not detected. Thus, each histogram consists of at least $2^{11}-1 = 2047$ summary log-odds ratios. Figure 1(b) is comparable but for small meta-analyses. The fitted lines are kernel density estimates (smoothed histogram outlines). The overall visual effect is that of compact effect sizes. The histograms are unimodal and somewhat symmetric over a relatively narrow range of effects.

2.2. Examples of all-subsets meta-analyses from heterogeneous datasets

Figure 2(a and b) is a counterpart to Figure 1(a and b), in which each of the underlying meta-analyses exhibited heterogeneity. There is a stark difference between the histograms corresponding to homogeneous and heterogeneous meta-analyses. In the latter, the densities are often not unimodal. Some examples have two modes, some more than two, and the range of the summary effect sizes is wider. The graphs allow a visualization of the difference between the homogeneous and heterogeneous datasets.

3. Exploratory data analysis

The histograms in Figures 1 and 2 provide a first step in the analysis of homogeneity and heterogeneity. We now examine two examples (the first two panels) from Figure 1(a). For each example, we present the forest plot, the all-subsets density of the summary log-odds ratio, and the scatterplot of I^2 values relative to the effect sizes. The two examples are provided in Figures 3 and 4.

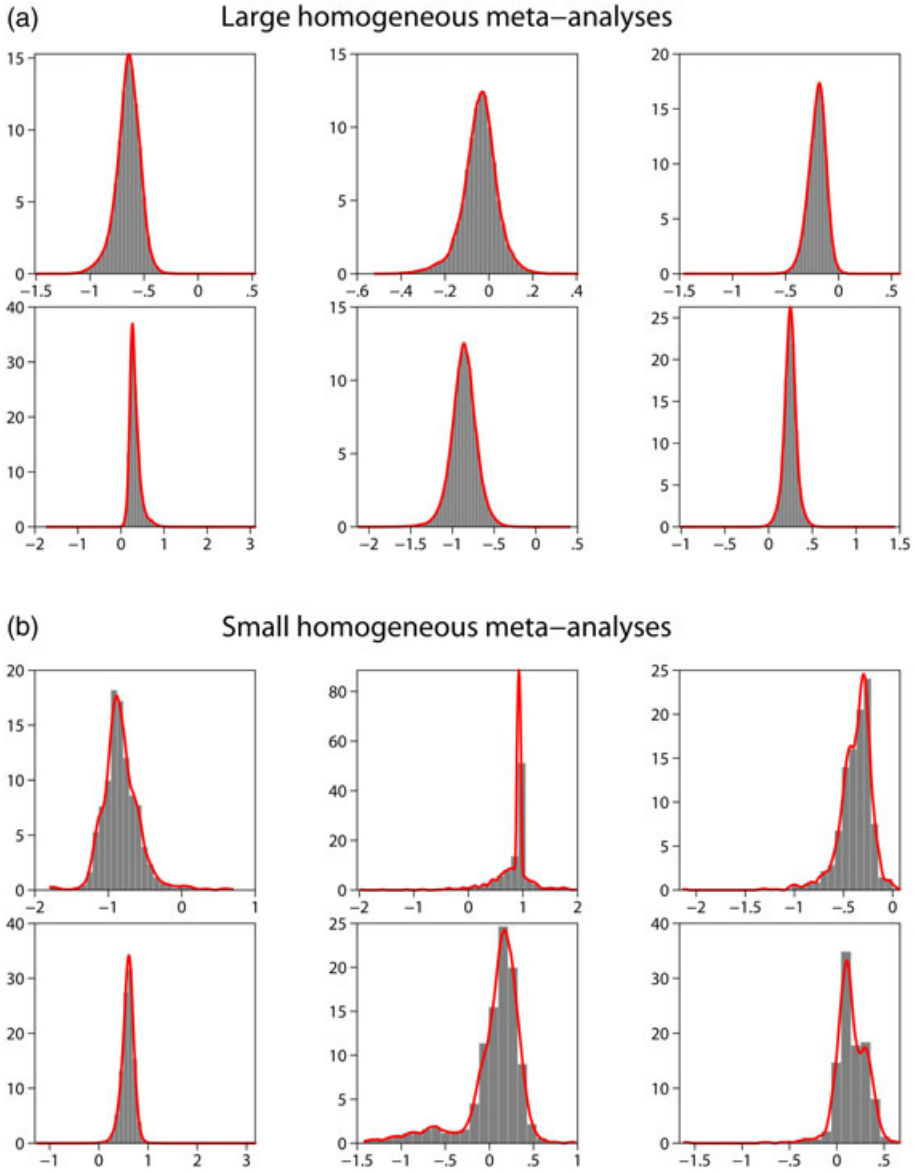

Figure 1. Histograms of all-subsets effect size estimates for 12 different homogeneous ($I^2 < 25\%$) meta-analyses, selected from the Cochrane Database of Systematic Reviews. The histograms in panel 1(a) represent 'large' meta-analyses (11–20 studies), and in panel 1(b) 'small' meta-analyses (5–10 studies). The horizontal axis shows the summary log-odds ratio for meta-analysis subsets. The vertical axis shows the percent of subsets with each summary estimate value. The fitted lines are kernel density estimates (smoothed histogram outlines).

