Galaxy Plot: A New Visualization Tool of Bivariate Meta-Analysis Studies

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ABSTRACT

Funnel plots have been widely used to detect small study effects in the results of univariate meta-analyses. However, there is no existing visualization tool that is the counterpart of the funnel plot in the multivariate setting. We propose a new visualization method, the *galaxy plot*, which can simultaneously present the effect sizes of bivariate outcomes and their standard errors in a two-dimensional space. We illustrate the use of *galaxy plot* by two case studies, including a meta-analysis of hypertension trials with studies from 1979 to 1991, and a meta-analysis of structured telephone support or non-invasive telemonitoring with studies from 1966 to 2015. The *galaxy plot* is an intuitive visualization tool that can aid in interpretation of results of multivariate meta-analysis. It preserves all of the information presented by separate funnel plots for each outcome while elucidating more complex features that may only be revealed by examining the joint distribution of the bivariate outcomes.

KEYWORDS: Bivariate Meta-Analysis, Funnel Plot, Small Study Effects, Visualization Tool

ABBREVIATIONS: cardiovascular disease (CVD), diastolic blood pressure (DBP), individual patient data (IPD), multivariate meta-analysis (MMA), publication bias (PB), systolic blood pressure (SBP)

INTRODUCTION

Two major issues faced in meta-analysis are heterogeneity and small study effects. Heterogeneity, including clinical heterogeneity and statistical heterogeneity, refers to the variability of study results that cannot be explained by sampling error [1]. Small study effect is the tendency for smaller studies to produce larger effect estimates, which may be due to different types of patients, interventions in small studies, and publication bias (PB), a type of bias that occurs when the decision of publication depends on the direction or significance of results [1] [2] [3].

In order to better understand the impact of heterogeneity and small study effects, several visualization tools have been developed in univariate meta-analysis, including forest plot and funnel plot [1] [4] [5]. Recently, multivariate meta-analysis (MMA) has received increasing attention [6]. Compared with univariate meta-analysis, MMA models multiple outcomes simultaneously. By modeling the correlations among outcomes (known as "borrowing information from correlated outcomes"), MMA has better statistical properties including smaller standard errors for parameter estimates and improved estimation of between-study variances [6]. However, visualization tools for MMA are underdeveloped.

A general visualization tool, akin to the funnel plot, which helps investigators to understand the nature of the data (e.g., heterogeneity and symmetry), is lacking for MMA. Riley et al. introduced a confidence ellipse plot (also known as the bubble plot in Stata package mvmeta.ado and in Jackson, et al., 2011 [6]) for bivariate meta-analysis [7]. The confidence ellipse plot is a visualization of joint confidence regions (at 50% level) for bivariate outcomes from individual studies. In bivariate network meta-analysis where multiple treatments are compared simultaneously, the estimated overall effect of each treatment, for example, treatment efficacy is plotted against safety outcome using a scatter plot [8]. However, an intuitive visualization method which presents the relative contribution of each study in bivariate meta-analysis is still not available.

To fill this methodological gap in visualization, one must account for the following features. First, there are within-study and between-study correlations in MMA. Within-study correlation arises when the effects are measured using the same set of subjects. Between-study correlation occurs if the underlying (true) effects are correlated across studies, such as estimated sensitivities and [6]. Correlation can be helpful in imputing missing outcomes [6]. Thus, an intuitive visualization tool for correlation is desirable. Secondly, MMA is not immune to biases. Small study effects in MMA is sometimes more difficult to detect comparing to the univariate meta-analysis setting, because the publication process may depend on the outcomes jointly. In such cases, funnel plots can be applied to either a combined univariate effect measure, or the two outcomes separately. However, the former has information loss in the process of combining the two outcomes as reported in Bürkner & Doebler (2014) [9], while the latter does not reflect the joint symmetry of both outcomes and can sometimes be contradictory.

In this paper, we propose a novel visualization tool, the *galaxy plot*, for visualizing bivariate meta-analysis data, which faithfully retains the information in two separate funnel plots, while providing useful insights into outcome correlations, between-study heterogeneity and joint asymmetry. To the best of our knowledge, this is the very first effort to generalize the funnel plot to the bivariate meta-analysis setting. We expect further statistical procedures for bias detection and reduction can be developed based on this new visualization tool (such as multivariate trim and fill method), although such tasks are beyond the scope of this work.

