



Universiteit
Leiden
The Netherlands

N-3 PUFAs for depression: treatment effect or absence-of-placebo effect?

Memarpouri, A.; Does, A.J.W. van der; Molendijk, M.L.

Citation

Memarpouri, A., Does, A. J. W. van der, & Molendijk, M. L. (2022). N-3 PUFAs for depression: treatment effect or absence-of-placebo effect? *Translational Psychiatry*, 12. doi:10.1038/s41398-022-02072-z

Version: Publisher's Version
License: [Creative Commons CC BY 4.0 license](https://creativecommons.org/licenses/by/4.0/)
Downloaded from: <https://hdl.handle.net/1887/3453373>

Note: To cite this publication please use the final published version (if applicable).

CORRESPONDENCE OPEN



n-3 PUFAs for depression: treatment effect or absence-of-placebo effect?

© The Author(s) 2022

Translational Psychiatry (2022)12:298; <https://doi.org/10.1038/s41398-022-02072-z>

Dear Editor,

In a meta-analysis, Liao et al. [1]. conclude that n-3 PUFAs have a therapeutic effect on depression. Here we argue that this conclusion is premature.

Firstly, in contrast with their stated inclusion criteria, the data from 2 trials [2, 3] did not include an inert placebo arm. Also in contrast with an inclusion criterion, another trial was carried out in a non-(clinically) depressed sample [4]. Furthermore, data from a single trial were included twice [5, 6] and placebo conditions of this trial, and that of one other trial [7], were double-counted in analyses. The use of dependent data in meta-analyses gives a false impression of precision [8].

We carried out a random-effect meta-analysis on the corrected dataset, which yielded a Standardized Mean Difference (SMD; Cohen's *d*) of -0.31 (95% Confidence Interval (CI) = -0.57 to -0.05) favoring n-3 PUFAs over placebo in the treatment of depression. Liao et al. report an SMD of -0.26 (95% CI = -0.47 to -0.09). Consequently, the errors do not invalidate the study conclusion, but note that the CI has widened.

Liao et al. [1]. included a trial performed by Marangell et al. [9], who in their report had presented a null-finding on the differences in the efficacy of n-3 PUFAs versus placebo in the treatment of depression ($P = 0.43$, page 996). In the meta-analysis, the same RCT is presented as having a large and statistically significant effect (SMD = -0.82). This mismatch is due to the parameter for efficacy that Liao et al. [1]. used: *data at a single point at the end of the trial*. This parameter is inferior to the crucial time x treatment interaction. Marangell et al. [9]. indeed report a large difference between the treatment and placebo group post-treatment; however, this is due to the fact that randomization failed. The control group scored significantly higher on the primary outcome measure at baseline, and this difference was not affected by treatment. To present this particular RCT as a positive trial is contrary to the findings reported in the original paper.

We noticed that the apparent positive effect of n-3 PUFAs was partly driven by a low or absent placebo effect. In antidepressant trials, placebo responses are typically higher on interviewer-rated scales (SMD = -1.85 ; 95% CI = -2.01 to -1.69) relative to self-report (SMD = -0.67 ; 95% CI = -0.85 to -0.49) [10]. We calculated the pooled treatment effect (interview-based) in the (active) n-3 PUFAs treatment arms and found it to be -1.36 (95% CI = -1.75 to -0.97). Consequently, the effect of n-3 PUFAs on depression outcome appears lower than the effect of placebos in antidepressant treatment trials. In this particular meta-analysis [1], the smallest placebo responses were observed in the four included studies performed in Iran [7, 11–13]. In fact, placebo responses reported in trials from

Iran (SMD = -0.18 ; 95% CI = -0.44 to 0.06) are lower ($P < 0.001$) than those observed in non-Iran-based trials (SMD = -1.34 ; 95% CI = -1.73 to -0.96). There is no difference in the weighted average response to n-3 PUFAs treatment in Iranian versus non-Iranian studies (SMD's of -1.32 and -1.34 respectively, $P = 0.94$). Consequently, the Iranian findings are driven by a lack of response in the placebo condition. The size of the placebo effect may depend on many factors, and a direct comparison between n-3 PUFAs studies and antidepressant studies is hazardous. Still, placebo effects have been demonstrated even with 'open-label placebo' [14, 15], rendering its absence in Iranian studies hard to explain. The authors of these RCTs did not respond to our requests for information. It may be interesting to note that only eight of 24 effect sizes in the meta-analysis show that n-3 PUFAs outperform placebo, without considering substantial publication bias. Six of these significant studies yielded unexpected low placebo responses (i.e., SMD's < 0.4) [the Iranian studies and refs. [16, 17]].

Notably, the results from Iranian studies put a stamp on the outcomes of the meta-analysis. When excluded from the analysis, the overall result of the meta-analysis (following the approach by Liao et al. [1]) is a null-finding (SMD = -0.11 ; 95% CI = -0.36 to 0.10). Also, in case proper effect-size estimates are imputed for the Iranian studies (e.g., SMD = -1.00), a random-effects model over corrected data yields a null effect (SMD = -0.18 ; 95% CI = -0.40 to 0.04).

We argue that the quality of the underlying data reported by Liao et al. [1]. does not allow the conclusion that n-3 PUFAs demonstrate a therapeutic effect on depression. This is in line with a recent Cochrane review showing a lack of treatment effects of n-3 PUFAs on depression [18].