An examination of a forest plot does not generally provide a clear determination of whether the *Q* statistic had a statistically significant value. However, in Figures 3 and 4, the all-subsets histograms are relatively symmetric and unimodal. Further, the scatterplots of I^2 values are compact, with the preponderance of values on the *y*-axis being between 0% and 50%. The joint display of the histogram and scatterplot shows the correspondence between them. The conclusion from these visualizations is that the underlying meta-analyses in Figures 3 and 4 do not exhibit heterogeneity.

We next turn to the two examples (Figures 5 and 6) of histograms that showed heterogeneity. These are taken from the first two panels of Figure 2(a). As in the case of the forest plots from the homogeneous datasets (Figure 1), the forest plot does not provide a convincing visualization of homogeneity or heterogeneity.

In Figure 5, the histogram is bimodal, and the scatterplot of I^2 values shows that a set of subsets has high I^2 values. Furthermore, the segregation into two clusters indicates that these may be two subgroups of primary studies with discordant effect sizes.

Figure 6 provides an additional example of a heterogeneous meta-analysis. The histogram of all-subsets effect sizes is multimodal with two almost non-overlapping subhistograms. The scatterplot of I^2 values shows a high proportion having values over 50% and appears to be separated into two clusters; within the left hand cluster,

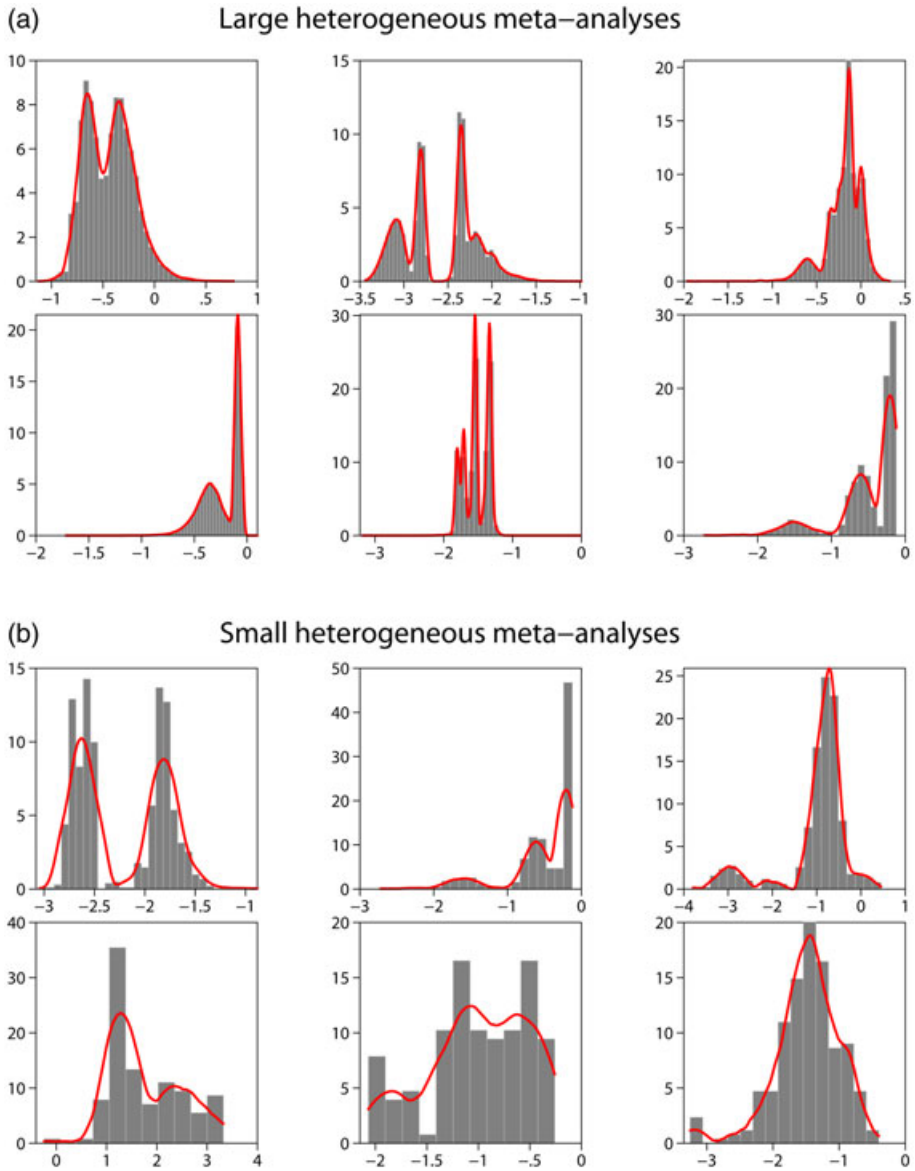

Figure 2. Histograms of all-subsets effect size estimates for 12 different heterogeneous ($I^2 > 75\%$) meta-analyses, selected from the Cochrane Database of Systematic Reviews. Panel 2(a) has 'large' meta-analyses (11–20 studies). Panel 2(b) has 'small' meta-analyses (5–10 studies). Axes are similar to Figure 1.

there are many subsets with very high I^2 values. The right hand cluster also exhibits high I^2 values. The overall visualization indicates that there exist at least two discordant subgroups of primary studies.

