Response to commentary on 'zinc supplementation is associated with a reduction in serum markers of inflammation and oxidative stress in adults: a systematic review and meta-analysis of randomized controlled trials'

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Response to Commentary on 'Zinc supplementation is associated with a reduction in serum markers of inflammation and oxidative stress in adults: A systematic review and meta-analysis of randomized controlled trials'

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Dear Editor,

We thank you for giving us the opportunity to reply to the comment on our recent systematic review and meta-analysis regarding the effect of Zinc (Zn) supplementation on inflammation and oxidative stress (1). We have read the comments carefully, and have addressed them below.

First, we excluded references cited by the authors (2-7) at the screening process, as they did not meet our inclusion criteria **(Table 1),** which were explained in both the clinical and statistical aspects within the methods *"At the initial stage, we selected any parallel randomized controlled trials (RCTs) …"* (1). Furthermore, we did not ignore to include Khorsandi et al (8) in our review and analyses (1). Moreover, we did assess the potential for publication bias, conducted "trim and fill" analysis and reported their results in the article (1). This indicates our results are robust and are unaffected by the addition of further trial data.

Regarding the studies conducted on pregnant women reporting interleukin 6 (IL-6); the sensitivity analysis revealed that removing each study did not change the results, in agreement with the authors suggestion, we have excluded them and conducted a re-analysis of serum IL-6 levels. As shown in **Figure 1A**, in line with our previous report, serum IL-6 was not significantly affected following Zn intake (ES = -1.25 pg/mL, 95 % CI = [-2.54, 0.05], $P = 0.06$, $I^2 = 93.4$ %).

Secondly, Venneria et al (9) administered two different doses to subjects with different baseline characteristics, and therefore did not apply the same intervention. Hence, in consultation with a statistical expert, and as for other meta-analyses (10, 11), we considered this article as two separate trials and included them as two different effect sizes. We also conducted a re-analysis based on the comments received and eliminated the intervention with the lower dose of Zn (15 mg/day). The result was consistent with our previous report and showed no significant change in MDA

levels **(Figure 1B)**. In addition, this result was supported by sensitivity analysis in the article (1) showing that removing each study did not change the significance of overall result.

Finally, in agreement with a statistical expert and based on relevant references (12, 13), we commonly used correlation coefficient (r) = 0.5 (14-17) as an average to minimize the bias of estimates. In addition, it is noteworthy that all of our methodology protocols and approaches were officially registered with PROSPERO (*https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=213987*) (1). As clearly stressed in the methods section (1), all the recommendations of the PRISMA checklist have been followed. We designed the main question of our work in the introduction, planned all methodological approaches and wrote the results and discussion sections in accordance with the PRISMA statement.

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References:

1. Hosseini R, Ferns GA, Sahebkar A, Mirshekar MA, Jalali MJC. Zinc supplementation is associated with a reduction in serum markers of inflammation and oxidative stress in adults: A systematic review and meta-analysis of randomized controlled trials. 2020;138:155396.
2. Aboomardani M, Rafraf M, Arefhosseini R, Rashidi MJPS. Effect of zinc supplementation on serum mlondealdehyde and lipid profiles on beta thalassemia major patients. 2012;18(1):25-32.
3. Foster M, Petocz P, Samman S. Inflammation markers predict zinc transporter gene expression in women with type 2 diabetes mellitus. Journal of Nutritional Biochemistry. 2013;24(9):1655-61.
4. Mazani M, Argani H, Rashtchizadeh N, Ghorbanihaghjo A, Hamdi A, Asghari Estiar M, et al. Effects of Zinc Supplementation on Antioxidant Status and Lipid Peroxidation in Hemodialysis Patients. Journal of Renal Nutrition. 2013;23(3):180-4.
5. Dias PCS, Sena-Evangelista KCM, Paiva M, Ferreira DQC, Ururahy MAG, Rezende AA, et al. The beneficial effects of rosuvastatin are independent of zinc supplementation in patients with atherosclerosis. J Trace Elem Med Biol. 2014;28(2):194-9.
6. Mujica-Coopman MF, Borja A, Pizarro F, Olivares M. Effect of Daily Supplementation with Iron and Zinc on Iron Status of Childbearing Age Women. Biological Trace Element Research. 2015;165(1):10-7.
7. Freiberg MS, Cheng DM, Gnatienko N, Blokhina E, Coleman SM, Doyle MF, et al. Effect of Zinc Supplementation vs Placebo on Mortality Risk and HIV Disease Progression Among HIV-Positive Adults With Heavy Alcohol Use: A Randomized Clinical Trial. JAMA network open. 2020;3(5):e204330.
8. Khorsandi H, Nikpayam O, Yousefi R, Parandoosh M, Hosseinzadeh N, Saidpour A, et al. Zinc supplementation improves body weight management, inflammatory biomarkers and insulin resistance in individuals with obesity: A randomized, placebo-controlled, double-blind trial. Diabetology and Metabolic Syndrome. 2019;11(1).
9. Venneria E, Intorre F, Foddai MS, Azzini E, Palomba L, Raguzzini A, et al. Antioxidant effect of zinc supplementation on both plasma and cellular red-ox status markers in a group of elderly Italian population. J Nutr Health Aging. 2014;18(4):345-50.
10. Akhlaghi M, Ghasemi Nasab M, Riasatian M, Sadeghi F. Soy isoflavones prevent bone resorption and loss, a systematic review and meta-analysis of randomized controlled trials. Critical Reviews in Food Science and Nutrition. 2020;60(14):2327-41.
11. Anjom-Shoae J, Milajerdi A, Larijani B, Esmaillzadeh AJBJoN. Effects of grape seed extract on dyslipidaemia: a systematic review and dose–response meta-analysis of randomised controlled trials. 2020:1-14.
12. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. Introduction to meta-analysis: John Wiley & Sons; 2011.
13. Follmann D, Elliott P, Suh I, Cutler JJJoce. Variance imputation for overviews of clinical trials with continuous response. 1992;45(7):769-73.
14. Cicero AFG, Pontremoli R, Fogacci F, Viazzi F, Borghi C. Effect of Bempedoic Acid on Serum Uric Acid and Related Outcomes: A Systematic Review and Meta-analysis of the available Phase 2 and Phase 3 Clinical Studies. Drug Safety. 2020;43(8):727-36.
15. Jandari S, Ghavami A, Ziaei R, Nattagh-Eshtivani E, Rezaei Kelishadi M, Sharifi S, et al. Effects of Momordica charantia L on blood pressure: a systematic review and meta- analysis of randomized clinical trials. International Journal of Food Properties. 2020;23(1):1913-24.
16. Sepandi M, Abbaszadeh S, Taghdir MJPr. Effect of L-Arginine supplementation on lipid profiles and inflammatory markers: A systematic review and meta-analysis of randomized controlled trials. 2019;148:104407.
17. Hadi A, Pourmasoumi M, Ghaedi E, Sahebkar AJPr. The effect of Curcumin/Turmeric on blood pressure modulation: A systematic review and meta-analysis. 2019;150:104505.

Table 1. Excluded studies with explanation of the reasons for doing so

Excluded studies	**Reason**
Aboomardani et al. (2)	Non-English language
Dias et al. (5)	Lacked essential data (unit of outcomes)
Foster et al. (3)	Did not specify the type of zinc supplement (gluconate or sulfate), that we discuss in the review
Freiberg et al. (7)	Used a mixture of zinc doses in men and women, and reported the combined data, and hence it was not possible to extract and assess the clinical effects
Mazani et al. (4)	Crossover designed study
Mujica-Coopman et al. (6)	Reported geometric means and range±1 SD, and according to our consultation with a statistician, we could not extract useful data

Supplementary material:

Figure 1. The effect of Zn on serum IL-6 (A) and MDA (B) following excluding a study