A paradox in random-effects meta-analysis

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Meta-analysis is an important tool for combining multiple scientific studies, and has been increasingly used in evidence-based medicine for the past several decades. The evidence from meta-analysis is nowadays regarded as the strongest evidence in medical practice. The key idea of meta-analysis is to collect data from similar studies in an effort to increase the statistical power, and consequently obtain more reliable results than those from each individual study. In other words, we often encounter the scenarios as in panel (a) of Figure 1, where the effect sizes in some studies are statistically significant while the others are not; by performing a meta-analysis, we are able to aggregate information from all the included studies so that the overall effect can be detected as statistically significant.

Following the main purpose of meta-analysis, it would be hard to imagine if the opposite scenario will occur. That is, if a new treatment is significantly better than the existing one in each study, by meta-analysis we conclude, however, that there is no significant difference between the two treatments. To explain why such a scenario is unbelievable, one may refer to, for example, the claim by Jacob Stegenga who is a philosopher of science at the University of Cambridge. In a recent Science article¹ entitled “The Metawars”, the author quoted Stegenga's words as follows: “When the evidence points clearly in one direction, there is little need for a meta-analysis.”

When reading the above Science paper, we suddenly realized that Stegenga's claim may not be correct and, instead, it yields an interesting paradox. To verify the paradox does exist, we checked our recently published paper² on a meta-analysis of fusion surgery for lumbar spinal stenosis. As displayed in panel (b) of Figure 1, each of the two studies³ ⁴ showed that the hospital stay for the experimental group is significantly longer than that for the control group. Then if Stegenga’s claim is followed, one would naturally conclude that the overall result is still significant. On the other side, noting that the heterogeneity measure ($I^2$) is 94%, by the Cochrane Handbook the random-effects model was chosen to combine the two studies. Surprisingly, the meta-analytic results did not show any significant difference between the two lengths of hospital stay. This example, therefore, confirmed our conjecture that the new paradox is real.
To investigate how often the paradox occurs in practice, with “meta-analysis” as the only keyword in the title, we searched the Web of Science for all papers published in *JAMA* in the past 10 years since January 01, 2009 and found 152 related papers. After checking the forest plots in these papers, we found one and only one publication with the new paradox occurring. To explore the association of the use of plant-based therapies and menopausal symptoms, as displayed in panel (c) of Figure 1, both studies showed that the experimental group has a significantly decreased frequency of night sweat in 24 hours compared with the control group. And hence if we follow Stegenga’s claim, the use of plant-based therapies shall be recommended automatically. Nevertheless, with the heterogeneity measure at 99%, the random-effects meta-analysis was applied and it provided a different conclusion. This hence gives another example of the new paradox.

In accordance with the above findings, we now state our new paradox as follows: “For meta-analysis of continuous outcomes with at least two studies, assume that the individual effect sizes are all significantly larger (or smaller) than zero. A paradox occurs if the overall effect from the random-effects model is, however, not significantly larger (or smaller) than zero.” Accordingly, for meta-analysis of binary outcomes, a similar statement for the paradox can be made by comparing the effect sizes to one rather than zero. All other arguments remain the same as those with continuous outcomes. To our knowledge, this paradox has never been reported in the literature on meta-analysis.

The new paradox may cause great confusion for medical doctors and researchers. In practice, if the meta-analytic evidence is different from each individual evidence, how do we interpret the final results? Taking the fusion surgery study as an example, if we follow the common practice that the meta-analytic evidence is at the peak of the evidence pyramid, then we would draw the conclusion of no significant difference between the two hospital stays. Yet on the other side, both studies were published in the prestigious journal *NEJM*, and they were of very high quality and reliable themselves. Hence, certain researchers would be more willing to accept the viewpoint delivered in each paper that the lengths of hospital stay are in fact different. With the above contradictory viewpoints, the new paradox has been putting us in a dilemma on what final conclusion can be made.

To explain why the new paradox occurs, we are also working hard on a statistical article that aims to deeply expose the underlying reasons behind the paradox. Due to space limit, we will not unfold the main theoretical results in this short report but rather present two interesting remarks. First, the paradox is more likely to occur when the number of studies is relatively small and the heterogeneity is very large. Second, for the fixed-effect model with no heterogeneity, the paradox will never occur. Unlike the random-effects model, it can be shown that, for the fixed-effect model, the variance of the overall effect is smaller than every individual variance. In addition, noting that the overall effect is a weighted mean of all individual effect sizes, if all individual effect sizes are positively (or negatively) significant, the overall effect will be larger (or smaller) than the smallest (or largest) effect size. Combing the above two facts, the confidence interval of the overall effect will not cross the zero vertical line, and hence there is not paradox in the fixed-effect model.
In summary, with the new paradox, we advocate meta-analysts to be extremely careful when interpreting the final results from the random-effects meta-analysis with small number of studies and large heterogeneity.