4. Analyses for detecting outliers and influential studies

Suppose that the graphical display shows multimodality. Then, one of the standard sensitivity analyses is to drop what may be an outlying study, repeat the meta-analysis without it, and determine whether the graphical display still shows multimodality.

In Figure 7, we present the result of such a sensitivity analysis after dropping the study marked with an asterisk (in red) from the meta-analysis in Figure 5. The histogram is now unimodal, and the scatterplot shows a single cluster of summary effect sizes. The majority of I^2 values are under 50%, and there are no subsets with very high I^2 values. This suggests that the deleted study had a dramatic influence on this particular meta-analysis.

Of note, the aforementioned statistical analysis does not take into account the characteristics of the omitted study. Rather, it is a visualization procedure for detecting a study or a group of studies for further analyses; as such, all-subsets meta-analysis can serve as a signal for further exploratory analyses. Other methods for detecting influential studies or outliers and for including them in meta-analyses have been proposed (Baker and Jackson, 2008; Gumedze and Jackson, 2011; Viechtbauer and Cheung, 2010).

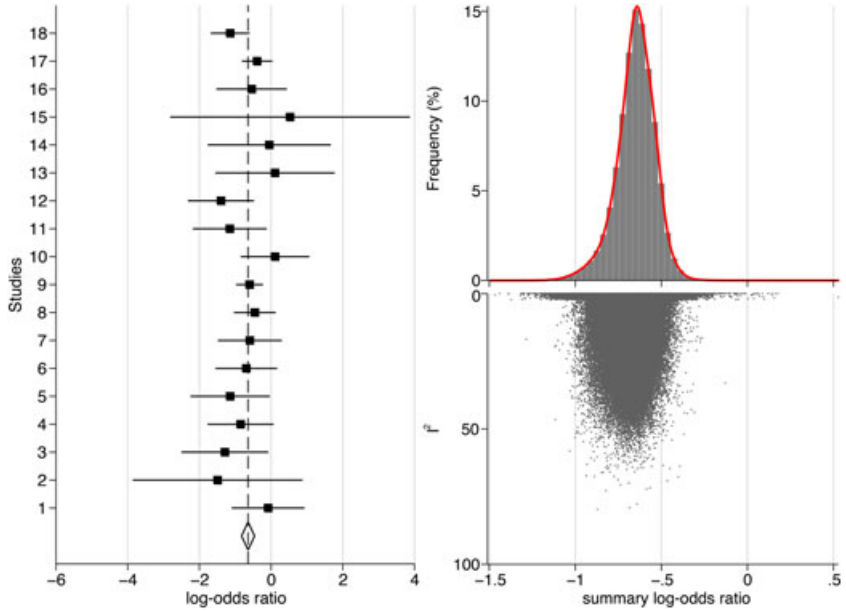

Figure 3. Juxtaposed forest plot, histogram of all-subsets summary effect sizes, and scatterplot of I^2 against summary effect sizes for a homogeneous meta-analysis from Figure 1 (the first example in panel 1(a)). In the forest plot, the diamond shows the overall fixed effect summary log-odds ratio. The histogram on the top right panel shows the distribution of the all-subsets summary effect sizes. Superimposed are smoothed lines, as described in Figure 1. Below the histograms (bottom right), we plot I^2 values against summary effect sizes across all-subsets. The latter plot is a smear of the histogram density over I^2 values.

