

## Not enough evidence

From: [Key Concepts for assessing claims about treatment effects and making well-informed treatment choices \(Version 2022\)](#)

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### 2.3d Be cautious of lack of evidence being interpreted as evidence of “no difference”.

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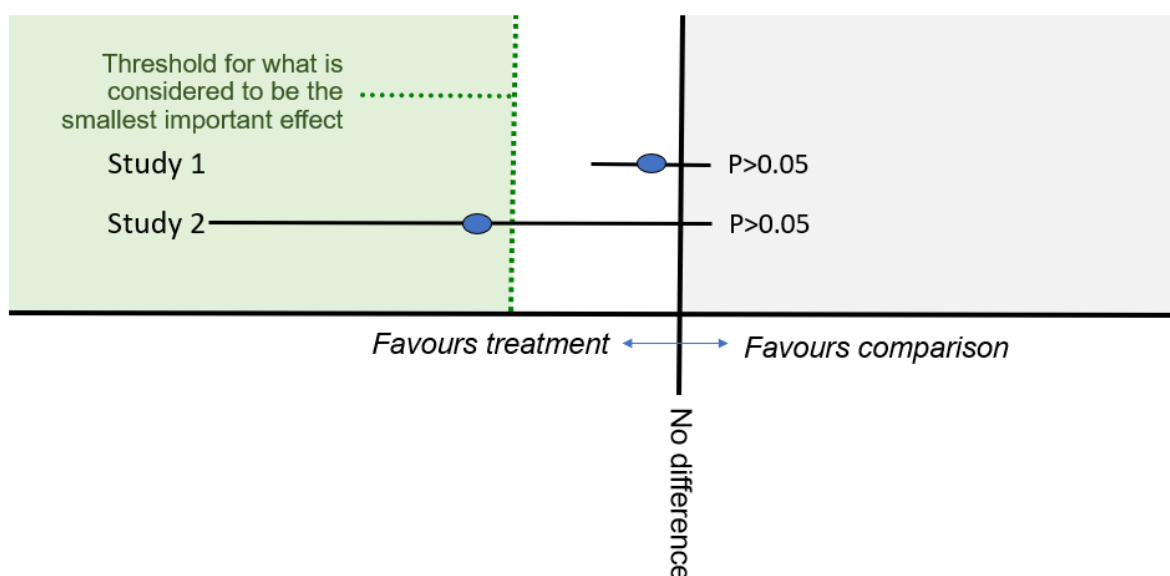
#### Explanation

[Systematic reviews](#) sometimes conclude that there is “no difference” between the treatments compared. However, studies can never show that there is “no difference” (“no effect”). They can only rule out, with specific degrees of confidence, differences of a specific size.

Misinterpreting “[statistically non-significant](#)” results and failing to recognise uncertainty in estimates of effect can sometimes impede further research to reduce the uncertainty and result in delays in the uptake of effective treatments. For example, a systematic review of randomized trials of thrombolytic therapy (medicine that prevents blood clots from growing) given to patients after an acute heart attack found a 22% relative reduction in mortality that was highly unlikely to have occurred by chance alone [[Yusuf 1985 \(SR\)](#)]. But only five of the 24 trials had shown a “statistically significant” effect ( $P < 0.05$ ). The lack of “statistical significance” of most of the individual trials and misinterpretation of those results led to a long delay before the value of thrombolytic therapy was appreciated.

#### Basis for this concept

By convention, a 5% probability that the results observed in a [treatment comparison](#) could have occurred by the play of chance ( $P > 0.05$ ) is considered “not significant” [[Altman 1995](#)]. Trials with “statistically non-significant” results are commonly referred to as “negative”. But this is misleading. Often those studies are not big enough to either rule in or rule out an important difference (effect) [[Freiman 1978 \(RS\)](#)]. This is illustrated in the figure below.



