Review Article

Effectiveness of Nutritional Supplements on Cognitive Functioning in Elderly Persons: A Systematic Review

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Background. The effectiveness of nutritional supplementation in improving cognitive functioning is evaluated in elderly people.

Methods. The authors systematically reviewed randomized controlled trials that compared nutritional supplementation with a placebo treatment. Trials were identified from a MEDLINE search and from reference lists of identified studies and review articles. From each trial, information was gathered on the number and age of persons studied; the type, dosage, and duration of the intervention; and the assessed outcome measures.

Results. From 1086 titles, 571 articles were excluded based on their titles. Of the remaining 467 articles, the abstracts were read and 422 articles were excluded based on information found there. The remaining articles were screened for quality aspects of the study design, leaving 21 proper randomized, controlled trials. These trials are discussed in three groups according to the type of supplementation: multinutrient intervention or single components with or without a putative mechanism. Twelve studies, which were evenly distributed among the three supplement groups, found significantly positive effects of nutritional intervention on cognitive functioning, whereas nine studies did not. None of the studies found a significantly negative effect of nutritional intervention.

Conclusions. Shortcomings in methodology varying from the duration of intervention to outcome measures partly explain discrepancies in findings. Despite the heterogeneity in trial design, the results of this review suggest that nutritional supplements may improve the cognitive functioning of elderly persons and do no harm. Further well-designed studies are needed to support these findings.

The aging population is increasing and the risks for malnutrition and impaired cognitive functioning increase with advancing age. Cognitive problems influence behavior, social activities, and independence, especially in elderly people. Therefore, it is important to evaluate the cognitive functioning of this population. Because malnutrition might influence cognition and a decline in cognitive functioning might influence eating behavior, a vicious cycle with more nutritional deficiencies and more cognitive problems is likely to develop.

The relation between malnutrition and cognitive functioning is complicated. Besides being a cause of cognitive impairment, malnutrition might also be a consequence of it. Cross-sectional studies have shown that low blood levels of certain nutrients are associated with impaired cognitive functioning in elderly persons (1–4). Longitudinal studies have shown that persons with suboptimal nutritional status seem to be at a higher risk for development of cognitive impairment (5–7). For this reason, it is important to determine whether cognitive functioning of elderly people would be improved by consumption of a nutritional supplement.

According to the literature, a few factors influence the effectiveness of a nutritional intervention on cognitive functioning: the stage of cognitive decline or nutritional deficiency of the investigated population, the applied nutrient and its dose, and the duration of intervention.

Most likely, benefits of nutritional supplementation can be expected mainly early after the onset of cognitive impairment. In later stages, the process of demyelination becomes irreversible and existing neuronal damage is not likely to be reversed (4,8). It is also hypothesized that the effects will be smaller in apparently healthy persons or those with a more advanced impairment of cognitive status. Therefore, the selection of the target group is important in intervention trials. Based on findings from the literature, it is not clear in which groups of elderly people improvement by nutritional intervention is most effective. Therefore, for this
review, we wanted to evaluate studies in healthy elderly volunteers and in elderly patients. In our literature search, we did not select studies for the stage of cognitive decline of the target group they investigated.

In addition, we wanted to determine whether a single nutrient can improve cognitive functioning or whether a combination of more nutrients is needed. Table 1 presents single and mixtures of nutrients with their possible mechanisms in affecting cognition. Jorissen and Riedel (9) and Gonzalez-Gross and colleagues (4) have reviewed nutrition-related risk factors for cognitive impairment. Nutritional factors such as amino acids, antioxidants, lipids, and vitamins seem to have a relation to cognitive decline. The applied doses of the supplemented nutrients also might influence the effectiveness. For this review, we defined nutritional supplements as any nutritional intervention aimed at improving the dietary intake of participants. Therefore, we did not include trials that provided their participants with medication.

Furthermore, in studying the relationship between nutritional supplementation and cognitive functioning, besides population selection and diet factors, the duration of the intervention also influences the effectiveness of treatment.

Regarding the fact that cognitive problems are diverse, it is also interesting to know which domain of cognitive functioning is impaired and in which domain improvement by nutrition is possible. Outcome measurements should be selected with care in studies relating diet to cognitive functioning, because of the complexity and multiplicity of cognitive functioning and the impossibility of measuring all cognitive functions using a single study design.

The purpose of our systematic review was to evaluate the existing evidence based on studies on the effectiveness of nutritional supplementation in improving cognitive functioning in elderly persons. We selected only randomized controlled trials of high quality. Therefore, we used a priori defined criteria for selection. Our hypothesis was that cognitive functioning would be improved in elderly people by a complete supplement, as combined factors in the diet cause cognitive decline. The factors we have noted already may influence the effect. We performed a MEDLINE search for articles describing intervention studies on this subject.