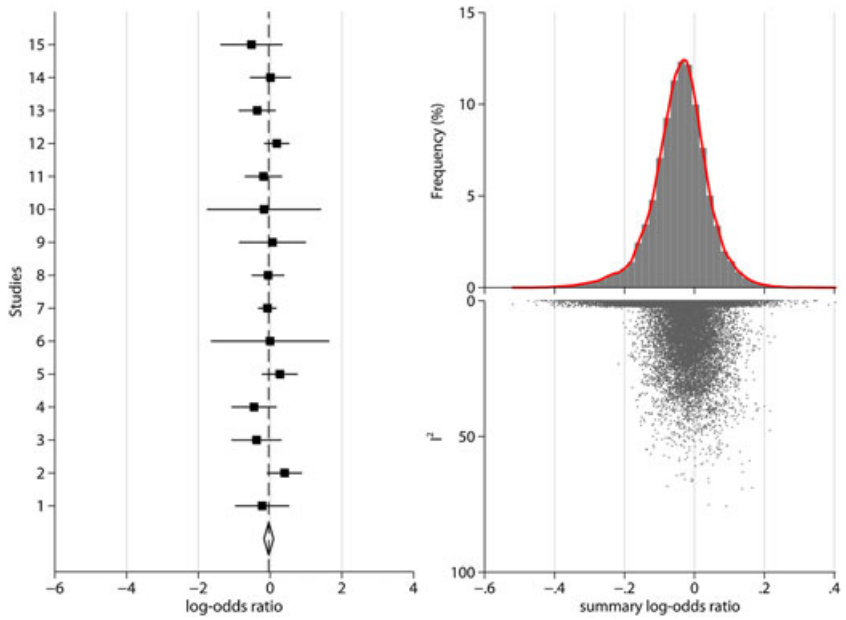

Figure 4. Juxtaposed forest plot, histogram of all-subsets summary effect sizes, and scatterplot of I^2 against summary effect sizes for another homogeneous meta-analysis (second example in Figure 1(a)). Layout is similar to Figure 3.

Figure 8 shows a reanalysis of Figure 6 where the study with the asterisk (in red) has been removed. This results in a smoother histogram but not an entirely symmetric one. The spike in the histogram indicates the existence of at least one additional influential study (the sixth study in the forest plot of Figure 6 that is marked with two asterisks and is shown in blue). In the scatterplot, the proportion of subsets with high I^2 values has decreased. However, there still remain a substantial number of subsets with I^2 values suggestive of considerable heterogeneity. The systematic reviewers may consider another iteration by removing the remaining influential study.

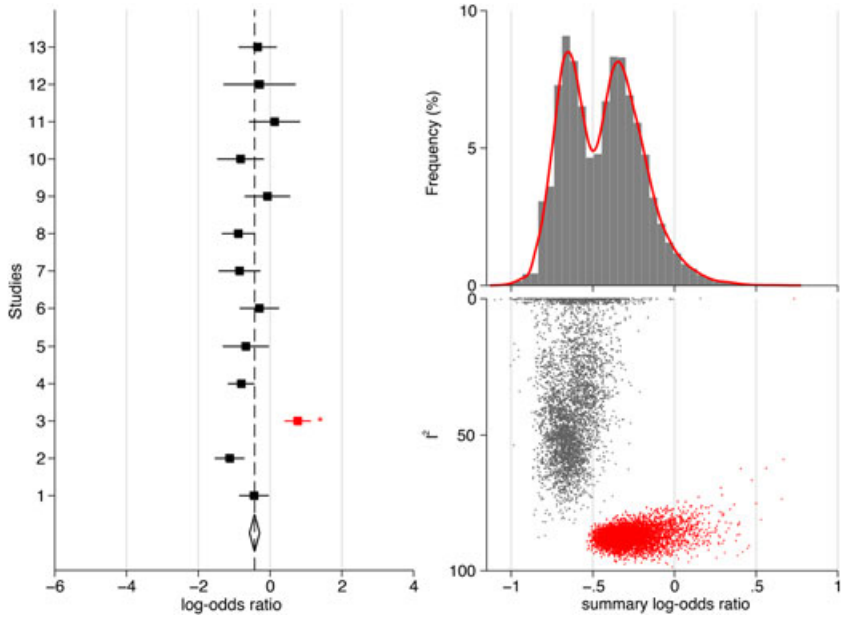

Figure 5. Juxtaposed forest plot, histogram of all-subsets summary effect sizes, and scatterplot of I^2 against summary effect sizes for a heterogeneous meta-analysis from Figure 2 (the first example from Figure 2(a)). Layout is similar to Figure 3. Note that contrary to the unimodal histograms in the homogeneous examples, the histograms from heterogeneous meta-analyses are multimodal. Modes correspond to subsets that include influential studies (here, a single outlying study marked with an asterisk and shown in red). In the scatter plot of I^2 values over summary estimates, we colored red points corresponding to subsets including this influential study.

