




## REVIEW ARTICLE

# Nutritional supplements for neuropsychiatric symptoms in people with dementia: A systematic review and meta-analysis

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## Objectives

The aim of the present study was to assess the effects of nutritional supplementation on neuropsychiatric symptoms among people with dementia.

**Methods/Design:** Randomized controlled trials (RCTs) were searched in the Databases PubMed, EMBASE, SCOPUS, Cochrane Central Register of Controlled Trials and Clinicaltrials.gov from inception until January 31, 2020. Studies of RCTs carried out on people with any type of dementia who were taking nutritional supplements and had neuropsychiatric symptoms were included in this systematic review and meta-analysis. Neuropsychiatric symptoms were assessed with the validated Neuropsychiatric Inventory (NPI). Effect sizes were calculated with standardized mean differences (SMD) and 95% confidence intervals (95%CI), applying a random effect model.

**Results:** The search yielded 1034 studies with four studies being included in the meta-analysis with a total of 377 people with dementia (mean age 69.3 [SD: 7.7] years). The diagnoses comprised mild to late Alzheimer's disease and frontotemporal dementia. Two studies included a multicomponent supplementation, one an omega-3, and one a special supplement tailored for cognitive impairment. The median follow-up was 18 weeks, with a range from 12 to 24 weeks. Pooled data showed that nutritional supplementation did not improve NPI (SMD = -0.33; [95% CI: -0.74 to 0.08];  $P = 0.11$ ;  $I^2 = 45\%$ ).

**Conclusions:** The findings of this meta-analysis demonstrated no significant impact on NPI through nutritional supplementation. However, the generalization of the results is limited, as different supplements were used in different stages of dementia with a short follow-up time.

## KEYWORDS

neuropsychiatric syndromes, nutritional supplements, people with dementia

## 1 | INTRODUCTION

Dementia is a clinical syndrome characterized by neurodegeneration and cognitive decline with a progressive deterioration of dependence.<sup>1</sup> It was estimated that 50 million people lived with dementia worldwide in 2019, with 10 million new cases every year, and this is projected to triple by 2050.<sup>2</sup> As the global population ages, not only dementia but also dementia-related problems increase the burden to families, caregivers and healthcare systems.<sup>3</sup>

People with dementia may experience serious adverse events (eg, falls, fractures, postural hypotension, metabolic syndrome, cardiac arrhythmia, sedation and cognitive decline),<sup>4</sup> leading to long-term hospitalization, decreased quality of life for caregivers and patients and increased mortality.<sup>5</sup> Additionally, behavioral and psychological symptoms in dementia (BPSD) are among the most common causes of this burden and often occur as a result of deterioration in mood, thought, perception and behavior.<sup>6,7</sup> Although several studies have highlighted the role of genetic, neurochemical and neuropathological factors,<sup>8-14</sup> the underlying pathogenesis of BPSD in detail is not yet clear.

BPSD affect nearly all people with dementia,<sup>15</sup> and are prevalent in the mild stages of dementia, increasing within the progression of the neurodegenerative process.<sup>16</sup> One recent study demonstrated that the prevalence of a single BPSD was 74% among people with mild cognitive impairment (MCI), and 85% among people with mild to moderate dementia, respectively.<sup>17</sup> Considering these high proportions, it is clear that the prevention and treatment of BPSD is of utmost importance. Pharmacological therapies are used to reduce the frequency and severity of BPSD, when non-pharmacological interventions are ineffective.<sup>18</sup> However, they provide only moderate symptom control.<sup>18</sup> Therefore, new interventions are considered a preferable alternative.

Nearly half of elderly people with dementia have a risk of malnutrition which also increases cognitive impairments and the incidence of behavioral disorders.<sup>19,20</sup> Therefore, nutritional supplements are thought to have an effect on BPSD. Concerning supplementation, the World Health Organization (WHO) does not recommend multi-complex supplements, Vitamin B, C or E or poly-unsaturated fatty acids to reduce the risk of cognitive decline.<sup>2</sup> Additionally, the results of a Cochrane Review showed that the effects of vitamins (E, C, B) and mineral supplements as treatments for MCI are very limited.<sup>21</sup>

However, the effectiveness and improvements toward BPSD remain unclear.<sup>22</sup> Therefore, the aim of the present study was to conduct a systematic review and meta-analysis of randomized controlled trials (RCTs) to determine whether nutritional supplementations have an effect on BPSD in people with dementia.

## 2 | METHODS

This systematic review adhered to the PRISMA statement<sup>23</sup> and followed a pre-planned, but unpublished protocol.