METHOD

An interesting analogy in astronomy

Ioannidis (2015) suggested that other disciplines may shed light on approaches to address the small study effects [10]. Inspired by images of galaxies, our literature review on astronomy led to an interesting analogy between bias reduction methods in systematic reviews and inferring the center of mass of a system of stars. As illustrated in Figure 1, one can make the following observations: First, in astronomy, objects with higher signal-to-noise level are more likely to be detected. The signal-to-noise level of an object is normally determined by its surface area, luminous intensity (temperature) and distance to the earth. Similarly, in meta-analysis, studies with more significant results are more likely to be published. Second, also in astronomy, rotation curves are often used to determine the total mass of an object system (i.e. a galaxy) [11]. Because all the matter in the universe interacts gravitationally, we should be able to measure the mass of objects even if they are invisible by their effects on nearby objects. Similarly, in meta-analysis, the pooled effect is a weighted sum of individual study effects, and we may borrow information from correlated outcomes. Third, in astronomy, the detection of invisible objects and the estimation of the center of the physical system are two important topics. Similarly, in meta-analysis, identifying the presence of missing studies and estimating the true pooled effects are two important objectives.

Galaxy plot

In this paper, we focus on the extension of the funnel plot to the bivariate meta-analysis setting. As demonstrated in Figure 2, the key idea is to integrate two separate univariate funnel plots into one plot. Specifically, we visualize each study using an ellipse centered at the estimated effect sizes of the two outcomes, with major and minor axes inversely proportional to the standard errors of the estimated effect sizes. Hence a larger ellipse represents a larger and more precise study. With this new visualization, the "center of mass" of the physical system of disks coincides with the weighted sum of the overall effect size using the random effects meta-analysis model [12]. We term this new plot the *galaxy plot* for its similarity to images of galaxies [13].

The *galaxy plot* has the following features. First, it presents *basic features* of the bivariate data to be meta-analyzed by introducing an intuitive presentation of bivariate effect sizes of each study (i.e., location of ellipse). Second, it allows systematic reviewers to study other features, such as the heterogeneity of the studies, factors that can potentially explain the heterogeneity, the symmetry in a bivariate space, and outlying studies. More details of the above features is discussed in Section 2.3. Similar to the univariate funnel plot, symmetry in bivariate plot can be used to identify small study effects with the following rationale. Larger ellipses with higher precisions are expected to stay in the center of the "galaxy", with smaller ellipses scattering more widely. Deviation from such a pattern may be an indication of potential small study effects (or PB). More precisely, the univariate funnel plot essentially investigates the symmetry of the marginal distribution of each outcome. In contrast, the *galaxy plot* is capable of studying the symmetry of the *joint distribution* of bivariate outcomes. As discussed later in Section 2.2, the *galaxy plot* in Figure 2 suggests a pattern of missing studies in the lower left corner. The suppression of publication for these studies could be due to an underlying mechanism: studies with smaller (weighted) sum of effect sizes are less likely to be published. On the other hand, the two separate funnel plots are symmetric and failed to reveal such asymmetry in the joint distribution. This example highlights a potential "blind-spot" of investigations using separate funnel plots.

Visualization with the galaxy plot using simulated data

We now illustrate the steps of visualizing basic and specific features of bivariate data to be meta-analyzed using the *galaxy plot*. To best present various types of features, we use simulated data in this subsection. A dataset is generated from a bivariate normal random-effects model [14]. The underlying overall bivariate effect size was set to (2, 2). To reflect the heterogeneity across studies, we sample the within-study variance from the square of a normal distribution *N* (0.25, 0.50), and set the between study variance to 0.25. The number of studies is set to 17 to represent a relatively large dataset.

Basic features. We visualize basic features of a bivariate meta-analysis in the following steps:

Step 1. The positions of ellipses. The x-axis is the estimated effect size of outcome Y_1 and the y-axis is the estimated effect size of outcome Y_2. For the *i*-th individual study, an ellipse is drawn centered at its estimated effect sizes $(\hat{\theta}_{i1}, \hat{\theta}_{i2})$.