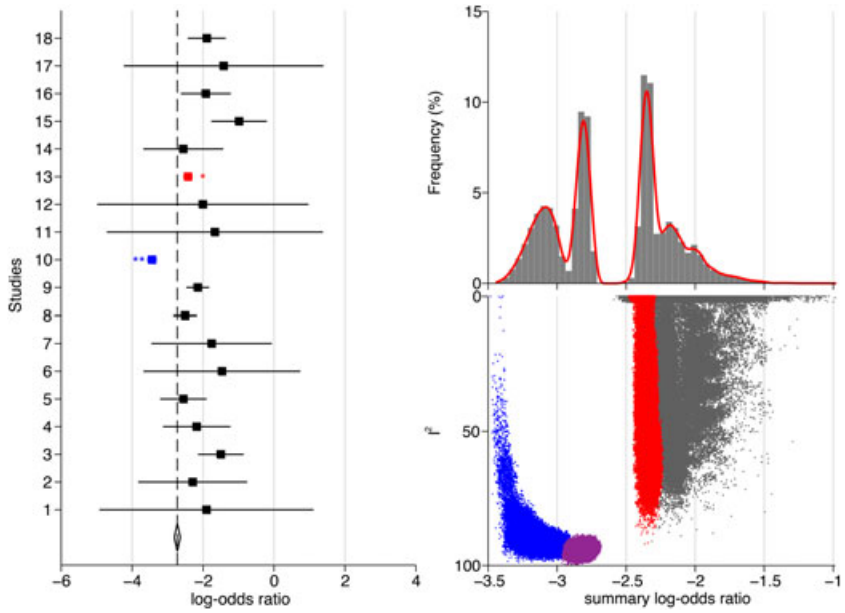

Figure 6. Juxtaposed forest plot, histogram of all-subsets summary effect sizes, and scatterplot of I^2 against summary effect sizes for a heterogeneous meta-analysis from Figure 1 (the second example in Figure 2(a)). Layout is similar to Figure 3. Here, two studies are very precise (they have narrow confidence intervals; the first is marked with a single asterisk, in red, and the other with two asterisks, in blue). In the scatterplot, we color red subsets that include the red but not the blue study; and blue subsets that include the blue but not the red study. We colored purple subsets that include both studies; because the estimates of the two influential studies are disjoint, the purple cluster is at very high I^2 values (near 100%). This example shows the usefulness of the scatterplot in interpreting the histogram of effect sizes. Note that the right and left peaks in the histogram correspond to the red and blue clusters, respectively. The middle peak corresponds to the purple cluster and not to yet another influential study.

5. Thrombolytics and magnesium for myocardial infarction

To highlight the difference in all-subsets graphical analysis between homogeneous and heterogeneous meta-analyses, we use two classic, widely studied examples, namely, the use of thrombolytic agents (Lau *et al*., 1992) and magnesium (Teo *et al*., 1991) for the treatment of myocardial infarction.

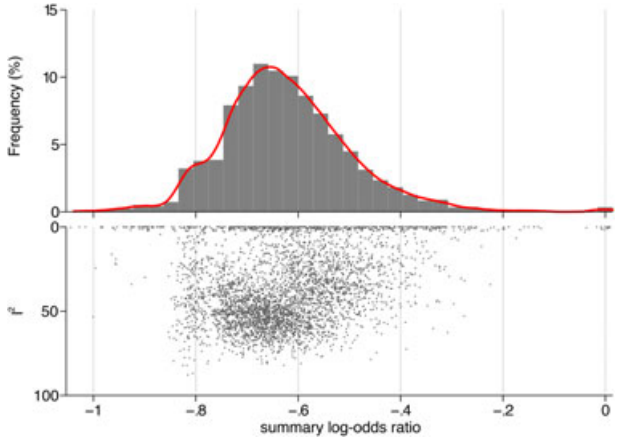

Figure 7. Sensitivity analysis for the heterogeneous meta-analysis shown in Figure 5. Layout is similar to Figure 3. Removal of one study (the red study in Figure 5) drastically reduces heterogeneity.

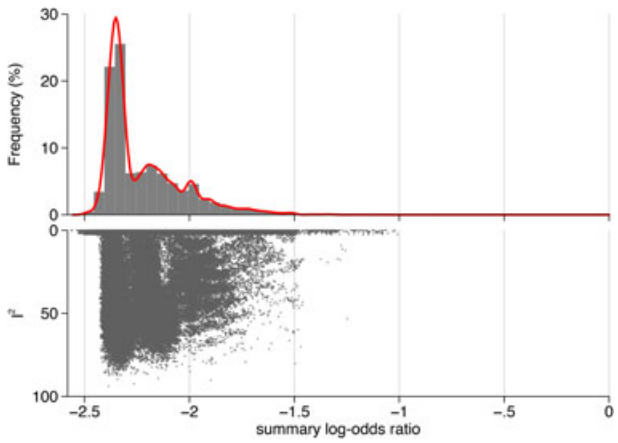

Figure 8. Sensitivity analysis using all-subsets meta-analyses for the heterogeneous meta-analysis shown in Figure 6. Layout is similar to Figure 3. Removal of one study (the study marked with an asterisk in Figure 6, in red) results in substantial reduction of heterogeneity; however, the histogram of all-subsets estimates shows a large spike with a long tail to the right, indicating the presence of another influential study (the study marked with two asterisks in Figure 6, in blue).