Arian Memarpouri ^{1,2}, Willem van der Does^{1,3} and Marc L. Molendijk ^{1,4}✉

¹Clinical Psychology Department, Leiden University, Leiden, The Netherlands. ²Cognitive Psychology Department, Leiden University, Leiden, The Netherlands. ³Leiden University Treatment and Expertise Center (LUBEC), Leiden, The Netherlands. ⁴Leiden Institute of Brain and Cognition, Leiden University Medical Center, Leiden, The Netherlands. ✉email: m.l.molendijk@fsw.leidenuniv.nl

REFERENCES

- Liao Y, Xie B, Zhang H, He Q, Guo L, Subramaniapillai M, et al. Efficacy of omega-3 PUFAs in depression: a meta-analysis. *Trans Psychiatry*. 2019;9:190.
- Jazayeri S, Tehrani-Doost M, Keshavarz SA, Hosseini M, Djazayeri A, Amini H, et al. Comparison of therapeutic effects of omega-3 fatty acid eicosapentaenoic acid and fluoxetine, separately and in combination, in major depressive disorder. *Aus NZ J Psychiatry*. 2008;42:192–8.
- Gertsik L, Poland RE, Bresee C, Rapaport MH. Omega-3 fatty acid augmentation of citalopram treatment for patients with major depressive disorder. *J Clin Psychopharmacol*. 2012;32:61–4.

Received: 8 March 2022 Revised: 14 July 2022 Accepted: 18 July 2022
Published online: 26 July 2022

4. Antypa N, Smelt AHM, Strengholt A, Van Der Does AJW. Effects of omega-3 fatty acid supplementation on mood and emotional information processing in recovered depressed individuals. *J Psychopharmacol.* 2012;26:738–43.
5. Mischoulon D, Nierenberg AA, Schettler PJ, Kinkead BL, Fehling K, Martinson MA, et al. A double-blind, randomized controlled clinical trial comparing eicosapentaenoic acid versus docosahexaenoic acid. *J Clin Psychiatry.* 2015;76:54–61.
6. Rapaport MH, Nierenberg AA, Schettler PJ, Kinkead B, Cardoos A, Walker R, et al. Inflammation as a predictive biomarker for response to omega-3 fatty acids in major depressive disorder: a proof-of-concept study. *Mol Psychiatry.* 2016;21:71–9.
7. Mozaffari-Khosravi H, Yassini-Ardakani M, Karamati M, Shariati-Bafghi SE. Eicosapentaenoic acid versus docosahexaenoic acid in mild-to-moderate depression: a randomized, double-blind, placebo-controlled trial. *Eur Neuropsychopharmacol.* 2013;23:636–44.
8. Cheung MWL. A guide to conducting a meta-analysis with non-independent effect sizes. *Neuropsychol Rev.* 2019; 29: 387–96.
9. Marangell LB, Martinez JM, Zboyan HA, Kertz B, Kim HFS, Puryear LJ. A double-blind, placebo-controlled study of the omega-3 fatty acid docosahexaenoic acid in the treatment of major depression. *Am J Psychiatry.* 2003;160:996–8.
10. Rief W, Nestoriuc Y, Weiss S, Welzel E, Barsky AJ, Hofmann SG. Meta-analysis of the placebo response in antidepressant trials. *J Affect Disord.* 2009;13:1–6.
11. Gharekhani A, Khatami MR, Dashti-Khavidaki S, Razeghi E, Noorbala AA, Hashemi-Nazari SS, et al. The effect of omega-3 fatty acids on depressive symptoms and inflammatory markers in maintenance hemodialysis patients: a randomized, placebo-controlled clinical trial. *Eur J Clin Pharm.* 2014;70:655–65.
12. Ravi S, Khalili H, Abbasian L, Arbabi M, Ghaeli P. Effect of omega-3 fatty acids on depressive symptoms in hiv-positive individuals: a randomized, placebo-controlled clinical trial. *Ann Pharmacother.* 2016;50:797–807.
13. Tajalizadekhoob Y, Sharifi F, Fakhrzadeh H, Mirarefin M, Ghaderpanahi M, Badamchizade Z, et al. The effect of low-dose omega 3 fatty acids on the treatment of mild to moderate depression in the elderly: a double-blind, randomized, placebo-controlled study. *Eur Arch Psychiatry Clin Neurosci.* 2011;261:539–49.
14. Kirsch I, Ness AR, Appleton KM. Treatments for depression: Side-effects, adverse events and health risks. *J Affect Disord.* 2019;259:38–9.
15. Kaptchuk TJ, Stason WB, Davis RB, Legedza AR, Schnyer RN, Kerr CE, et al. Sham device v inert pill: randomised controlled trial of two placebo treatments. *BMJ.* 2006;332:391–7.
16. Nemets B, Stahl Z, Belmaker RH. Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. *Am J Psychiatry.* 2002;159:477–9.
17. Rondanelli M, Giacosa A, Opizzi A, Pelucchi C, La Vecchia C, Montorfano G, et al. Long chain omega 3 polyunsaturated fatty acids supplementation in the treatment of elderly depression: effects on depressive symptoms, on phospholipids fatty acids profile and on health-related quality of life. *J Nutr Health Aging.* 2011;15:37–44.
18. Appleton KM, Voyias PD, Sallis HM, Dawson S, Ness AR, Churchill R, et al. Omega-3 fatty acids for depression in adults. *Cochrane Database Syst. Rev.* 2021. <https://doi.org/10.1002/14651858.CD004692.pub5>.

AUTHOR CONTRIBUTIONS

Concept and design: all authors. Drafting of the manuscript: MM. Statistical analysis: MM. Critical revision of the manuscript for important intellectual content: all authors.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Marc L. Molendijk.

Reprints and permission information is available at <http://www.nature.com/reprints>

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit <http://creativecommons.org/licenses/by/4.0/>.

© The Author(s) 2022