Step 2. The sizes of ellipses. The major and minor axes of the ellipse are c_1/S_{i1}^2 and c_2/S_{i2}^2, where S_{i1} and S_{i2} are standard errors of the estimated effect sizes for outcomes Y_1 and Y_2, respectively. Constants c_1 and c_2 are chosen to be 0.06 to facilitate visualization. Larger ellipses represent larger and more precise studies.

Step 3. The center of mass and the contribution of each study. The overall estimates of bivariate outcomes from the random effects model are marked with a star, which is also the center of mass of the physical system of ellipses. As illustrated in the lower panel of Figure 2, the most precise study (largest ellipse) is the closest to the center of mass, and it contributes most to the pooled estimate.

Novel features of the galaxy plot.

A). *Galaxy-confidence plot*. In meta-analysis, visualizing confidence intervals of effect sizes often helps in correctly interpreting the results. For example, if the confidence interval for an individual study overlaps with a line representing no effect, it demonstrates that at the given confidence level, the effect size from that study cannot be distinguished from no effect, which would not be illustrated by only displaying precision. Figure 3A illustrates the proposed *galaxy-confidence plot*. Rather than using cross-hairs to display paired precisions in the basic *galaxy plot*, the *galaxy-confidence plot* uses cross-hairs to represent confidence intervals, with the cross point showing the point estimate of the bivariate outcomes. The confidence intervals are then compared with lines representing no effect (i.e., black dashed lines) to illustrate the statistical significance of effect sizes.

B). *Galaxy-correlation plot*. The within-study correlation is often unknown in MMA. However, for some meta-analyses, e.g., individual patient data (IPD)-meta-analysis, the within-study correlation can be calculated using the individual level data. Here we propose a *galaxy-correlation plot inspired by the* magnetic fields used in physics. The magnetic field at any given point is specified by both a direction and a magnitude. Similarly, we integrate the within-study correlation in the *galaxy-correlation plot*. As shown in Figure 3B, for each individual study, we display its within-study correlation by an arrow starting from the center of the ellipse. We restrict the range of arrow to the right side of the ellipse, and the range of the correlation (-1, 1) is mapped to the radian range (-90°, 90°): an arrow straight down represents perfect negative correlation (-90°, correlation=-1), lying on the x-axis represents no correlation (0°, correlation=0), and straight up represents perfect positive correlation (90°, 1).

C). *Galaxy-heterogeneity plot*. Investigating and understanding between-study heterogeneity is one of the central tasks of meta-analysis. Similar to a funnel plot for univariate meta-analysis [15] [16] [17] heterogeneity can cause asymmetry in the *galaxy plot*. The *galaxy-heterogeneity plot* enables investigations of heterogeneity in a bivariate space and facilities investigation of potential causes of asymmetry. For example, we used simulated data to illustrate potential cause of heterogeneity in Figure 3C. The blue ellipses represent studies comparing treatment (with low dosage level) against placebo, while the green ellipses in represent studies comparing treatment (with high dosage level) against placebo. The difference in distributions of the blue and green ellipses indicates the presence of heterogeneity caused by different dosage levels and suggests subgroup analysis for further investigation.

D). Investigation of small study effects. Investigating small study effects in MMA is one of the main features of the *galaxy plot*. Figure 3D integrates information on small study effects into the *galaxy plot*. To illustrate, we introduce PB, an important potential cause of small study effects [18] in the simulated data, by suppressing five studies with the smallest values of the sum of the two effect sizes. We investigated the small study effects via symmetry of the *galaxy plot*. Without small-study effects, the *galaxy plot* should be central symmetric (point symmetric) around the center of mass, and studies of similar sizes should scatter on an ellipse around the center of mass. To facilitate visualization, we add two "axes of symmetry", which are two lines passing through the estimated center of mass with the directions of the two eigenvectors of the covariance matrix of the bivariate outcomes, respectively. In Figure 3D, we observe that the *galaxy plot* is not symmetric around the estimated center of mass and the *axes of symmetry*; and the largest ellipses are not close to the estimated center of mass. On the other hand, the funnel plot is symmetric for Y_1 [Figure 3E] but asymmetric for Y_2 [Figure 3F]. A possible reason for this discrepancy is the *galaxy plot* may have increased power over the separate funnel plots via joint analysis of bivariate outcomes. Recently, Hong et al. demonstrated the advantage of a joint test of small study effects over the univariate tests [19]. Following the same argument, novel bivariate tests based on the *galaxy plot* could potentially have more power than the univariate tests. A pedagogical example is provided in Web Figure 1 of the Supplementary Materials to explain the underlying mechanism.

