

VU Research Portal

Multinutrient Supplementation for Prevention of Major Depressive Disorder in Overweight Adults - Reply

Brouwer, Ingeborg A; Penninx, Brenda W H J; Visser, Marjolein

published in

JAMA

2019

DOI (link to publisher)

[10.1001/jama.2019.6483](https://doi.org/10.1001/jama.2019.6483)

document version

Publisher's PDF, also known as Version of record

document license

Article 25fa Dutch Copyright Act

[Link to publication in VU Research Portal](#)

citation for published version (APA)

Brouwer, I. A., Penninx, B. W. H. J., & Visser, M. (2019). Multinutrient Supplementation for Prevention of Major Depressive Disorder in Overweight Adults - Reply. *JAMA*, 322(4), 366-367.
<https://doi.org/10.1001/jama.2019.6483>

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal ?

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

E-mail address:

vuresearchportal.ub@vu.nl

Multinutrient Supplementation for Prevention of Major Depressive Disorder in Overweight Adults

To the Editor The MoodFOOD randomized clinical trial¹ found that neither multinutrient supplementation nor food-related behavioral activation therapy reduced major depressive disorder episodes in overweight or obese adults with depressive symptoms. However, the low rate of conversion to major depressive disorder of only 10% after 12 months vs 33% expected means that the study was likely underpowered, and the interpretation that nutrients “showed no effect” was potentially incorrect.

The authors discussed various single-nutrient studies showing no benefit in the treatment of depression before concluding that micronutrients are unlikely candidates for prevention. These are different questions. Meta-analyses show that omega-3 eicosapentaenoic fatty acid supplements can be effective in treating major depressive disorder but not subclinical depressive symptoms.² For prevention, including approximately 1 g of eicosapentaenoic fatty acid in the MoodFOOD supplementation was thus a reasonable choice.

We also query the choice of other nutrients, only 2 vitamins and 2 minerals at dosages below the recommended dietary allowance (400 µg of folic acid, 20 µg of vitamin D, 30 µg of selenium, 100 mg of calcium). This choice does not reflect current knowledge with respect either to specific nutrients most strongly implicated in depression³ and doses required or to the importance of combining a wide range of micronutrients at levels likely to confer benefits for optimal brain function and improve oxidative stress and inflammation.^{4,5}

Another limitation the authors highlighted is the lack of any nutritional status measures. Costs and other practicalities make including such measures difficult, but without them, meaningful conclusions cannot be drawn. Before treatment, did these participants actually lack the nutrients that were supplied? If so, did supplementation normalize those deficiencies? Equally important, did they lack other nutrients not provided? Whenever individualized treatment is impractical, an overinclusive approach (within safe limits) to both nutrients and dosages seems preferable to risking some deficiencies remaining unaddressed.⁴

Overweight and obesity may affect both nutrient status and requirements and mood, so the high body mass index of this sample would limit generalization of any findings to other populations. Unfortunately, overall findings were inconclusive—although depression, anxiety, and health measures improved on average in all groups, suggesting trial participation itself was beneficial. Given the high prevalence and costs of depression, limitations of existing treatments, and evidence implicating nutritional factors, further large-scale, high-quality trials of both diet and supplement interventions are warranted.

Julia J. Rucklidge, PhD

Alexandra J. Richardson, PhD

Author Affiliations: Department of Psychology, University of Canterbury, Christchurch, New Zealand (Rucklidge); Department of Physiology, Anatomy & Genetics, University of Oxford, Oxford, United Kingdom (Richardson).

Corresponding Author: Julia J. Rucklidge, PhD, Psychology, University of Canterbury, Private Bag 4800, Christchurch, Canterbury 8081, New Zealand (julia.rucklidge@canterbury.ac.nz).

Conflict of Interest Disclosures: Dr Richardson reported receiving personal fees from Oxford University Consulting. No other disclosures were reported.

