Letter to the Editor

Several meta-analyses missing from an umbrella review of *n*-3 fatty acids on depression symptoms: comments concerning Lu *et al.*

I have read with interest the study by Lu *et al.*[1], who summarised the available evidence regarding the effects of *n*-3 PUFA on symptoms of depression. Unfortunately, the study likely failed to provide a truly comprehensive perspective on the topic and may have presented unreliable conclusions.

According to the authors, the last search was performed in June 2021, but at least one eligible meta-analysis (published in March 2021) is missing[2]. Considering that Lu *et al.* were interested in any population of adults, according to their Population, Intervention, Comparison and Outcomes (PICO) criteria, the study by O'Deane *et al.* (2021)[2] provided relevant data and should have been included. This high-quality review presents a Grading of Recommendations Assessment, Development and Evaluations (GRADE) assessment based on thirty-two trials suggesting that increasing *n*-3 PUFA probably has little or no effect on the risk of depression symptoms in those without depression at baseline (moderate quality of evidence), and there is a signal of increased risk of depressive symptoms associated with increasing *α*-linolenic acid intake. Effects on depression severity and remission were unclear (very low quality of evidence), and overall data were considered insufficient to recommend *n*-3 supplements for reducing depression risk or treating an existing depression[2].

Lu and colleagues cited three versions of a high-quality Cochrane Review by Appleton *et al.* (2006, 2010 and 2016) but overlooked its latest update from November 2021, which includes the most extensive dataset (*n* 33) among all published meta-analyses[3]. The review concludes there is insufficient evidence to determine the effects of *n*-3 PUFA as a treatment for Major Depressive Disorder. Importantly, sensitivity analyses restricted to low risk of bias trials convincingly suggest that the often observed benefit in meta-analyses is probably a reflection of publication bias and overestimated results from small, high risk of bias trials[3]. The latest Cochrane Review was probably omitted because Lu *et al.* conducted their last search in June 2021. For this very reason, by the time the article was submitted to the *British Journal of Nutrition* (October 2023), their own review had already been outdated for over 2 years. This is not an uncommon occurrence in biomedical research[4,5], despite explicit recommendations in the Cochrane Handbook to 'rerun searches for relevant sources prior to publication if the initial search date is more than 12 months (preferably six months) from the intended publication date'[6].

In order to identify other potentially missing studies, I first attempted replicating the bibliographic search using the search strategy provided in the supplementary material. Surprisingly, the search yields 14 679 results on PubMed alone (from inception to 30 June 2021). This is largely inconsistent with the authors' report of a 'comprehensive systematic search' that retrieved only 101 records across five allegedly examined databases – of which an uncommon proportion of nearly 60 % records were duplicates. Restricting to records indexed during the gap from June 2021 to October 2023, a total of 7246 studies were found to be screened. Out of these records, I have identified several additional eligible meta-analyses of randomised controlled trials, according to Lu *et al.*'s pre-specified PICO criteria: Iqbal *et al.* (September 2023)[7]; Osouli-Tabrizi *et al.* (May 2023)[8]; Tung *et al.* (September 2023)[9]; Candido *et al.* (June 2023)[10]; Kelaiditis *et al.* (April 2023)[11]; Simon *et al.* (Jan 2023)[12]; Decandia *et al.* (May 2022)[13]; Arsenyadis *et al.* (April 2022)[14]; Nevins *et al.* (November 2021)[15]; Hang *et al.* (July 2021)[16]; and Kishi *et al.* (July 2021)[17]. In total, thirteen out of (at least) thirty-five eligible studies are missing from the review.

Attempts to synthesise large bodies of evidence are undeniably challenging; however, it is imperative that such studies are conducted according to the highest possible standards. Failing to do so entails a risk of seriously misleading researchers, practitioners, policymakers and consumers. I hereby contend that the conclusions of Lu *et al.* were unfortunately based on an outdated umbrella review at high risk of selection bias. Their study fails to mention over a third of the available research (including a high-quality Cochrane Review) and thus cannot be taken as reliable evidence to address the efficacy, safety or applicability of *n*-3 fatty acids for depression.

