Authors' response to Almirall *et al*

Almirall *et al* have reanalysed their previously published data[1] (that we have previously critiqued[2]) and shown that benzodiazepine exposure is associated with a reduced risk of pneumonia in younger patients.[3] They report both bivariate and multivariate analyses[3] but, by contrast with our analysis[4] have only adjusted for a few comorbidities. For example, it is unclear why they have adjusted for temperature change, that is presumably a consequence of the outcome of interest: pneumonia. The biological rationale for their finding is also unclear, the authors justify their data by suggesting that REM sleep depression may reduce the incidence of bronchial aspiration. Critically, they ignore data that REM sleep deprivation leads to disordered thermogenesis and increased mortality[5]; in addition to data showing direct impairments of immune function by benzodiazepines.[6] While we acknowledge the limitations of our data[4] that depend on the clinical diagnosis of lower respiratory tract infection, this may lend generalisability to clinicians as a readily diagnosed endpoint.[4] If present, misclassification of benzodiazepine exposure would likely shift the data towards unity; however, we observed a clinically important risk of both pneumonia and death from

pneumonia, reducing concerns over this issue.[4] This is paralleled by our basic science investigations that demonstrate increased mortality from *Steptococcus pneumoniae*[6] and other studies showing increased mortality to other pathogens.[7] Nonetheless, we acknowledge the limitations of database studies and argue that prospective cohort and randomised controlled trials are definitely required. Though we stress that meta-analysis of randomised controlled trials of eszopiclone, remalteon, zalepon and zolpidem suggest a similar vulnerability to infection[8] as we discovered in our analysis of data with benzodiazepines and the non-benzodiazepine zopiclone.[4]

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