The original meta-analysis of thrombolytic agents included 65 trials (Lau *et al*., 1992). Because it is computationally infeasible to perform an all-subsets analysis for 65 trials without modifying our algorithms, for illustrative purposes, we analyze the first 19 studies included in the meta-analysis, published between 1957 and 1977 (dataset provided by the corresponding author). This was the first time that the cumulative meta-analysis reached a *p*-value less than 0.001. As shown in Figure 9, the histogram of all-subsets estimates for the meta-analysis of thrombolytic agents is strongly unimodal and symmetric, and the same is true for the scatterplot of I^2 estimates over the summary effect size. These two displays might serve as canonical examples of statistical homogeneity.

The first meta-analysis of magnesium trials appeared in 1991 and suggested a strong beneficial effect for this agent. This result was contradicted by the large ISIS-4 (Fourth International Study of Infarct Survival) randomized trial that identified no benefit from magnesium use. Several explanations have been offered to explain this discrepancy, including publication bias, differences in underlying control rates between ISIS-4 and the smaller trials, between-study differences in the timing of treatment administration, and the emergence of other effective treatments for myocardial infarction (Woods, 1996). In Figure 10, we present the all-subsets graphical analysis of the magnesium trials using data from (Higgins and Spiegelhalter, 2002). Here, we find a clearly multimodal distribution. The large peak corresponds to subsets of studies that include the ISIS-4 trial, which has by far the largest sample size. The second largest peak corresponds to subsets that include LIMIT-2 (Second Leicester Intravenous Magnesium Intervention Trial) (another influential trial) but not ISIS-4. The effect sizes in the subgroups that include ISIS-4 *versus* those that exclude it are clearly disjoint.

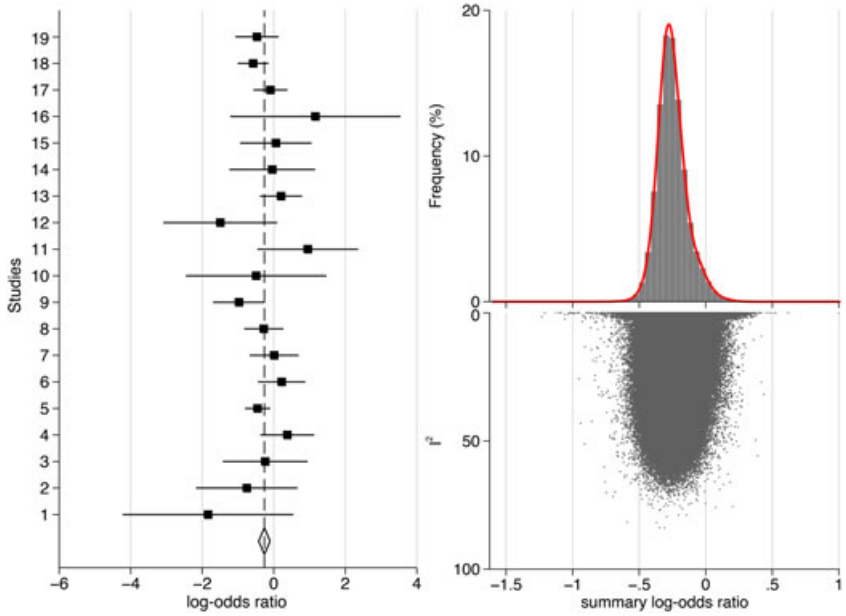

Figure 9. Use of all-subsets analyses for the first 19 studies included in the thrombolytics for acute myocardial infarction meta-analysis. Layout is similar to Figure 3.