### Key points

- Pooled effects of this meta-analysis showed no effects of nutritional supplements on behavioral and psychological symptoms in people with dementia.
- However, results showed high heterogeneity among the studies in terms of sample characteristics as well as the investigated supplements.
- Consequently, more research is needed.

### 2.1 | Data sources and literature search strategy

Two investigators (SS and AS) independently conducted a literature search using PubMed, EMBASE, SCOPUS, Cochrane Central Register of Controlled Trials and Clinicaltrials.gov without language restriction, from database inception until January 31, 2020 for RCTs, investigating the effect of nutritional supplementations in the treatment of NPIs in people affected by dementia. Any inconsistencies were resolved by consensus with a third author (SH).

In PubMed, the following search strategy was used: “(supplement\*) AND (Alzheimer OR dementia) and (neuropsych\*)”. An adapted search was conducted in other databases. Conference abstracts and reference lists of included articles were hand-searched to identify any other potentially relevant articles.

### 2.2 | Study selection

Inclusion criteria for this meta-analysis were: (a) RCTs, (b) people with any type of dementia; (c) at least one group treated with a nutritional supplement; and (d) using neuropsychiatric symptoms (eg, Neuropsychiatric Inventory = NPI)<sup>24</sup> as validated outcomes. For neuropsychiatric symptoms, we intended the onset of delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, aberrant motor activity, night-time behavioral disturbances and appetite and eating abnormalities.<sup>24</sup> For nutritional supplementations, we intended nutrients (or a combination of nutrients) that may otherwise not be consumed in sufficient quantities.

### 2.3 | Data extraction

The data were extracted from the included articles in a standardized Excel sheet, and checked by an independent investigator. For each article, we extracted data concerning the authors, year of publication, country, type of dementia, setting, type of nutritional intervention, number of participants and their mean age and standard deviation (SD) and duration of follow-up (in weeks). Additionally, the percentage of women with dementia was extracted.

## 2.4 | Outcomes

The primary outcome was the changes in NPI between baseline and follow-up in people treated with a nutritional supplementation vs placebo.

## 2.5 | Assessment of study quality

The quality of the included studies was assessed using the Jadad's scale.<sup>25</sup> This scale quantifies the trial quality based on the description and appropriateness of randomization (2 points), blinding procedures (2 points) and description of withdrawals (1 point). A value less than 3 (over a maximum of 5) usually indicates a low-quality study at high risk of bias.<sup>25</sup>

## 2.6 | Data synthesis and statistical analysis

All analyses were performed using Comprehensive Meta-Analysis (CMA) Version 3. When multiple assessments were made, the longest follow-up time was included in the analyses. The primary analysis compared the values of NPI between people with dementia treated with nutritional supplementation vs placebo. We calculated the difference between the means of the treatment and control groups using the follow-up data through standardized mean differences (SMD) with their 95% confidence intervals (CIs), applying a random-effect model.<sup>26</sup>

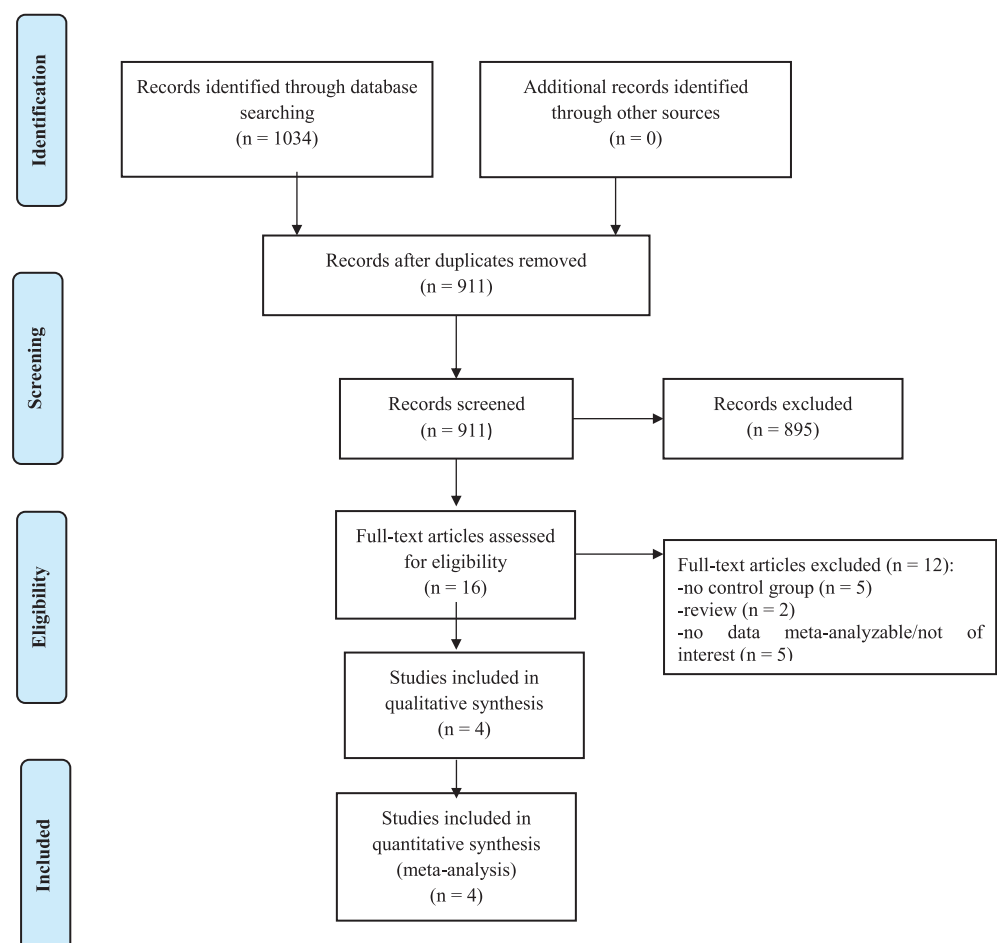
Heterogeneity across studies was assessed by the  $I^2$  metric. Given significant heterogeneity ( $I^2 \geq 50\%$ ,  $P < 0.05$ ) and for outcomes having at least four studies, we planned to run a meta-regression analysis taking as moderators mean age, baseline values of NPI, setting, type of dementia, the follow-up duration of the RCTs included.