E). *Other features*. The *galaxy plot* is also useful for the investigation of other features. For example, identifying outcome reporting bias in MMA. A possible approach to investigate outcome reporting bias is to display the studies with only one outcome reported in the corresponding axis. For example, Let (X_i, Y_i) denote the bivariate outcome of the ith study. If $X_i = x$ is observable but $Y_i = NA$ is missing, we will use a line segment on X axis to represent the study, where position of the segment is at value x on the X axis, and the length of the segment represents the precision.

Alternatively, the galaxy plot can be combined with imputation methods to assess outcome reporting bias in MMA. Baker and Jackson (2006) considered methods to correct for small study effects by incorporating impact factors of journals for published studies [20]. Such information can be incorporated into the *galaxy plot* as different colors of ellipses (see case study in Section 3). The proposed galaxy plot was implemented in an R software package xmeta, which is available at https://cran.r-project.org/ web/packages/xmeta.

CASE STUDIES

An individual patient data (IPD)-meta-analysis of hypertension trials

Wang et al. (2005) investigated the contribution of lowering systolic blood pressure (SBP) and diastolic blood pressure (DBP) to cardiovascular disease (CVD) prevention [21]. They selected trials testing active anti-hypertensive drugs, and IPD was sought from trials in the Individual Data Analysis of Gueyffier et al. or at the Studies Coordinating Centre in Leuven (Belgium) [22] [23] [24]. Ten trials providing IPD for a total of 28,581 patients were included. An IPD-meta-analysis of the 10 trials was conducted to evaluate whether and to what extent cardiovascular outcomes were associated with the differential reduction in SBP and DBP.

Figure 4 visualizes the IPD-meta-analysis of 10 hypertension trials. In Figure 4A, we consider CVD and stroke as bivariate outcomes. The x- and y- axes represent log(risk ratio) of CVD and stroke, respectively. The pooled effects are estimated as (-0.237, -0.383), which is indicated by the red center of mass in the plot. We observe that larger ellipses scatter narrowly near the center of mass, while smaller ellipses scatter widely with more variability. We observe that three studies are far away from others, and are considered to be potential outliers. In Figure 4B, we zoom in to focus on the studies within the dashed square and illustrate a *galaxy-correlation plot* that reveals the pattern of within-study correlations. The bivariate outcomes CVD and stroke are apparently positively-correlated since all studies have positive within-study correlations. The range of within-study correlations is from 0.30 to 0.78. Besides cardiovascular outcomes, we also consider SBP and DBP as bivariate outcomes. In Figure 4C, the *x*- and *y*-axes represent the changes in SBP and DPB. The pooled effects are estimated as (-10.17, -4.58), which is marked by the red center of mass. The range of within-study correlations is from 0.45 to 0.79. In this example, the ellipses in 4 B and 4 C scattered vertically and horizontally in the *galaxy plot*, respectively, indicate no strong between-study correlation.

Structured telephone support or non-invasive telemonitoring for patients with heart failure

To improve care and clinical outcomes of heart failure, and to reduce healthcare utilization, specialized disease management programs are conducted, such as structured telephone support and non-invasive home telemonitoring. To compare the structured telephone support and the non-invasive home telemonitoring interventions with standard practice for patients with heart failure, Inglis et al. conducted a systematic review including 41 randomized clinical trials, and considered mortality, hospitalizations and quality of life as outcomes [25].

Using data from this study, we visualize bivariate outcomes of quality of life and all cause-mortality. We only consider 11 out of 41 trials that reported both outcomes. Figure 5A and 5B are funnel plots for each outcome separately, with effect sizes reported as log odds ratios. Figure 5C is the basic *galaxy plot*, with *x*- and *y*- axes representing quality of life and all-cause mortality, respectively. The range of log odds ratios for quality of life is (-0.3, 0.6), and the range of log odds ratios of all-cause mortality is (0.38, 1.65). The pooled effect is estimated at (0.1, 0.9).

