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## *Letter to the Editor*

# Invited letter to editor in response to profiling inflammatory cytokines following zinc supplementation: a systematic review and meta-analysis of randomised controlled trials

The letter from Jafari and Ghobadi highlighted several issues regarding our recent systematic review, which should be addressed. First, they indicated that three papers were not included in our systematic review. Indeed, these three records were excluded. According to the Cochrane checklist, the quality of the study by Guo *et al.*[1] was low enough to be excluded from our systematic review. Indeed, their study did not score any positive points in the items of the above-mentioned checklist. In that pilot study, random sequence generation was ambiguous. Besides, no allocation concealment process or blinding was performed in that study. Also, the lack of intention-to-treat method in that study led to incomplete outcome data. Most notably, there was reporting bias in that study; some of the measured biomarkers mentioned in the Method section were not entirely reported in the Results section, such as CD-3, creatinine, glucose and blood urea nitrogen. On the other hand, biomarkers such as albumin, Hb, CD-8 and CD-19 were fully reported before and after supplementation. However, the cause of this issue was not reported in the study.

In the study by Ahmad *et al.*[2], it was not clear how the values listed for IL-2 were expressed. Indeed, they did not indicate that the values were shown in mean values and standard deviation or mean values with their standard errors. When these values are not clear, accurate analysis cannot be performed on them. In the study by Rahfiludin *et al.*[3], they measured culture supernatants instead of serum/plasma levels. Since these *in vitro* experiments are not equal to the *in vivo*-derived cytokines in the serum/plasma, we excluded that study from our study.

Second, Jafari and Ghobadi mentioned that we should have excluded the Kara *et al.*[4] study because our exclusion criteria excluded non-randomised studies and trials conducted on juvenile subjects. First, the definition of 'adolescence' based on the WHO is 'the phase of life between childhood and adulthood, from ages 10 to 19'[5]. Although we could not find a precise definition of the word 'juvenile' on the WHO website, according to the UN international children's emergency fund definition[6], 'a juvenile is every male or female over seven and under twelve years of age.' Besides, we mentioned in the PICO statement of the systematic review that the population for this study is individuals over 15 years old.

Moreover, Jafari and Ghobadi suggested that we exclude a study by Beserra de Moura *et al.*[7], which is not randomised due to different plasma Zn status (deficient, sufficient) in intervention and control groups. Due to the limited number of studies, we included all controlled-clinical trial studies, regardless of being randomised or not; however, we mistakenly stated that the non-randomised studies were excluded from our study. This typographical mistake will be corrected in the proofing process. Regarding the status of plasmatic Zn, since some studies did not determine the basic serum/plasma level of Zn in the study population, subgroup analysis based on basic Zn level was not performed. If the number of studies had been sufficient and all studies reported serum Zn levels, we would have performed a subgroup analysis based on serum Zn levels to assess individuals' responses accordingly. Thus, this limitation was stated in the manuscript.

In the case of Roshanravan *et al.*'s study[8] on pregnant women, we had intended to exclude this study because the effect of Zn supplementation might be different in pregnant women, as the letter from Jafari and Ghobadi mentioned. However, after sensitivity analysis, we found that excluding this study did not significantly alter our results and Zn supplementation could still significantly reduce the level of IL-6. Besides, as shown in Fig. 5(a), the effect size in this study was not significantly different from other studies. We did not exclude this study from our study for these reasons and the limited number of included studies.

Due to the limited number of studies, some limitations were raised in our study, which were mentioned in the Discussion section. However, based on the aforementioned reasons, we do not believe that our results are unreliable.

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