Nuisance mediators and missing data in mediation analyses of pain trials

[Commentary on O'Neill et al. 2020. Examining what factors mediate treatment effect in chronic low back pain: a mediation analysis of a Cognitive Functional Therapy clinical trial. European Journal of Pain]

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This journal recently published a paper by O'Neill and colleagues, entitled "Examining what factors mediate treatment effect in chronic low back pain: a mediation analysis of a Cognitive Functional Therapy clinical trial" (O'Neill et al., 2020). Although the limitations in O'Neill et al. preclude robust conclusions about the mechanisms of Cognitive Functional Therapy (CFT), their study highlights wider issues for understanding treatment mechanisms for chronic pain. This commentary focuses on two issues: the need for mediation analyses to explain why treatments do not work, and the misreporting of missing data in mediation analyses.

Mediation analyses should be conducted in trials that do not demonstrate positive treatment effects

Mediation analyses of pain interventions are often conducted in trials that demonstrate positive treatment effects (to explain how treatments work). But only few mediation analyses are conducted in trials that do not demonstrate positive treatment effects (to explain why treatments do not work). Perhaps this is motivated by the traditional idea that a mediation analysis should only be conducted in trials that demonstrate a treatment effect. This approach is misguided, there are important reasons why mediation analyses should be conducted when trials do not demonstrate positive treatment effects.

When a trial demonstrates that a treatment does not have a causal effect on a primary outcome, it is still possible that there are indirect treatment effects that reflect important underlying mechanisms. On the face of it, this might seem paradoxical: *How can there be an indirect treatment effect when the treatment is ineffective?*

This is possible because interventions like CFT comprise multiple components and exert their causal effects by triggering multiple mechanisms. Some effective mechanisms, such as self-efficacy, will have positive effects on the primary outcome. But other mechanisms, that are not purposely targeted by the intervention can have opposing effects on the primary outcome. Triggering these 'nuisance' mediators (Dunn et al., 2015) will counteract (or partially counteract) the effects of positive mechanisms. A hypothetical example of a nuisance mediator in O'Neill's study might be the discontinuation of analgesic medicines that could counteract the analgesic effects gained by improving self-efficacy. Similarly, unintentionally triggering harmful mechanisms can also counteract the effects of positive mechanisms. For example, CFT might cause people to over-exert or ruminate which might increase pain intensity. So even when a trial shows no effect of treatment, there may still be important indirect effects through the targeted mechanisms, if the treatment also triggers nuisance or harmful mechanisms.

Mediation analyses of trials should be conducted when treatments are ineffective. They can be used to quantify the effects of nuisance or harmful mediators, in addition to purposely targeted mediators. This is hardly common practice, but important progress could be made if this approach is routinely implemented in pain trials.

Misrepresentation of missing data in mediation analyses

Most mediation analyses of trials have missing data. Capturing sufficient data for mediation analyses can be more demanding and costly because additional data on selected mediators, outcomes and possible confounders must be collected over multiple time points. However, this does not allow for any excuses because any missing data impacts the credibility of information that comes from mediation analyses.

At first glance, the amount of missing data in O'Neill et al. might not appear substantial. Table 1 in O'Neill et al. shows that between 130 to 145 of 206 participants contributed follow-up data for the outcomes and mediators. However, these numbers underrepresent the size of the missing data problem. The devil is in the detail. For an individual to be included in the mediation analysis, they must contribute data on the treatment, mediator, outcome and all possible confounders for a given model. An individual with missing data on any one of these variables would be excluded from the analysis. This means that the actual number of individuals analysed in O'Neill et al. is alarmingly low; between 42 and 57%. Approximately half of the sample were missing in their complete case analyses. The authors use multiple imputation, but with this much missing data it is highly doubtful that even the most sophisticated imputation method will recover reliable information from the observed data (Hughes et al., 2019). Consequently, these results must be interpreted with caution and should not guide teaching or clinical practice before the findings are replicated. O'Neill and colleagues should be commended for transparently reporting the number of participants that were analysed in each mediation model, as should all other mediation analyses in the field.

To summarise, mediation analyses of pain trials should be conducted even when trials do not demonstrate treatment effects (perhaps with an additional focus on nuisance and harmful mediators). Strict protocols and efficient data collection methods should be used to minimise missing data, but when they do occur, the precise number of participants in each mediation model must be clearly reported.

References

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