We further investigated heterogeneity and small study effects. We first considered the intervention as a potential factor for heterogeneity. We observe in Figure 5C that ellipses with interventions are scattered close to the center of mass, while ellipses with telemonitoring interventions are scattered far away from the center of mass, suggesting evidence of heterogeneity. Within clusters for each intervention, we do not observe severe asymmetry, indicating that the asymmetry of the *galaxy plot* may be due to heterogeneity, rather than small study effects. Besides intervention, publication year and journal impact factor as potential factors for heterogeneity are illustrated in Figure 5E and 5F. In Figure 5E, we observe that most studies published after 2008 are scattered below the center of mass, while those published before or in 2008 are scattered above the center of mass, suggesting publication year as another cause of heterogeneity. In addition, as shown in Figure 5F, the largest ellipse closest to the center of mass has the largest impact factor, while the smaller ellipses scattered away from the center have smaller impact factors. This implies that studies published in top journals contribute more to the pooled effect.

DISCUSSION

We proposed a novel visualization tool, the *galaxy plot*, to intuitively present effect sizes and precision for bivariate outcomes from individual studies. In addition, the *galaxy plot* facilities the investigation and evaluation of the symmetry of the joint distribution of published studies, and assists to explore the potential causes of asymmetry and sources of heterogeneity.

One limitation of the galaxy plot, as well as the funnel plot, is that the interpretation based on these visualizations can be subjective, especially for small number of studies. Thus, the interpretation of the galaxy plot should be made with caution.

The *galaxy plot* focuses on visualizing bivariate outcomes, where the outcomes can be mean differences for continuous variables, log odds ratios or log risk ratios for binary variables, or other type of estimates which have the property of asymptotic normality. In addition, for meta-analysis of studies with more than two outcomes, a practical suggestion is to choose the two outcomes of interest and jointly study their basic features and additional features, such as heterogeneity and small study effects in two-dimensional space. This strategy can provide additional insights and opportunities.

The *galaxy plot* helps to detect small study effects but does not correct for them. One direction of the future work is a nonparametric multivariate extension of the trim and fill method proposed by Duval & Tweedie (2000) [26] based on the *galaxy plot* to correct for small study effects. It will also be important to explore and investigate multivariate extensions of the egger's test [27]. In addition, quantifying heterogeneity in bivariate effect sizes among studies while incorporating their precision may be worthy of investigation.

In summary, the galaxy plot should be able to incorporate any of the traditional methods used with the funnel plot such as subgrouping, regression, sensitivity analyses, outlier identification, investigation of reporting bias and imputation.

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Figure 1. Galaxy plot: an analogy in Astronomy. The galaxy photo in Figure 1A was taken by our coauthor Dr. Lingzhen Zeng. The star in the galaxy plot represents the overall estimate for the bivariate outcome.

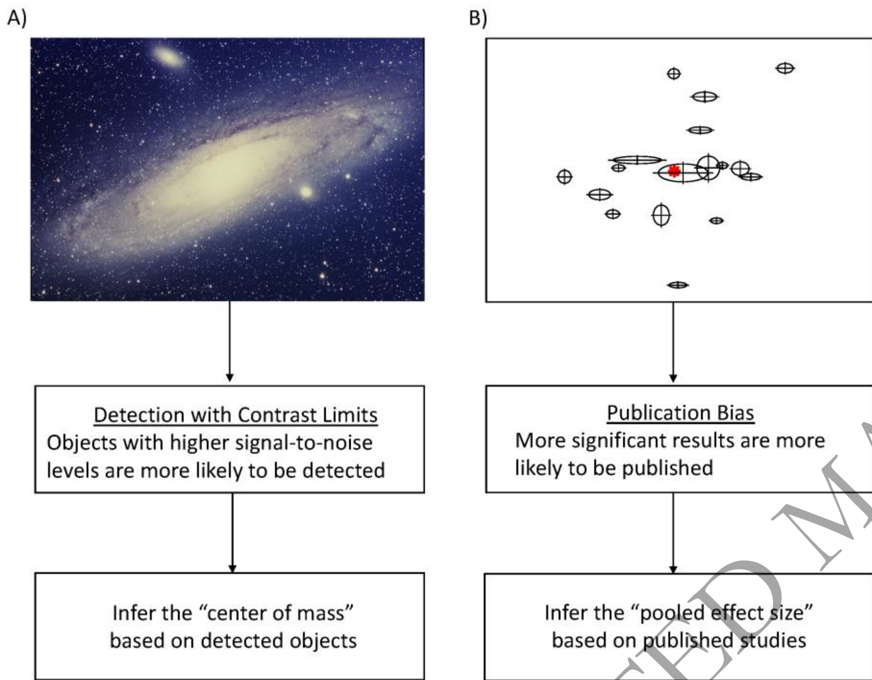
Figure 2. From the funnel plot to the galaxy plot. Simulated data is used in the illustration. The figure illustrates two separate funnel plots for bivariate outcomes and the corresponding galaxy plot. In the funnel plot, the X-axis is the effect size and the Y-axis is standard error of the effect. In the galaxy plot, the X-axis and Y-axis are the effect sizes of the two outcomes respectively; larger ellipses in the galaxy plot represent larger studies; the star represents the overall estimate for the bivariate outcomes.