The blue dots in this figure indicate the estimated effect for each study. The horizontal lines indicate the 95% [confidence intervals](#). The dotted green vertical line indicates the smallest effect considered

to be important. The results for Study 1 in the figure indicate that an important impact is highly unlikely. It clearly rules out the likelihood of an effect that large or larger. On the other hand, the results for Study 2 are inconclusive. It clearly does not rule out an important effect. The results for both studies are “statistically nonsignificant” ( $P > 0.05$ ), but the interpretation of the two studies should be quite different. The first study was big enough to rule out an important difference. The second study was not. It is inconclusive, not “negative”.

A survey of systematic reviews published in 2001-2002 found unqualified claims of “no difference” or “no effect” in 21% of review abstracts (summaries) [Alderson 2003 (RS)]. In 2017, such claims were found in 6% to 8% of systematic reviews [Marson Smith 2021 (RS)]. This may indicate greater awareness of the problem. However, the survey found 71 examples of misleading interpretations. These included, for example, “evidence for no effect”, “does not affect”, and “found no beneficial or harmful effects”. This suggests that there is still a problem with misinterpreting lack of evidence as “no difference”. A survey of press releases and associated media coverage in 2010 found misleading claims of “equivalence” in 7% of the abstracts of randomized trials that were the basis for the press release [Yavchitz 2012 (RS)]. Those misinterpretations were reflected in the press releases and related news reports. A survey of abstracts of randomized trials published in four high-profile journals in 2016-2017 found that 54% of the authors concluded that there was no treatment benefit, 12% that there was “no significant benefit”, and 13% that there was “no significant difference” [Gates 2019 (RS)]. Only 3% referred to uncertainty when drawing conclusions. The authors of that survey concluded: “Despite many years of warnings, inappropriate interpretations of [randomized trial] results are widespread in the most prestigious medical journals.”

Considering the [precision](#) of effect estimates when making judgements about the certainty of the evidence, and not reporting effects as “significant” or “non-significant” can reduce the chances of being misled [Altman 1995].

## Implications

Don't be misled by statements of “no difference” between treatments (“no effect”). Consider instead the degree to which it is possible to confidently rule out a difference of a specified size.

## References

### Systematic reviews

Yusuf S, Collins R, Peto R, Furberg C, Stampfer MJ, Goldhaber SZ, et al. Intravenous and intracoronary fibrinolytic therapy in acute myocardial infarction: overview of results on mortality, reinfarction and side-effects from 33 randomized controlled trials. *Eur Heart J*. 1985;6(7):556-85. <https://doi.org/10.1093/oxfordjournals.eurheartj.a061905>

### Research studies

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Freiman JA, Chalmers TC, Smith H, Jr., Kuebler RR. The importance of beta, the type II error and sample size in the design and interpretation of the randomized control trial. Survey of 71 “negative” trials. *N Engl J Med*. 1978;299(13):690-4. <https://doi.org/10.1056/nejm197809282991304>

Gates S, Ealing E. Reporting and interpretation of results from clinical trials that did not claim a treatment difference: survey of four general medical journals. *BMJ Open*. 2019;9(9):e024785. <https://doi.org/10.1136/bmjopen-2018-024785>

Marson Smith PR, Ware L, Adams C, Chalmers I. Claims of 'no difference' or 'no effect' in Cochrane and other systematic reviews. *BMJ Evid Based Med*. 2021;26(3):118-20. <https://doi.org/10.1136/bmjebm-2019-111257>

Yavchitz A, Boutron I, Bafeta A, Marroun I, Charles P, Mantz J, et al. Misrepresentation of randomized controlled trials in press releases and news coverage: a cohort study. PLoS Med. 2012;9(9):e1001308. <https://doi.org/10.1371/journal.pmed.1001308>

### **Other references**

Altman DG, Bland JM. Absence of evidence is not evidence of absence. BMJ. 1995;311(7003):485. <https://doi.org/10.1136/bmj.311.7003.485>