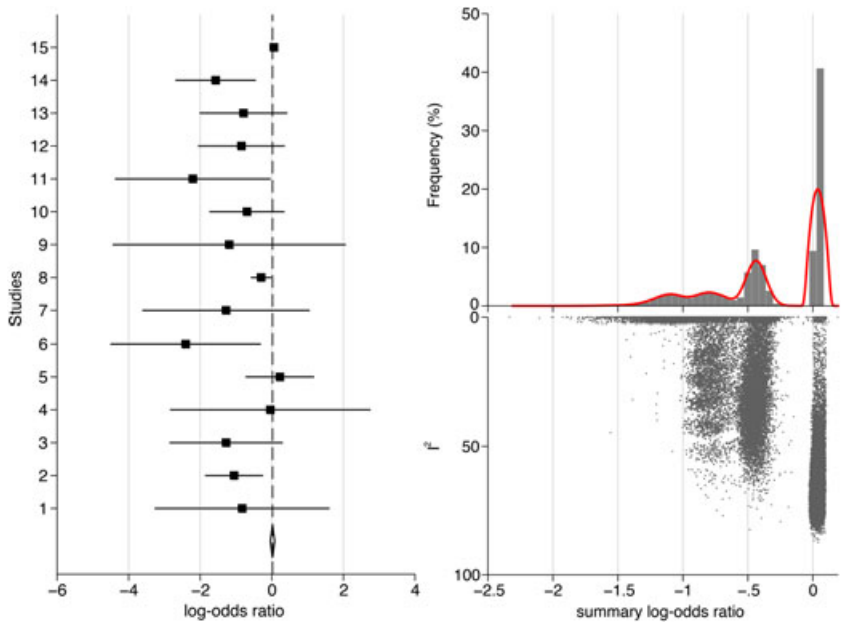

Figure 10. Use of all-subsets analyses for 15 studies of magnesium for the treatment of myocardial infarction. Layout is similar to Figure 3.

6. Subgroup effects in all-subsets graphical meta-analysis

It may be possible to visualize the effects of study level covariates such as including only male or female subjects or by methodological items related to study design, such as mode of randomization and allocation concealment. This leads to a dilemma for the researcher, namely, should the primary analysis be for separate subgroups of studies, or should the primary analysis be for the combined dataset, with subsequent subgroup analyses. We show here how the proposed methods can help visualize the effect of a study-level characteristic that is associated with differential treatment response.

Our example is a meta-analysis of randomized trials of aspirin for the primary prevention of stroke, among other outcomes (Berger *et al*., 2006). The meta-analysis included six studies: three enrolled exclusively men, one enrolled exclusively women, and two enrolled both men and women but provided separate estimates of the treatment effect for each sex. In total, the analysis included eight 'study' entries, three consisted only of women

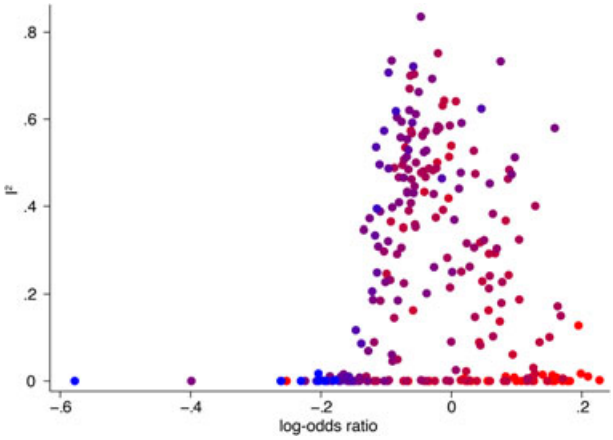

Figure 11. Visualization of treatment effect heterogeneity using all-subsets meta-analysis for randomized trials assessing aspirin therapy for the prevention of stroke. The figure presents the scatterplot of I^2 values over the summary effect size (log-odds ratio) of each subset of studies. Subsets that only included studies of women are depicted in blue circles; subsets that only included studies of men are depicted in red. Subsets that included both studies of men and women are depicted in shades of purple. As the proportion of women-only studies decreases from 100% to 0 (from left to right), the color map of the scatterplot changes from blue to purple to red. The gradual shift in the colors suggests that the study-level factor is associated with differences in the treatment effect.

and five only of men. No study was excluded on the basis of not providing sex-specific information. Figure 11 color codes these subsets as blue and red, respectively. Aspirin appeared to have a protective effect in women-only studies (odds ratio 0.83, 95% confidence interval, CI, 0.70–0.97). In men-only studies, the average effect was in the opposite direction (1.13, 95% CI, 0.96–1.33).

We now perform an all-subsets graphical analysis consisting of 255 subsets ($2^8 - 1$). Of these, 31 contain only men ($2^5 - 1$), 7 ($2^3 - 1$) only women, and 217 contain both men and women. For illustration, consider subsets of size 6 that include two out of the three studies of women and four out of the five studies of men. The proportion of women-only studies is 33%. Because there is an association between sex and effect size, the color of the points changes along the *x*-axis: as the proportion of women-only studies decreases from 100% to 0 (from left to right), the color map of the scatterplot changes from blue to purple to red. The gradual shift in the colors suggests that the study-level factor is associated with differences in the treatment effect.