Figure 3. Visualizing specific features of a bivariate meta-analysis. The stars in the galaxy plots represent the overall estimate for the bivariate outcome. Cross-hairs in 3A represent paired confidence intervals, and black dashed lines represent no effect. Arrows in ellipses in 3B show within-study correlations. The blue ellipses in 3C represent studies comparing treatment (with low dosage) and placebo, while the green ellipses represent studies comparing treatment (with high dosage) and placebo. The squares in 3C represent the estimated center of masses for the two groups of studies. 3D is the investigation of small study effects.

Figure 4. An IPD-meta-analysis of hypertension trials. CVD vs. stroke and SBP vs. DBP are considered as two sets of bivariate outcomes. The stars in the galaxy plots represent the overall estimate for the bivariate outcomes. The arrows represent the within-study correlation. 4B is zoomed in from the dashed square in 4A.

Figure 5. *Galaxy plots* for the systematic review of structured telephone support (STS) and non-invasive tele-monitoring (TM) for patients with heart failure. The stars in the galaxy plots

represent the overall estimate for the bivariate outcomes. The blue or green ellipses in Figure 5D represent the studies with different interventions; those in 5E represents studies published before or after 2008; different colors in 5F represent different impact factors of the journals.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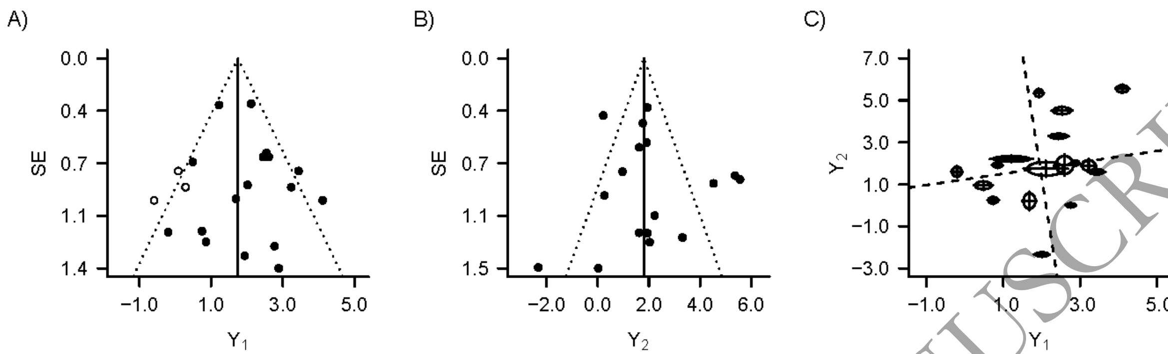
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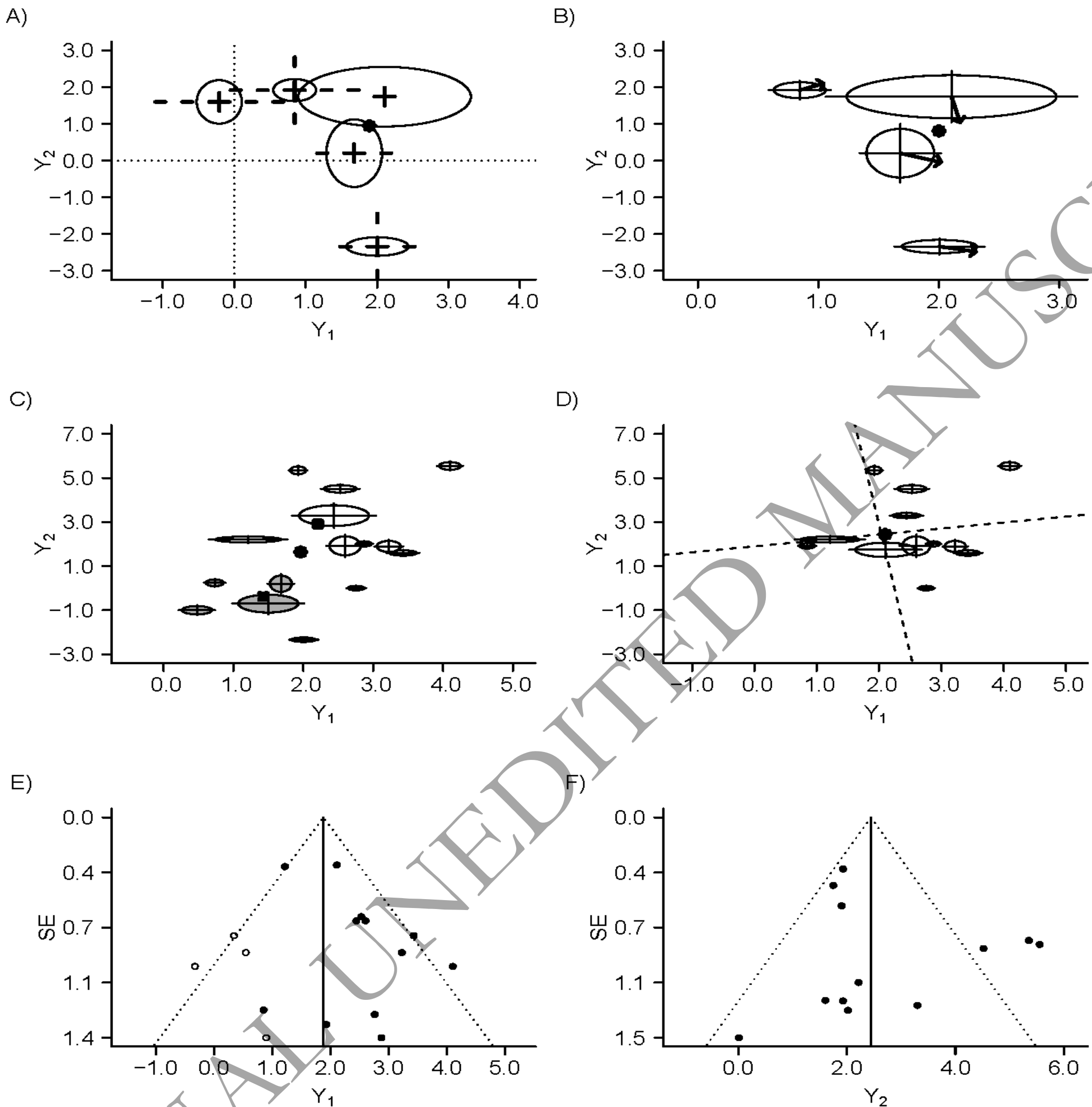
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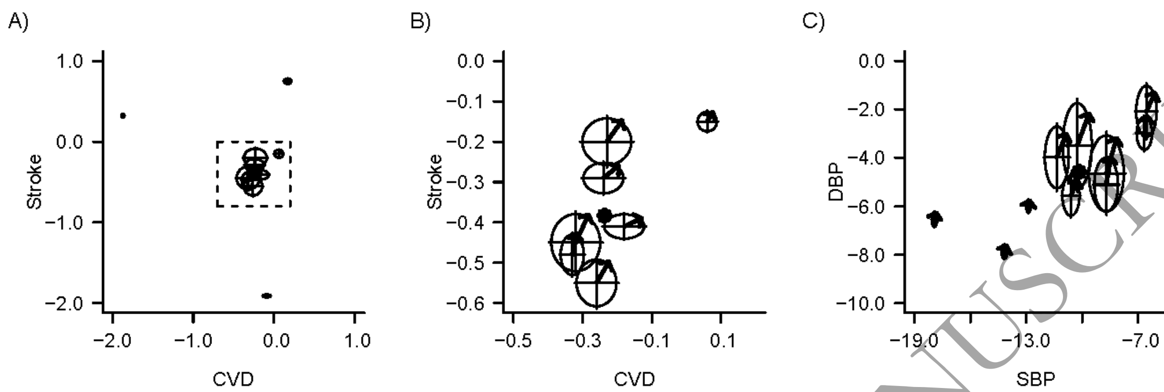
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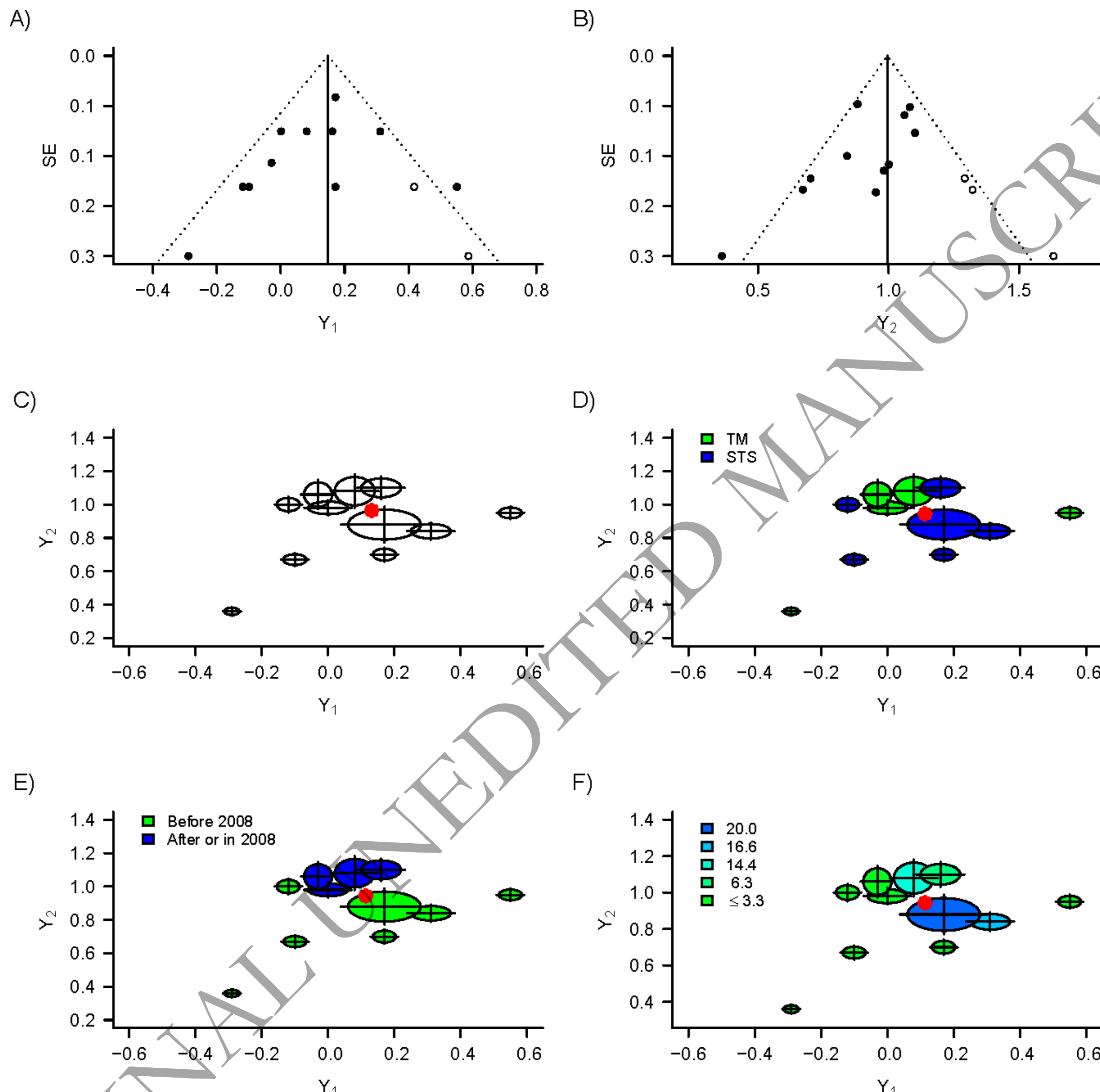
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