Author's response to reviews

Title: Simpson's paradox visualized: The example of the Rosiglitazone meta-analysis

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Response to reviewer’s comments

Manuscript
'Simpson’s paradox visualized: The example of the Rosiglitazone meta-analysis'

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Referee 1 (Klaus Fiedler)

After describing the purpose of the paper (first three paragraphs), the referee poses three questions that will be discussed and answered in the following.

Paragraph beginning with ‘The most important problem...’

The referee observes that the ‘message conveyed in this article is ... that the overall view on the pooled (meta-analytic) data is ... less valid than the partial correlation visible within the singular trials’. This is a correct interpretation of our message. Further, he argues that ‘which level of analysis is ... more appropriate for the problem at hand, cannot be answered statistically but depends on the theoretical and practical assumptions’. This is true, too. However, applied to our context it means that the focus of interest in a meta-analysis of randomized clinical trials is always the same as in the single trials on which it is based. Therefore I disagree that the message that simple pooling is inadequate is ‘misleading’.

The aim of each randomized trial (and hence of the meta-analysis) is to evaluate the effect of the active treatment (e.g., rosiglitazone) compared to the control. This comparison is valid by randomization. Clearly, different trials may represent patient groups differing, for instance, in their health status. This phenomenon, referred to as between-trials heterogeneity in the meta-analytical approach, is treated as a nuisance parameter, for which reason a meta-analysis must be stratified for trial. This is general consensus (for a reference, see the fundamental book of Anne Whitehead [1], now cited in this context on page 3). The primary aim of a meta-analysis is not, as the referee considers, predicting ‘the groups Y risk’ (that is, the overall risk of an event within a trial) or ‘the risk of an individual with unknown group membership’. Any comparison between individuals not randomized within the same trial would lack validity.

Paragraph beginning with ‘Apart from this...’

The referee wonders why dichotomous and continous variables are distinguished. This is explained by the fact that the aim of the paper is to present plots clarifying Simpson’s paradox for the setting of a meta-analysis with a dichotomous outcome. For example, if X (the treatment) and Y (the event of interest) are continuous, a scatterplot can be plotted. A plot of this kind is now added to the paper for illustration (new Figure 1). If, however, both variables are dichotomous, as in all examples throughout the paper, the same plot would hardly look like a scatterplot, and hence for this setting we have to develop other types of plots. This is what we undertake in this article.
Another point is that the Baker-Kramer plot, referred to in the paper, requires that the con-
founder is binary. This is mentioned in the background section (page 2) and outlined in the
discussion (page 7 and Table 2). While I agree with the referee that there is no fundamen-
tal difference in the logic between the binary and the continuous case, there are unavoidable
differences in the graphical illustration of both.

Further, the referee asks why the use of difference vs. ratio makes a difference. This is partly
answered by the second referee (his bullet point 6). We answer it using the second example (first
paragraph on page 6): For relative measures, such as the odds ratio, the transformation used
in non-linear. Therefore, a direct overlay of the first two plots would result in a plot where the
dots don’t lie on the lines. Instead, we now propose a generalized version of the overlay plot,
where the lines are replaced with curves (revised Figure 3 = former Figure 2).

Paragraph beginning with ‘The final meta-analysis...’

The source of the 157 meta-analyses sample is now described more explicitly, see response to
referee 2.

The referee’s last sentence is not clear to me. We do not speak about a ‘significant Simpson
check’. Rather, we were interested in estimating the frequency of an effect reversion and finding
more examples. Therefore we carried out Simpson checks, as described, for all 157 meta-analyses
of the sample. We found 9 examples where the sign changed. Somewhat disappointingly (from
the didactical point of view), in none of these 9 meta-analyses the treatment effect is significant,
and thus the change of the sign is of no statistical importance.

This is clarified in the text (page 7/8).

Referee 2 (Christopher Cates)

Minor essential revisions

1. The source of the 157 meta-analyses sample is now described more explicitly (page 7).
   There was no further selection.

2. The sentence is deleted.

3. Clarified in the text (page 2): In my view, a perfect example is one where all single trials
   have an effect of the same sign, while the pooled analysis reverses this sign. This holds for
   Example 2.

4. Done.

5. I would like to thank the referee for his valuable hints to potential reasons of clinical
   heterogeneity in the Rosiglitazone meta-analysis. These are incorporated in the discussion
   (page 6).

6. Agreed. This was already stated on page 6 (first paragraph).

References