Publication bias was assessed by a visual inspection of funnel plots and calculating the Egger bias test.<sup>27</sup> Then, to account for publication bias, the trim-and-fill method was used,<sup>28</sup> based on the assumption that the effect sizes of all the studies are normally distributed around the center of a funnel plot; in the event of asymmetries, the test adjusts for the potential effect of unpublished studies.<sup>28</sup> Finally, the fail-safe number (ie, the number of missing studies that would bring  $P$ -value over the alpha) was considered.<sup>28</sup> For all analyses, a  $P$ -value less than 0.05 was considered statistically significant.

## 3 | RESULTS

### 3.1 | Search results

Altogether, the searches yielded 1034 records. After excluding 1018 articles based on title/abstract review, 12 articles were retrieved for full text review and four RCTs<sup>29–32</sup> were finally included (Figure 1).



**FIGURE 1** PRISMA flow-chart [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

**TABLE 1** Descriptive characteristics of the randomized controlled trials included

Author (year)	Country	Type of dementia	Setting	Type of nutritional supplementation	N of people with dementias	Mean age (SD)	Follow-up (weeks)	Jadad's score
Freund-Levi et al., 2007	Sweden	Mild to moderate AD	Community-dwelling	omega-3:430 mg DHA and 150 mg EPA	174	72.8 (9.0)	24	5
Pardini et al., 2015	Italy	Frontotemporal dementia	Community-dwelling	Souvenaid	52	56.0 (6.0)	24	5
Remington et al., 2015	USA	AD	Community-dwelling	multicomponent supplement: 400 µg folic acid, 6 µg B12, 30 I.U. 88 alpha-tocopherol, 400 mg SAM (200 mg active ion), 600 mg NAC, 500 mg ALCAR	141	79.2 (8.3)	12	5
Remington et al., 2009	USA	Moderate to late AD	Nursing home	multicomponent supplement: 400 µg folic acid, 6 µg B12, 30 I.U. 88 alpha-tocopherol, 400 mg SAM (200 mg active ion), 600 mg NAC, 500 mg ALCAR	10	NA	12	3
<b>Total</b>					<b>377</b>	<b>69.3 (7.7)</b>	<b>Median = 18 (range: 12-24)</b>	<b>Median = 5 (range: 3-5)</b>

Abbreviations: AD, Alzheimer's disease; DHA, docosahexanoic acid; EPA, eicosapentaenoic acid; SAM, S-adenosyl methionine; NAC, N-acetyl cysteine; ALCAR, acetyl-L-carnitine; SAM, S-adenosyl methionine; NAC, N-acetyl cysteine.

