Correspondence

Interpreting exploratory immune signals and parent-reported outcomes after labour epidural analgesia: a reply

We thank Cao et al. for their thorough appraisal of our findings [1], and for identifying precisely the interpretive limitations of the cytokine moderation analysis [2]. We agree these results warrant explicit exploratory framing and take this opportunity to present a clarification of our analysis and report how our conclusions hold up across alternative analytic approaches.

The dichotomisation of inflammatory markers at the median was a deliberate choice rather than an inadvertent limitation. With only 61 participants available for the moderation analysis, continuous modelling carried a risk of producing unstable or misleading estimates in the presence of non-linear associations that our sample was insufficiently powered to detect. The median split minimised parametric assumptions, although we acknowledge, it discards information. Prompted by this correspondence, we repeated the interaction analyses dichotomising at the 25th and 75th percentiles, and separately, modelling each marker continuously (Fig. 1).

The results are instructive. Our published median-split analysis identified tumour necrosis factor superfamily member 14 (TNFSF14) and chemokine (C-X-C motif) ligand 6 (CXCL6) as having significant interaction terms (uncorrected for multiple testing); the 75th-percentile split flagged TNFSF14 and interleukin (IL)7; the 25th-percentile split instead flagged monocyte chemoattractant protein 1 (MCP1), IL17C and cystatin-D (CST5); and the continuous models flagged TNFSF14, IL7, IL18R1 and chemokine (C-C motif) ligand 19 (CCL19). Only TNFSF14 recurred across most specifications (the median split, the 75th-percentile split and the continuous model). The set of markers identified as significant thus depended heavily on how expression was modelled. We regard this specification-dependence as confirming central point of Cao et al.: these are hypothesis-generating signals rather than evidence of a defined susceptible immune subgroup, with TNFSF14 the most durable candidate for targeted replication.

The counterintuitive directionality of the association and its restriction to women with low, rather than elevated, cytokine expression reinforces rather than resolves the need for confirmation. No immediately apparent mechanistic account exists in the literature for why attenuated TNFSF14 signalling would render child behavioural development differentially sensitive to labour epidural analgesia, and we would not advance a causal interpretation ahead of independent replication with prespecified biomarker hypotheses, prospectively determined analytic thresholds and multiplicity correction applied from the outset.

We further accept that treating labour epidural analgesia as a binary exposure leaves the mechanistic pathway insufficiently characterised. Epidural regimen, duration and intrapartum fever status are each relevant when an inflammatory pathway is being considered, and these parameters were not captured at sufficient granularity to evaluate their contribution to the observed cytokine interactions. Epidural-related maternal fever is well-documented and has been linked to adverse neonatal outcomes in the short term, although whether this translates to longer-term neurodevelopmental consequences remains an open question in the literature [3]. Future studies should incorporate these exposure characteristics as primary descriptors.

The concern regarding the Child Behavioural Checklist as a maternal report is well founded. Parent-rated scores at 18 months reflect the mother's own psychological state as well as the child's behaviour, a finding supported by our own cohort data, where more persistent perinatal depressive symptoms and impaired mother–infant bonding were each associated with higher toddler behavioural difficulty scores [4]. We agree that including an independent observer assessment alongside parent report would strengthen future findings [5].

The principal clinical conclusion of our paper nonetheless remains unchanged: labour epidural analgesia was not independently associated with adverse behavioural outcomes at any of the three developmental timepoints examined. Among the cytokine signals, TNFSF14 emerges as the most specification-robust candidate and the most appropriate focus for targeted replication. More broadly, the cytokine findings should be regarded as hypothesis-generating rather than as evidence of a biologically defined susceptible subgroup. Replication in larger studies with prespecified biomarker hypotheses and broader characterisation of the epidural exposure remains the necessary next step.

