Sub-group analyses

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

2.4b Be cautious of results for a selected group of people within a study.

Explanation

Average effects do not apply to everyone. However, comparisons of treatments often report results for selected groups of participants to assess whether the effect of a treatment is different for different types of people (e.g., men and women or different age groups). These analyses are often poorly planned and reported. Most differential effects suggested by these "subgroup" analyses are likely to be due to the play of chance and are unlikely to reflect true treatment differences.

For example, in 1983 the authors of a paper that presented 146 subgroup analyses of the Beta Blocker Heart Attack trial, found that the results were normally distributed – a pattern that would be expected if the variation in results was simply due to the play of chance *[Oxman 2012b]*. Roughly 2.5% of the subgroup analyses had results that statistically were "significantly" worse and 2.5% had results that were "significantly" better. Five years later the International Study of Infarct Survival 2 (ISIS-2) trial found that aspirin reduced mortality after heart attack overall (P<0.00001) but increased mortality by a small amount in patients born under Gemini and Libra astrological signs. The authors included this subgroup analysis in their report to illustrate the likelihood of misleading subgroup analyses. Six years after that, the DICE (Don't Ignore Chance Effects) collaborators in their meta-analysis of trials of DICE therapy (rolling dice) for acute stroke found that red dice are deadly, based on a predefined subgroup analysis by colour of dice. All these findings illustrate the important message that chance influences the results of treatment comparisons and systematic reviews. Unfortunately, researchers, health professionals, patients and the public continue to be misled by subgroup analyses.

Basis for this concept

Reviews of published randomized trials and protocols have found that subgroup analyses are commonly reported (38-87% of the time), and that appropriate statistical analyses (tests of interaction) are not used 38-91% of the time *[Oxman 2012b]*. In addition, planned subgroup analyses are commonly not reported (48-69% of the time) and 43-91% of randomized trials report subgroup analyses that were not planned. When subgroup analyses are reported, authors claim differences in 25-69% of cases, and these results are commonly featured prominently (15-45% of the time).

A systematic review of randomized trials published in core journals in 2007 found that 44% of the trials reported subgroup analyses *[Sun 2012 (SR)]*. The review authors assessed the credibility of the subgroup claims using explicit criteria. They found that the credibility of most of subgroup claims, including strong claims, was usually low. Subsequent systematic reviews have found that inadequate specification and reporting of subgroup analyses remain problematic in protocols and reports of randomized controlled trials *[Fan 2019 (SR), Gabler 2016 (SR), Kasenda 2014 (RS), Wallach 2017 (SR)]*. Justifications or rationales for subgroup analyses were only rarely provided in trial protocols and reports, and large discrepancies were found between planning of subgroup analyses in protocols and their reporting in publications of randomized trials. A systematic review of subgroup analyses based on sex found that "statistically significant" sex-treatment interactions were only slightly more frequent than would be expected by chance *[Wallach 2016 (SR)]*.

Several different checklists have been developed that can help to assess the credibility of claims about subgroup effects *[Gil-Sierra 2020 , Oxman 2002 , Oxman 1992 , Sun 2014]*.

Implications

Findings based on results for subgroups of people within treatment comparisons may be misleading.

References

Systematic reviews

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