### 3.2 | Study and participant characteristics

Full descriptive details of the included studies are reported in Tables 1 and Supplementary Table 1. All the studies included a total of 377 people with dementia, with a mean age of 69.3 (SD: 7.7) years. All except one<sup>31</sup> included people having a diagnosis of Alzheimer's disease, and all except one<sup>29</sup> were carried out on community-dwelling people. The type of nutritional intervention is fully reported in the Table 1. Two studies<sup>29,30</sup> included a multicomponent nutritional supplement, one included an omega-3 supplement,<sup>32</sup> and one<sup>31</sup> a supplement tailored for cognitive impairment. The median follow-up was 18 weeks, with a range from 12 to 24 weeks. In all studies, the NPI was used for assessing the association between nutritional supplementations and neuropsychiatric symptoms. All the studies have a sufficient quality, as indicated by the Jadad's score (Table 1).

Supplementary Table 1 shows sample characteristics in the included studies. The 204 people with dementia randomized to the nutritional supplementation group did not differ in mean age (69.0 [SD: 8.1] vs 69.7 [SD: 9.0] years,  $P = 0.84$ ), mini-mental state examination (22.9 [SD: 3.4] vs 22.7 [SD: 3.9] points,  $P = 0.78$ ), or NPI (16.0 [SD: 2.2] vs 15.0 [SD: 2.2] points,  $P = 0.95$ ) at baseline (Supplementary Table 1).

### 3.3 | Effect of nutritional supplementations on neuropsychiatric symptoms

All four studies<sup>29-32</sup> indicated that the use of nutritional supplements did not improve neuropsychiatric symptoms (SMD =  $-0.33$  [95%CI:

$-0.74$  to  $0.08$ ];  $P = 0.11$ ;  $I^2 = 45\%$ ) (Figure 2). No evidence of a publication bias emerged (Egger's test =  $-2.46$  [1.78];  $P = 0.30$ ), even if the trim and fill analysis further attenuated the effect of nutritional supplementations (adjusted SMD =  $-0.08$  [95%CI:  $-0.53$  to  $0.38$ ]). The fail-safe number was four.

In one RCT with data not meta-analyzable (NPI was given in categories),<sup>33</sup> the use of supplement tailored for cognitive impairment did not improve neuropsychiatric symptoms ( $P = 0.73$ ).

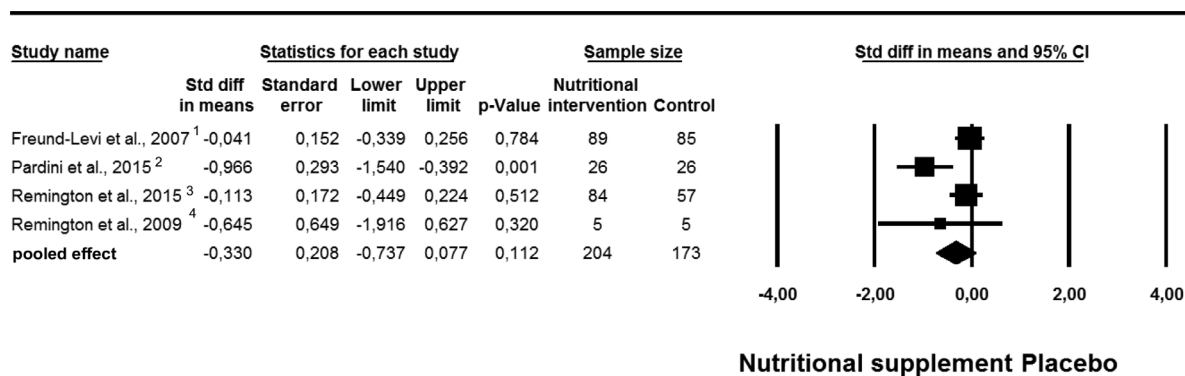
### 3.4 | Adverse events

No severe adverse events were reported in any study, and the incidence of adverse events was similar in both groups (OR = 1.10 [95% CI: 0.31-3.88]  $P = 0.88$ ), being gastrointestinal symptoms the most common. Three studies reported data regarding side effects.<sup>29-31</sup>

## 4 | DISCUSSION

A total of four RCTs were included in the present meta-analysis, whereas two of those studies<sup>29,30</sup> were carried out with a multicomponent nutritional supplement, one with an omega-3,<sup>32</sup> and one<sup>31</sup> with a supplementation tailored for cognitive impairment. The results indicate non-significant improvement in NPI by nutritional supplementation in this group.