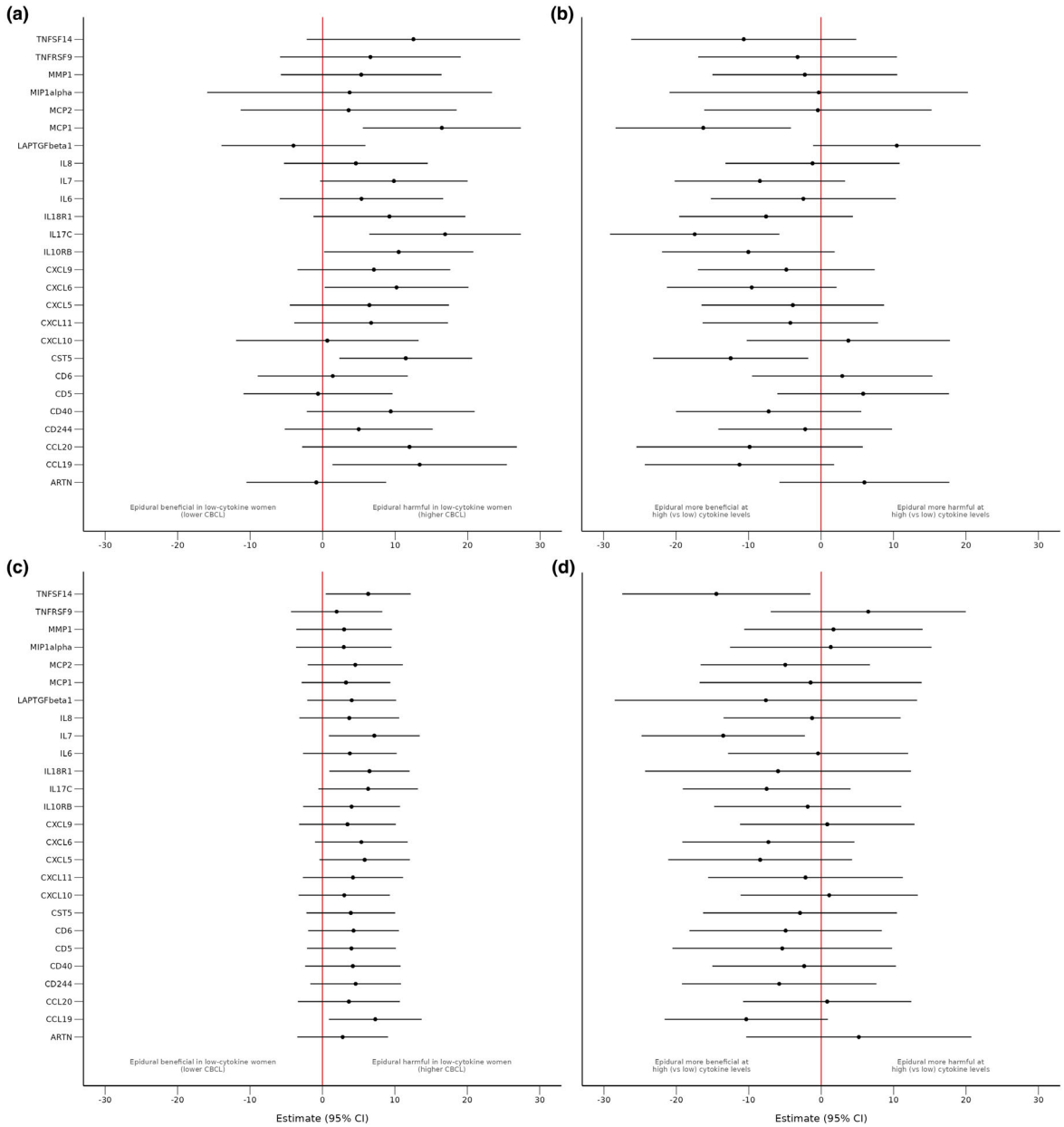

Figure 1 Effect modification by maternal pro-inflammatory cytokine levels of the association between labour epidural analgesia and total Child Behaviour Checklist (CBCL) score at 18 months. Each panel is a forest plot of pooled linear-model estimates with 95% confidence intervals (CBCL points), one row per cytokine (26 cytokines), adjusted for gestational age (day of cytokine sampling), body mass index and inflammatory disorders, and pooled across 20 multiply imputed datasets. Cytokine concentrations were dichotomised at a percentile cut point: (a, b) at the 25th percentile (low = below the 25th percentile; high = at or above it); and (c, d) at the 75th percentile (low = below the 75th percentile; high = at or above it).

Sana Asif
Richard A. White
Alkistis Skalkidou
Uppsala University Hospital,
Uppsala, Sweden
Email: sana.asif@uu.se

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