REFERENCES

1. Vrieze J. The metawars. *Science*. 2018;361(6408):1185–1188.

2. Wu A, Tong T and Wang X. A rethink of fusion surgery for lumbar spinal stenosis. *J Evid Based Med*. 2016;9(4):166–169.

3. Försth P, Ólafsson G, Carlsson T, et al. A randomized, controlled trial of fusion surgery for lumbar spinal stenosis. *N Engl J Med*. 2016;374(15):1413–1423.

4. Ghogawala Z, Dziura J, Butler W, et al. Laminectomy plus fusion versus laminectomy alone for lumbar spondylolisthesis. *N Engl J Med*. 2016;374(15):1424–1434.

5. Franco O, Rajiv C, Jenna T, et al. Use of plant-based therapies and menopausal symptoms: a systematic review and meta-analysis. *JAMA*. 2016;315(23):2554-2563.

6. Cheng G, Wilczek B, Warner M, Gustafsson J and Landgren B. Isoflavone treatment for acute menopausal symptoms. *Menopause*. 2007;14(3):468-473.

7. Lipovac M, Chedraui P, Gruenhut C, et al. The effect of red clover isoflavone supplementation over vasomotor and menopausal symptoms in postmenopausal women. *Gynecol Endocrinol*. 2012;28(3):203-207.
(a) A typical example of meta-analysis with five hypothetical studies

| Study     | Experimental | Control | MD | 95%−CI  | Weight (fixed) | Weight (random) |
|-----------|--------------|---------|----|---------|----------------|-----------------|
|           | Total Mean  | Total Mean | MD | 95%−CI  |                |                 |
| Study 1   | 100 0.1 1.0 | 100 0.0 1.0 | 0.1 | [ -0.2; 0.4] | 14.1%          | 16.0%           |
| Study 2   | 200 0.3 1.0 | 100 0.0 1.0 | 0.3 | [ 0.1; 0.5] | 18.8%          | 19.4%           |
| Study 3   | 300 0.5 1.0 | 100 0.0 1.0 | 0.5 | [ 0.3; 0.7] | 21.1%          | 20.8%           |
| Study 4   | 400 0.2 1.0 | 100 0.0 1.0 | 0.2 | [ 0.0; 0.4] | 22.5%          | 21.6%           |
| Study 5   | 500 0.4 1.0 | 100 0.0 1.0 | 0.4 | [ 0.2; 0.6] | 23.5%          | 22.1%           |
| Total     | 1500        | 500     | 0.3 | [ 0.2; 0.4] | --             | 100.0%          |

Heterogeneity: $I^2 = 39\%$, $\tau^2 = 0.0091$, $p = 0.16$

(b) The paradox in Wu et al. (2016)

| Study     | Experimental | Control | SMD | 95%−CI  | Weight (fixed) | Weight (random) |
|-----------|--------------|---------|-----|---------|----------------|-----------------|
|           | Total Mean  | Total Mean | SMD | 95%−CI  |                |                 |
| Försth et al. (2016) | 113 7.4 8.4 | 119 4.1 6.1 | 0.45 | [ 0.19; 0.71] | 83.5%          | 52.1%           |
| Ghogawala et al. (2016) | 30 4.2 0.9 | 33 2.6 0.9 | 1.76 | [ 1.17; 2.34] | 16.5%          | 47.9%           |
| Fixed−effect model | 143        | 152     | 0.67 | [ 0.43; 0.90] | 100.0%         | --              |
| Random−effects model |            |         | 1.08 | [−0.20; 2.35] | 100.0%         | 100.0%          |

Heterogeneity: $I^2 = 94\%$, $\tau^2 = 0.7990$, $p < 0.01$

(c) The paradox in Franco et al. (2016)

| Study     | Experimental | Control | MD | 95%−CI  | Weight (fixed) | Weight (random) |
|-----------|--------------|---------|----|---------|----------------|-----------------|
|           | Total Mean  | Total Mean | MD | 95%−CI  |                |                 |
| Cheng et al. (2007) | 30 −0.6 0.8 | 30 −0.2 0.7 | −0.40 | [−0.79; −0.01] | 70.3%          | 50.2%           |
| Lipovac et al. (2012) | 50 −3.9 1.5 | 59 0.0 1.7 | −3.90 | [−4.50; −3.30] | 29.7%          | 49.8%           |
| Fixed−effect model | 80        | 89      | −1.44 | [−1.77; −1.11] | 100.0%         | --              |
| Random−effects model |            |         | −2.14 | [−5.57; 1.29] | 100.0%         | 100.0%          |

Heterogeneity: $I^2 = 99\%$, $\tau^2 = 6.0573$, $p < 0.01$

Figure 1: Panel (a) displays a typical example of meta-analysis with five hypothetical studies, panel (b) presents the paradox in Wu et al. (2016), and panel (c) presents the paradox in Franco et al. (2016).