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## ACETAMINOPHEN SAFETY IN OLDER ADULTS

Reply to: "Acetaminophen Safety in Older Adults with OA: Key considerations."

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Dear Editors,

We thank Gallardo-Landauro *et al.* <sup>(1)</sup> for their interest in this study. We conducted a retrospective cohort study and reported that acetaminophen prescription was associated with a significantly higher risk of gastrointestinal, cardiovascular, and renal adverse effects in adults aged  $\geq 65$  years in age. We acknowledged the concerns raised by Gallardo-Landauro et al regarding the potential bias introduced by 'subclinical cases.' To paraphrase Gallardo-Landauro et al., we presume by this that they mean people with an outcome, that is at a mild and/or early phase and without a diagnosis recorded. To minimise any issues from reverse causality we used landmark analysis, inverse probability treatment weighting and propensity score matching to balance the acetaminophen-exposed and unexposed groups, incorporating multiple covariates<sup>(2)</sup>. However, as mentioned in the limitations, residual confounding remains an issue.

We acknowledge that some studies find no strong link between acetaminophen and cardiovascular risks, while others <sup>(3-5)</sup> suggest potential harm at high doses, as already mentioned in the main manuscript<sup>(2)</sup>.

We had already covered this in the study that over the counter (OTC) medications play a crucial role in self-care, but their use is often not recorded in electronic health records (EHRs), posing a challenge in studies like this. To minimize this limitation, our study <sup>(2)</sup> focused on individuals aged  $\geq 65$  years, who were less likely to purchase acetaminophen independently due to free prescriptions in this age group. However, OTC use may still have affected both exposure and non-exposure groups, likely leading to an underestimation rather than an overestimation of the hazard ratio (HR).

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