Cochrane
Effective Practice and
Organisation of Care

What are explanatory factors and why should they be included in protocols?

See also: 9.6 Investigating heterogeneity in the Cochrane Handbook

Explanatory factors are characteristics of populations (including their settings or contexts), interventions, the comparison, outcome measures, or study design (including the risk of bias) that could potentially explain differences in results. This may be, for example, due to different mechanisms of action. Explanatory factors can potentially explain differences in results both across studies and across subgroups within a study. They can be used to explore heterogeneity in subgroup analyses[1] and meta-regressions.[2]

Explanatory factors should be specified in the protocol of an EPOC review to:

- Ensure that data are collected to investigate potential interactions;
- Specify a priori a small number of factors to investigate for which there are good reasons to suspect an interaction.

This can reduce the risk of being misled by spurious findings which can more easily occur with post hoc (data driven) analyses, when lots of factors are examined and when there are not good reasons for anticipating an interaction (i.e. different effects across subgroups of studies or data divided up based on the factor).
The protocol should include explanations about why an interaction is hypothesised and a clear hypothesis about the direction of the interaction (i.e. in which subgroup would the effect be expected to be larger and why?). The protocol should also specify how potential interactions will be analysed.

Often there are not enough data to draw firm conclusions about the overall effect in EPOC (or most other) reviews. It is even less likely that there will be sufficient data to draw firm conclusions about subgroup analyses. Thus subgroup analyses should always be interpreted cautiously using criteria such as the ones in the Cochrane Handbook (pasted in below) or other published checklists.[3]

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[1] Subgroup analyses involve splitting the data into subgroups, so as to make comparisons between them, as a means of investigating heterogeneous results, or to answer specific questions about particular patient groups, types of intervention or types of study. They may be done for subsets of participants (within studies) or studies.

[2] Meta-regression is an extension to subgroup analyses that allows the effect of continuous, as well as categorical characteristics to be investigated. In principle meta-regression allows the effects of multiple factors to be investigated simultaneously. However, this is rarely possible due to inadequate numbers of studies. Meta-regression should generally not be considered when there are fewer than ten studies in a meta-analysis.

[3] Sun X, Briel M, Walter SD, Guyatt GH. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. BMJ 2010; 340:850-4.

Suggested citation: Cochrane Effective Practice and Organisation of Care (EPOC). What are explanatory factors and why should they be included in protocols? EPOC Resources for review authors, 2017. Available at: http://epoc.cochrane.org/resources/epoc-resources-review-authors

Even when there are not sufficient data to undertake subgroup analyses, specifying explanatory factors in the protocol can be used to guide discussion of the applicability of the findings. The same factors that might explain differences in results might also limit the applicability of the findings; e.g. from studies conducted in one population or setting to a different population or setting.

9.6.6 Interpretation of subgroup analyses and meta-regressions (from the Cochrane Handbook)
Appropriate interpretation of subgroup analyses and meta-regressions requires caution. For more detailed discussion see Oxman and Guyatt.[4]

- Subgroup comparisons are observational

It must be remembered that subgroup analyses and meta-regressions are entirely observational in their nature. These analyses investigate differences between studies. Even if individuals are randomized to one group or other within a clinical trial, they are not randomized to go in one trial or another. Hence, subgroup analyses suffer the limitations of any observational investigation, including possible bias through confounding by other study-level characteristics. Furthermore, even a genuine difference between subgroups is not necessarily due to the classification of the subgroups. As an example, a subgroup analysis of bone marrow transplantation for treating leukaemia might show a strong association between the age of a sibling donor and the success of the transplant. However, this probably does not mean that the age of donor is important. In fact, the age of the recipient is probably a key factor and the subgroup finding would simply be due to the strong association between the age of the recipient and the age of their sibling.

- Was the analysis pre-specified or *post hoc*?

Authors should state whether subgroup analyses were pre-specified or undertaken after the results of the studies had been compiled (*post hoc*). More reliance may be placed on a subgroup analysis if it was one of a small number of pre-specified analyses. Performing numerous *post hoc* subgroup analyses to explain heterogeneity is data dredging. Data dredging is condemned because it is usually possible to find an apparent, but false, explanation for heterogeneity by considering lots of different characteristics.

- Is there indirect evidence in support of the findings?

Differences between subgroups should be clinically plausible and supported by other external or indirect evidence, if they are to be convincing.

- Is the magnitude of the difference practically important?

If the magnitude of a difference between subgroups will not result in different recommendations for different subgroups, then it may be better to present only the overall analysis results.

[4] Oxman AD, Guyatt GH. A consumer's guide to subgroup analyses. Ann Intern Med. 1992 Jan 1;116:78-84.

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- Is there a statistically significant difference between subgroups?

To establish whether there is a different effect of an intervention in different situations, the magnitudes of effects in different subgroups should be compared directly with each other. In particular, statistical significance of the results within separate subgroup analyses should not be compared. See Section 9.6.3.1 in the Cochrane Handbook.

- Are analyses looking at within-study or between-study relationships?

For patient and intervention characteristics, differences in subgroups that are observed within studies are more reliable than analyses of subsets of studies. If such within-study relationships are replicated across studies then this adds confidence to the findings.

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