

## Response to: 'Paracetamol: is all the concern valid?' by Schwarz and Mullins

We thank Drs Schwarz and Mullins for their comments<sup>1</sup> on our paper,<sup>2</sup> and we agree with many of their points. The absolute risks of the studied adverse events were small, and paracetamol still has a better adverse event profile than traditional non-steroidal anti-inflammatory drugs (NSAIDs) or opioids. However, we would like to highlight that there are also non-pharmacological alternatives for chronic pain conditions, especially those of the musculoskeletal system: muscle strengthening, increased activity and weight loss if overweight.<sup>3</sup>

We appreciate that biases (including non-complete adjustment for confounders, narrow population of the included studies and the reliance on self-report and paracetamol prescription as methods to calculate the total ingested amount of paracetamol) make the observational data in our review difficult to interpret. We also appreciate, and highlighted in our discussion, the potential for confounding by indication and suggest that increasing doses of paracetamol might reflect sicker patients and might be a marker for those using increasing doses of over-the-counter NSAIDs. Four included studies did not adjust for concomitant NSAID use,<sup>4–7</sup> and channelling bias may lead those patients deemed unsuitable for NSAID therapy to be prescribed paracetamol as a 'safer' alternative. Those studies that did control for other analgesic use all showed dose–response relationships for their adverse event outcomes. We specified a priori if cohort-level evidence was found for an adverse event outcome, case–control evidence was not considered, though noted evidence from the case–control literature supporting the dose–response seen in the current review.<sup>8</sup>

We agree that the overall GRADE rating was very low for all outcomes, but would highlight that as all studies included were observational, the GRADE system of quality rating per outcome begins at 'low' quality, which is based solely on a study's observational design, and does not take into consideration that observational studies are the most appropriate study design to assess the risk of the studied long-term adverse event outcomes.

Given recent publications regarding paracetamol's weak peripheral anti-inflammatory mode of action,<sup>9</sup> we believe that data demonstrating side effects potentially reflecting this should be published. A recent well designed randomised controlled trial reporting equivalent blood loss with paracetamol and ibuprofen strengthens our belief.<sup>10</sup> Of course, clinicians first need to consider the efficacy in chronic painful musculoskeletal conditions,<sup>11 12</sup> but be mindful of the fact a paracetamol prescription is not one with zero risk.

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