1. Bot M, Brouwer IA, Roca M, et al; MoodFOOD Prevention Trial Investigators. Effect of multinutrient supplementation and food-related behavioral activation therapy on prevention of major depressive disorder among overweight or obese adults with subsyndromal depressive symptoms: the MoodFOOD randomized clinical trial. *JAMA*. 2019;321(9):858-868. doi:10.1001/jama.2019.0556
2. Hallahan B, Ryan T, Hibbeln JR, et al. Efficacy of omega-3 highly unsaturated fatty acids in the treatment of depression. *Br J Psychiatry*. 2016;209(3):192-201. doi:10.1192/bjp.bp.114.160242
3. LaChance LR, Ramsey D. Antidepressant foods: an evidence-based nutrient profiling system for depression. *World J Psychiatry*. 2018;8(3):97-104. doi:10.5498/wjp.v8.i3.97
4. Kaplan BJ, Rucklidge JJ, Romijn A, McLeod K. The emerging field of nutritional mental health inflammation, the microbiome, oxidative stress, and mitochondrial function. *Clin Psychol Sci*. 2015;3(6):964-980. doi:10.1177/2167702614555413
5. Benton D. To establish the parameters of optimal nutrition do we need to consider psychological in addition to physiological parameters? *Mol Nutr Food Res*. 2013;57(1):6-19. doi:10.1002/mnfr.201200477

In Reply Although the MoodFOOD trial¹ was, to our knowledge, the largest trial to date investigating 2 nutritional strategies for the prevention of depression in 1025 participants, we are aware of the limitations raised by Drs Rucklidge and Richardson, which were addressed in the article. The power of our trial for development of depressive disorder might have been limited, but—in contrast to the food-related behavioral intervention therapy—we did not find any indication for a preventive effect of the nutrient supplement on either episodes of depression or depressive symptoms. Placebo even outperformed supplements in their effects on both depressive and anxiety symptoms. Thus, we stand with our conclusion that these findings do not support the use of the tested interventions for prevention of major depressive disorder in this population.

The MoodFOOD intervention trial investigated the prevention of depression, not treatment. Unfortunately, it is difficult to perform a large-scale study with adequate power and a clinical outcome, so there are not many trials investigating the effect of nutrition or nutrients on the prevention of depression. Only 1 randomized clinical trial² on omega-3 supplementation involving mild to moderately depressed individuals was mentioned in the article because we considered that sample somewhat comparable with our study sample. This trial did not show a favorable effect of omega-3 polyunsaturated fatty acids either. Rucklidge and Richardson suggest the beneficial effects of omega-3 fatty acids in treatment based on results from a meta-analysis.³ However, effect sizes vary, and many studies are small; therefore, clinical relevance is arguable. Furthermore, evidence from the same trials was interpreted differently in a Cochrane analysis.⁴ For most nutrients, there is simply not enough evidence to come to a valid conclusion on the efficacy in the treatment of depression.

With type and dosage of supplements, we took a pragmatic approach in combining several promising nutrients based

on the state-of-the-art scientific literature in 2014, when the study started.⁵ We chose dosages that were reported to be effective in some individual studies, but we also chose dosages that were unlikely to harm any participants because nutritional supplements have also been shown to have negative health effects.⁶

Rucklidge and Richardson refer to the lack of nutritional data in the study. However, we obtained blood samples to determine nutrient status at baseline and during follow-up from approximately 67% of our sample. We are currently using these data to test whether participants with lower nutrient levels at baseline are more likely to benefit from the nutrient supplement than participants with higher levels, and to assess the effect of change in nutrient status during treatment on treatment effect. These explorative analyses will inform the optimal development of future trials focusing on the role of nutrition in the prevention of depression.

Ingeborg A. Brouwer, PhD
Brenda W. H. J. Penninx, PhD
Marjolein Visser, PhD

Author Affiliations: Department of Health Sciences, Vrije Universiteit, Amsterdam, the Netherlands (Brouwer, Visser); Department of Psychiatry, Amsterdam UMC, Amsterdam, the Netherlands (Penninx).

Corresponding Author: Marjolein Visser, PhD, Department of Health Sciences, Faculty of Science and Amsterdam Public Health Research Institute, Vrije Universiteit Amsterdam, De Boelelaan 1085, 1081 HV Amsterdam, the Netherlands (m.visser@vu.nl).

Conflict of Interest Disclosures: Dr Brouwer reported receiving grants from the European Union FP7 MoodFOOD project (grant agreement 613598). Dr Penninx reported receiving grants from Jansen Research and Boehringer Ingelheim. No other disclosures were reported.