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References

1. Lu Y, Qiao D & Mi G (2024) Clinical impacts of *n*-3 fatty acids supplementation on depression symptoms: an umbrella review of meta-analyses. *Br J Nutr* **131**, 841–850. https://doi.org/10.1017/S000711452300226X

2. Deane KHO, Jimoh OF, Biswas P, *et al.* (2021) *n*-3 and polyunsaturated fat for prevention of depression and anxiety symptoms: systematic review and meta-analysis of randomised trials. *Br J Psychiatry: J Mental Sci* **218**, 135–142. https://doi.org/10.1192/bjp.2019.234

3. Appleton KM, Voyias PD, Sallis HM, *et al.* (2021) *n*-3 fatty acids for depression in adults. *Cochrane Database Syst Rev 2021*, issue 11, CD004692. https://doi.org/10.1002/14651858.CD004692.pub5

4. Créquit P, Trinquart L, Yavchitz A, *et al.* (2016) Wasted research when systematic reviews fail to provide a complete and up-to-date evidence synthesis: the example of lung cancer. *BMC Med* **14**, 8. https://doi.org/10.1186/s12916–016–0555–0

5. Beller EM, Chen JK, Wang UL, *et al.* (2013) Are systematic reviews up-to-date at the time of publication? *Syst Rev* **2**, 36. https://doi.org/10.1186/2046–4053–2–36

6. Higgins JPT, Thomas J, Chandler J, *et al.* (editors) (2023) Cochrane Handbook for Systematic Reviews of Interventions Version 6.4 (updated August 2023) Cochrane. www.training.cochrane.org/handbook (accessed May 2024).

7. Iqbal AZ, Wu SK, Zailani H, *et al.* (2023) Effects of *n*-3 polyunsaturated fatty acids intake on vasomotor symptoms, sleep quality and depression in postmenopausal women: a systematic review. *Nutrients* **15**, 4231. https://doi.org/10.3390/nu15194231

8. Osouli-Tabrizi S, Mehdizadeh A, Naghdi M, *et al.* (2023) The effectiveness of *n*-3 fatty acids on health outcomes in women with breast cancer: a systematic review. *Food Sci Nutr* **11**, 4355–4371. https://doi.org/10.1002/fsn3.3409

9. Tung KTS, Wong RS & Mak RTW (2023) Maternal *n*-3 PUFA intake during pregnancy and perinatal mental health problems: a systematic review of recent evidence. *Curr Nutr Rep* **12**, 426–438. https://doi.org/10.1007/s13668–023–00484-x

10. Candido ACR, Ferraz SD, Uggioni MLR, *et al.* (2023) *n*-3 as an adjuvant in the treatment eating and psychological symptoms in patients with anorexia nervosa: a systematic review and meta-analyses. *J Hum Nutr Diet: Offic J Br Dietetic Assoc* **36**, 1970–1981. https://doi.org/10.1111/jhn.13187

11. Kelaiditis CF, Gibson EL & Dyall SC (2023) Effects of long-chain *n*-3 polyunsaturated fatty acids on reducing anxiety and/or depression in adults; a systematic review and meta-analysis of randomised controlled trials. *Prostaglandins, Leukotrienes, Essent Fatty Acids* **192**, 102572. https://doi.org/10.1016/j.plefa.2023.102572

12. Simon MS, Arteaga-Henríquez G, Fouad Algendy A, *et al.* (2023) Anti-inflammatory treatment efficacy in major depressive disorder: a systematic review of meta-analyses. *Neuropsychiatr Dis Treat* **19**, 1–25. https://doi.org/10.2147/NDT.S385117

13. Decandia D, Landolfo E, Sacchetti S, *et al.* (2022) *n*-3 PUFA improve emotion and cognition during menopause: a systematic review. *Nutrients* **14**, 1982. https://doi.org/10.3390/nu14091982

14. Arsenyadis F, Ahmad E, Redman E, *et al.* (2022) The effects of *n*-3 supplementation on depression in adults with cardiometabolic disease: a systematic review of randomised control trials. *Nutrients* **14**, 1827. https://doi.org/10.3390/nu14091827

15. Nevins JEH, Donovan SM, Snetselaar L, *et al.* (2021) *n*-3 fatty acid dietary supplements consumed during pregnancy and lactation and child neurodevelopment: a systematic review. *J Nutr* **151**, 3483–3494. https://doi.org/10.1093/jn/nxab238

16. Hang X, Zhang Y, Li J, *et al.* (2021) Comparative efficacy and acceptability of anti-inflammatory agents on major depressive disorder: a network meta-analysis. *Front Pharmacol* **12**, 691200. https://doi.org/10.3389/fphar.2021.691200

17. Kishi T, Sakuma K, Okuya M, *et al.* (2021) *n*-3 fatty acids for treating residual depressive symptoms in adult patients with bipolar disorder: a systematic review and meta-analysis of double-blind randomized, placebo-controlled trials. *Bipolar Disord* **23**, 730–731. https://doi.org/10.1111/bdi.13115