Nonetheless, since people with dementia are at higher risk of malnutrition, mainly caused by a declined ability to feed themselves,<sup>34</sup> and pharmacotherapy reduce eating drive,<sup>35,36</sup> nutritional



**FIGURE 2** Effect of nutritional supplementations on neuropsychiatric symptoms. Used supplements: omega-3 (430 mg DHA and 150 mg EPA)<sup>1</sup>; Souvenaid<sup>2</sup>; multicomponent supplement: (400 µg folic acid, 6 µg B12, 30 I.U. 88 alpha-tocopherol, 400 mg SAM [200 mg active ion], 600 mg NAC, 500 mg ALCAR)<sup>3</sup>; multicomponent supplement (400 µg folic acid, 6 µg B12, 30 I.U. 88 alpha-tocopherol, 400 mg SAM [200 mg active ion], 600 mg NAC, 500 mg ALCAR).<sup>4</sup> CI, confidence intervals; IV, inverse variance; SD, standard deviations

supplements might be helpful to prevent malnutrition, when nutritional goals cannot be met through dietary counselling.<sup>37</sup> Additionally, many of the nutrients are essential for brain tissue, as they are precursors of neurotransmitters, or have important functions in the metabolic process.<sup>38</sup> However, the present evidence does not support the use of supplements. Indeed, previous literature has suggested that supplements are unlikely to prevent cognitive decline in people with dementia.<sup>2,21,39</sup> In line with these guidelines, the results of the present meta-analysis also suggest that supplements need not be recommended to people with dementia, as we did not find any significant effect on NPI. However, when interpreting the results, the following facts should be kept in mind.

The included studies used completely different supplements. Therefore, making a general statement on the effects of supplements on BPSDs is difficult. Two out of four studies used a multicomponent nutritional supplement (folic acid, vitamin B12, vitamin E, S-adenosyl methionine, N-acetyl cysteine, acetyl-L-carnitine).<sup>29,30</sup>

One of these studies showed improvements in NPI with no statistical difference to the placebo group within 3 months,<sup>29</sup> whereas people with dementia in another study using the same supplements reported no changes in NPI, neither in the supplementation nor in the placebo group.<sup>30</sup> Additionally, although some studies have shown that omega-3 supplements may have a protective effect on neuropsychiatric diseases, as they modulate the release of important transmitters (acetylcholine, serotonin and dopamine),<sup>40</sup> the included study of Freund-Levi was not able to show any effect on NPI after 6 months.<sup>32</sup> The only study demonstrating a significant improvement in NPI was published by Pardini et al.<sup>31</sup> In this examination, Souvenaid, a tailored supplement for dementia, that showed to influence the ability in improving synaptic integrity, was given.<sup>31</sup> Notably, in this examination, younger people with frontotemporal dementia were included and had higher baseline NPI scores (supplementation: 24.0 [0.7]; placebo: 23.0 [0.6]) compared to Freund-Levi et al.<sup>32</sup> (supplementation: 15.6 [12.9-18.2]; placebo: 14.9 [12.1-17.7]) and Remington et al.<sup>30</sup> (supplementation: 11.5 [9.1]; placebo 10.8 [12.4]).

Consequently, as can be taken from these baseline NPIs, another reason for the non-effect could probably be that the NPI values were too low to see any effect in a rather short time. This, the so-called floor effect, makes it difficult for various tests to perform well.<sup>41</sup>

Another reason could be the differences in the study samples in the included studies. One study investigated people with mild to moderate AD,<sup>32</sup> another included people with moderate to late-stage AD,<sup>29</sup> the other younger people with frontotemporal dementia,<sup>31</sup> and in one study the dementia staging was omitted.<sup>30</sup> Since BPSDs start already from mild stages of dementia and increase with the progression,<sup>16</sup> nutritional interventions preventing BPSD might be interesting in early stage. Additionally, the fact that in the study of Remington et al.,<sup>30</sup> supplementation was more effective in people at earlier stages of AD, and it strengthens the importance of early interventions. Notably, in this case, only small treatment effects might be detected, making a long follow up time necessary.

This literature review presents different limitations. Due to a small number of studies in people with dementia, we could only include four studies. Further, as mentioned above, the supplements differ among the studies, lowering the strength of the conclusions of the meta-analysis. Additionally, the follow up time may have been too short to see effects on BPSD.

## 5 | CONCLUSIONS AND IMPLICATIONS

Taken together, the findings of this meta-analysis demonstrate no significant impact of various nutritional supplements in people with dementia on BPSD assessed by NPI. The generalization of the results is limited, as different supplements were used in different stages of dementia with a rather short follow-up time. Nevertheless, the necessity of nutritional supplementation might be given in order to prevent malnutrition. Consequently, more studies with the same supplements (eg, vitamin B, polyunsaturated fatty acids) are recommended in

earlier stages of dementia with a longer follow up time to provide more definitive answers, regarding the effectiveness of nutritional supplements in affecting NPI scores.

## CONFLICT OF INTEREST

None.

## DATA AVAILABILITY STATEMENT

Meta-analysis of published data, there is no primary data to share. Extraction tables available upon reasonable request from the corresponding author.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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