The role of absolute summaries in detecting intransitivity and model mis-specification in indirect treatment comparisons

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MSR127

Background

With sufficient data, statistical evidence of instransitivity in network meta-analysis may be detected through tests of inconsistency/incoherence, but these tests are underpowered or impossible in many networks with few or no connections. In these cases, decisions regarding potential intransitivity rely exclusively on evidence synthesis feasibility assessments that typically compare included trials on inclusion/exclusion, outcome definitions, estimands, baseline risk, and patient characteristics. The current research introduces a novel additional method to leverage expert opinion to flag potential intransitivity based on absolute outcomes estimated by the model and those at the trial level.

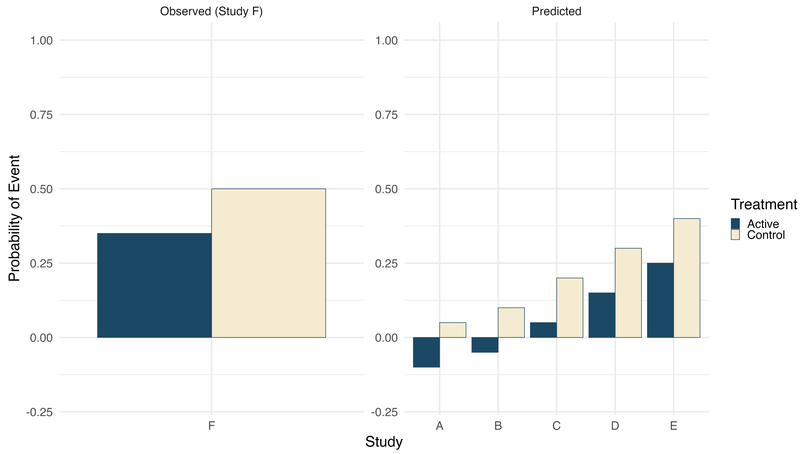
Methods

We use simulated data to illustrate three core applications of the use of absolute summaries:

1. Identifying implausible or impossible absolute effects at the limits of placebo response
2. Identifying violation of ordering constraints for ordinal outcomes

Identifying Implausible or Impossible Absolute Effects

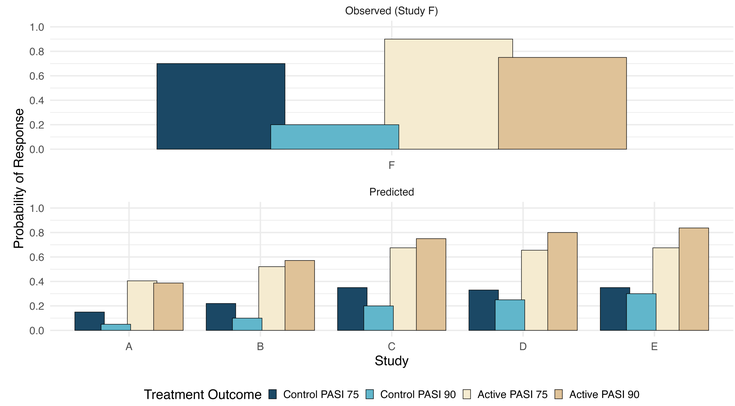
In some recent NICE submissions, sponsors have suggested that models based on risk difference may be more robust than those based on odds ratios. If using this approach, a simple test that should be included is whether the the largest observed risk difference is possible in all placebo controlled studies. Absolute probabilities less than.0 or greater than 1 may imply the need for additional adjustment or different choice of link.



A similar approach might show that larger observed odds ratios in studies with very low placebo response would imply that nearly the entire population is cured in studies with higher placebo response. This might suggest the need for eg, baseline risk adjustment.

Identifying Violation of Ordering Constraints for Ordinal Outcomes

Ordinal outcomes have known constraints that eg the proportion of patients with 75% or greater improvement from baseline must always be equal to those with 90% or greater. We can leverage these relationships to test when analyzing these outcomes as separate binomials result in predictions that violate these constraints.



The greater separation between PASI 75/90 in Study F allows for larger differences in the treatment effects between PASI 75/90 than is possible in other studies, where ORs from study F lead to PASI 90 greater than PASI 75.

Conclusions

Plotting absolute summaries from NMAs across all the included studies can be used to identify potential intransitivity or model specification in cases where there is insufficient power to detect it otherwise.

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ISPOR 2025 – Montreal, QC