7. Limitations

The combinatorial method proposed here is an 'exploratory' method rather than a 'confirmatory' tool. This graphical method is designed for the exploration of heterogeneity, which has an important role in systematic reviews. When the number of studies is small, the all-subsets graphical meta-analysis does not provide much resolution to detect heterogeneity. When the number of studies is large (say more than 27), the computations become time-consuming and quickly infeasible. However, meta-analyses in the medical literature typically include an intermediate number of studies (median of 5 in Cochrane reviews and 13.5 in non-Cochrane published systematic reviews) (Jadad *et al.*, 1998). Meta-analyses in the social sciences may involve large datasets; in such cases, an analysis can be carried out by using random samples of all the possible subsets, perhaps stratified by subset size.

8. Software

All-subsets graphical meta-analysis requires the use of specialized software. We implemented the methods described here on a widely used statistical package (STATA version SE/11.1, Stata Corporation, College Station, TX, USA). For efficiency, the actual combinatorial method is implemented as a C-language plug-in. The code and software to perform an analysis is available from the authors upon request. For meta-analyses of fewer than 27 studies, the all-subsets procedures can be completed in less than 3 s on a standard personal computer (e.g., Intel Core 2 Duo 2.26 GHz, 4 GB RAM). The method will also be available in the open-source meta-analysis suite OpenMeta-analyst (Center for Evidence-based Medicine, Brown University, Providence, RI, USA) (Wallace *et al.*, 2009).

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meta-analyses in Stata. IJD ran the statistical analyses. All authors interpreted the results. IJD and IO drafted the first version of the manuscript, which was critically revised by TAT. All authors approved the final version and shared the responsibility to submit for publication. No professional medical editors were involved in this paper.

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References

Baker R, Jackson D. 2008. A new approach to outliers in meta-analysis. *Health Care Management Science* **11**: 121–131.

Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL. 2006. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. *Journal of the American Medical Association* **295**: 306–313.

Cochran W. 1954. The combination of estimates from different experiments. *Biometrics* **10**: 101–129.

Cooper H, Hedges LV, Valentine JC. *The Handbook of Research Synthesis and Meta-Analysis*. Russell Sage Foundation Publications: New York, NY, 2009.

Egger M, Smith GD. 1998. Bias in location and selection of studies. *BMJ* **316**: 61–66.

Gumedze FN, Jackson D. 2011. A random effects variance shift model for detecting and accommodating outliers in meta-analysis. *BMC Medical Research Methodology* **11**: 19.

Higgins JP, Spiegelhalter DJ. 2002. Being sceptical about meta-analyses: a Bayesian perspective on magnesium trials in myocardial infarction. *International Journal of Epidemiology* **31**: 96–104.

Higgins JP, Thompson SG. 2002. Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* **21**: 1539–1558.

Higgins JP, Thompson SG, Spiegelhalter DJ. 2009. A re-evaluation of random-effects meta-analysis. *Journal of the Royal Statistical Society: Series A* **172**: 137–159.

Jadad AR, Cook DJ, Jones A, Klassen TP, Tugwell P, Moher M, Moher D. 1998. Methodology and reports of systematic reviews and meta-analyses: a comparison of Cochrane reviews with articles published in paper-based journals. *Journal of the American Medical Association* **280**: 278–280.

Lau J, Antman EM, Jimenez-Silva J, Kupelnick B, Mosteller F, Chalmers TC. 1992. Cumulative meta-analysis of therapeutic trials for myocardial infarction. *The New England Journal of Medicine* **327**: 248–254.

Lau J, Ioannidis JP, Schmid CH. 1998. Summing up evidence: one answer is not always enough. *Lancet* **351**: 123–127.

Teo KK, Yusuf S, Collins R, Held PH, Peto R. 1991. Effects of intravenous magnesium in suspected acute myocardial infarction: overview of randomised trials. *BMJ* **303**: 1499–1503.

Thompson SG, Higgins JP. 2002. How should meta-regression analyses be undertaken and interpreted? *Statistics in Medicine* **21**: 1559–1573.

Viechtbauer W, Cheung MWL. 2010. Outlier and influence diagnostics for meta-analysis. *Research Synthesis Methods* **1**: 112–125.

Wallace BC, Schmid CH, Lau J, Trikalinos TA. 2009. Meta-Analyst: software for meta-analysis of binary, continuous and diagnostic data. *BMC Medical Research Methodology* **9**: 80.

Woods KL. 1996. Review of research methodology used in clinical trials of magnesium and myocardial infarction–why does controversy persist despite ISIS-4? *Coronary Artery Disease* **7**: 348–351.

Yusuf S, Flather M. 1995. Magnesium in acute myocardial infarction. *BMJ* **310**: 751–752.