1. Bot M, Brouwer IA, Roca M, et al; MoodFOOD Prevention Trial Investigators. Effect of multinutrient supplementation and food-related behavioral activation therapy on prevention of major depressive disorder among overweight or obese adults with subsyndromal depressive symptoms: the MoodFOOD randomized clinical trial. *JAMA*. 2019;321(9):858-868. doi:10.1001/jama.2019.0556
2. Rogers PJ, Appleton KM, Kessler D, et al. No effect of *n*-3 long-chain polyunsaturated fatty acid (EPA and DHA) supplementation on depressed mood and cognitive function: a randomised controlled trial. *Br J Nutr*. 2008;99(2):421-431. doi:10.1017/S0007114507801097
3. Hallahan B, Ryan T, Hibbeln JR, et al. Efficacy of omega-3 highly unsaturated fatty acids in the treatment of depression. *Br J Psychiatry*. 2016;209(3):192-201. doi:10.1192/bjp.bp.114.160242
4. Appleton KM, Sallis HM, Perry R, Ness AR, Churchill R. Omega-3 fatty acids for depression in adults. *Cochrane Database Syst Rev*. 2015;(11):CD004692.
5. Roca M, Kohls E, Gili M, et al; MoodFOOD Prevention Trial Investigators. Prevention of depression through nutritional strategies in high-risk persons: rationale and design of the MoodFOOD prevention trial. *BMC Psychiatry*. 2016;16(1):192. doi:10.1186/s12888-016-0900-z
6. Mursu J, Robien K, Harnack LJ, Park K, Jacobs DR Jr. Dietary supplements and mortality rate in older women: the Iowa Women's Health Study. *Arch Intern Med*. 2011;171(18):1625-1633. doi:10.1001/archinternmed.2011.445

Collaborative Care for Adults With Obesity and Depression

To the Editor The study by Dr Ma and colleagues¹ tested an integrated collaborative care intervention for adults with comorbid depression and obesity. In the intervention group, behavioral-psychological therapy was typically combined with antidepressants, supported by weekly to

monthly sessions. As such, the low rate of sustained depression response of 29% for participants in the intervention group and 22% for participants in the usual care group at 12 months warrants further scrutiny.

Recruitment for depression was based on a score of 10 or higher on the self-reported 9-item Patient Health Questionnaire 9 (PHQ-9), and patients did not undergo a diagnostic interview for depression. Although acceptable in other populations, the specificity of this approach in populations with obesity is poorer, such that up to 50% of those recruited may not have had clinical depression.^{2,3}

In this context, it is striking that 41% of the study population had a diagnosis of binge eating disorder, and in these patients there was no difference between treatment groups on either co-primary outcome. Binge eating disorder is a feasible barrier to collaborative care for several reasons. First, common symptoms of binge eating disorder, including overeating, low mood, and feelings of guilt,⁴ are likewise captured by the depression measures used in the study to define inclusion (PHQ-9) and primary response (20-item Depression Symptom Checklist [SCL-20]).

Second, optimum treatment for binge eating disorder typically requires specific, high-intensity psychological therapies beyond the current collaborative care intervention, such as extended, modified cognitive behavioral therapy or dialectical behavioral therapy.⁴ Antidepressants produce limited benefit on weight or depression in patients with binge eating disorder.⁴ The stimulant lisdexamfetamine is the only current pharmacotherapy approved by the US Food and Drug Administration for binge eating disorder.⁵

Third, comorbid substance use and personality disorder, which are known barriers to depression treatment, are over-represented in individuals with binge eating disorder.⁴ Collectively, this suggests that binge eating disorder, either as a false-positive for depression or as a comorbidity, could have limited both weight loss and the number of patients achieving persistent depression response.

For future collaborative care of depressed patients with obesity, a more rigorous diagnosis of depression (through diagnostic interview or higher PHQ-9 cutoff score) would reduce the risk of patients with binge eating disorder being falsely categorized as having depression. For those with depression and comorbid binge eating disorder, either such patients should be excluded and directed toward higher-intensity treatments for binge eating disorder, or the intervention should be adapted to integrate such treatment.

Calum D. Moulton, MRCPsych
Thahesh Tharmaraja, BSc(Hons)
Christopher W. P. Hopkins, MRCPsych

Author Affiliations: Department of Psychological Medicine, King's College London, London, England (Moulton); School of Medicine, University of Birmingham, Birmingham, England (Tharmaraja); Berkshire Healthcare NHS Foundation Trust, Royal Berkshire Hospital, Reading, England (Hopkins).

Corresponding Author: Calum D. Moulton, MRCPsych, Institute of Psychiatry, Psychology and Neuroscience, Department of Psychological Medicine, King's College London, London SE5 9RJ, England (calum.moulton@kcl.ac.uk).