

# Most large treatment effects of medical interventions come from small studies

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In an examination of the characteristics of studies that yield large treatment effects from medical interventions, these studies were more likely to be smaller in size, often with limited evidence, and when additional trials were performed, the effect sizes became typically much smaller, according to a study in the October 24/31 issue of *JAMA*.

"Most effective interventions in [health care](#) confer modest, incremental benefits," according to background information in the article. "Large effects are important to document reliably because in a relative scale they represent potentially the cases in which interventions can have the most impressive effect on [health outcomes](#) and because they are more likely to be adopted rapidly and with less evidence. Consequently, it is important to know whether, when observed, very large effects are reliable and in what sort of experimental outcomes they are commonly observed. ... Some large treatment effects may represent entirely spurious observations. It is unknown how often studies with seemingly very large effects are repeated."

Tiago V. Pereira, Ph.D., of the Health Technology Assessment Unit, German Hospital Oswaldo Cruz, Sao Paulo, Brazil, and colleagues conducted a study to evaluate the frequency and features of very large treatment effects of [medical interventions](#) that are first recorded in a clinical trial. For the study, the researchers used data from the Cochrane Database of Systematic Reviews (CDSR) and assessed the types of treatments and outcomes in trials with very large effects, examined how often large-effect trials were followed up by other trials on the same

topic, and how these effects compared against the effects of the respective meta-analyses.

Among 3,545 available reviews, 3,082 contributed usable information on 85,002 forest plots (a graphical display designed to illustrate the relative strength of treatment effects in multiple studies). Overall, 8,239 forest plots (9.7 percent) had a nominally statistically significant very large effect in the first published trial, group A; 5,158 (6.1 percent) had a nominally statistically significant very large effect found only after the first published trial, group B; and 71,605 (84.2 percent) had no trials with significant very large effects, group C. The researchers found that nominally significant very large effects arose mostly from small trials with few events. For the index trials, the median [midpoint] number of events was only 18 in group A and 15 in the group B. The median number of events in the group C index trials was 14.

The authors also observed that 90 percent and 98 percent of the very large effects observed in first and subsequently published trials, respectively, became smaller in meta-analyses that included other trials; the median odds ratio decreased from approximately 12 to 4 for first trials, and from 10 to 2.5 for subsequent trials.

Topics with very large effects were less likely than other topics to address mortality. Across the whole CDSR, there was only 1 intervention with large beneficial effects on mortality and no major concerns about the quality of the evidence (for a trial on extracorporeal oxygenation for severe respiratory failure in newborns).

"... this empirical evaluation suggests that very large effect estimates are encountered commonly in single trials. Conversely, genuine very large effects with extensive support from substantial evidence appear to be rare in medicine and large benefits for mortality are almost entirely nonexistent. As additional evidence accumulates, caution may still be

needed, especially if there is repetitive testing of accumulating trials. Patients, clinicians, investigators, regulators, and the industry should consider this in evaluating very large treatment effects when the evidence is still early and weak," the researchers write.

**More information:** *JAMA*. 2012;308[16]:1676-1684

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