METHODS

Identification of Trials

We conducted a MEDLINE search (using SilverPlatter software, version 3.11: SilverPlatter International, N.V.) from January 1980 to September 2003. Starting with the key words “elderly,” “nutrition,” and “cognition,” we constructed three groups of Medical Subject Headings (MeSH) combined with key words to define our topic. We used another group of MeSH terms and key words to identify only trials. The search strategy was restricted to English, German, French, or Dutch language citations. We also used the check tag “human.” In addition, we manually checked the references of selected articles and of some reviews on nutritional supplementation and cognitive functioning.

Inclusion Criteria

We identified 1038 potentially eligible trials. If, according to the title, articles did not report on human elderly subjects, an intervention trial, nutritional supplementation, or cognitive function or nutritional status as primary outcomes, we did not consider the studies for our review. We excluded 571 studies accordingly. We further explored the 467 remaining articles by reviewing the abstract. We used the same criteria as for the title screen to exclude abstracts from our review, which ultimately resulted in 47 potentially eligible trials. We scored these articles on quality aspects using a checklist for randomized controlled trials of the Dutch Cochrane Centre, extended with items from the Delphi list (10). Considering the quality aspects, we excluded 26 articles from the review: 3 were not an intervention study, 14 did not use a placebo treatment, 4 were not double blind, and 4 did not describe a randomization procedure. Later, in Results, we evaluate only the 21 best-conducted trials (randomized, double-blind, placebo-controlled studies).

Data Extraction

From each trial we gathered information on the number and age of the persons examined; the description of the investigated population; the type, dosage, and duration of the intervention; and the assessed outcome measures. Our tables summarize this information.

RESULTS

As a result of the literature search, we identified 47 intervention trials. Only 21 of them were randomized, double-blind, placebo-controlled studies. We divided the trials into three groups (multinutrient intervention, single components with putative mechanisms, and single components without putative mechanisms). One group of interventions was performed with multinutrient supplements (Table 2). Two of these studies did not find a significant effect although the other two studies did. The second group consisted of interventions with single active components (Table 3). In three of these studies, no significant effects were present, and in the other four studies, a positive effect was found on one or more cognitive outcome measures. The trials with specific components with an unknown mechanism in view of cognitive functioning comprise the third group (Table 4). Four of the 10 reviewed studies showed no significant effect.

In summary, nine studies found no significant effect of nutritional intervention on cognitive functioning. The 12 remaining studies found significantly positive results. None of the studies found a significantly negative effect of nutritional intervention.

In each group of studies, we first searched for an overall explanation for the lack of effect. If such an explanation was missing, we further explored the characteristics of the studies without positive effects.
The first group of studies consisted of four trials that addressed the effect of a multinutrient supplement (Table 2). Except for the study of Hogarth and colleagues (11), all participants in these four studies were community-dwelling elderly people. In none of the studies were participants screened for existing vitamin deficiencies or impaired cognitive functioning before the intervention. The interventions in the study by Hogarth and colleagues (11) and the study by Bryan and colleagues (12) were short and involved a mega-dose of vitamins. Conversely, de Jong and colleagues (13) and Chandra (14) investigated a multivitamin supplement during 17 weeks and 1 year, respectively, and did not use high doses. Differences in population, doses, or duration could not explain the difference in effectiveness of the supplements. Typically, the studies that did not show a significant effect used simple, general tests for cognitive functioning. In contrast, positive effects were noted in the studies in which different domains of cognitive functioning were specifically measured. This suggests that the difference in result could be explained in part by the choice of outcome measures. None of the studies in Table 2 reported adverse effects of supplementation.

Table 3 lists studies that evaluated the effect of supplying a single nutrient rather than multiniutrients. In total, 7 studies of the 21 randomized, double-blind, placebo-controlled trials investigated 1 active component. In four intervention studies, B vitamins (B12, B6, and B9) were supplied. In one study, guarana (a Brazilian medicinal plant) was given, in one alpha-tocopherol, and in one inositol. In three of the four positive studies, patients with Alzheimer’s disease were examined, and in another study, apparently healthy elderly persons were enrolled. In all studies, participants were on average older than 70 years, except for the study of Galduroz and Carlini (15) in which they were younger. One of the significantly positive studies (16) was a long-term investigation with a supplementation period of 2 years. The period of supplementation in the other three positive studies was 4 or 12 weeks. In the vitamin studies (B vitamins and alpha-tocopherol), a high dose was used (4 to 3000 times the recommended daily allowance). Sano and colleagues (16) used no neuropsychological test battery, in contrast to the outcome measures in the other significantly positive studies. The nutrients that showed a positive effect were alpha-tocopherol, inositol, thiamine, and pyridoxine. However, the study by Nolan and colleagues (17) did not show a positive effect of thiamine. Overall, no clear pattern explains the difference in results between the studies.

In the study of Seal and colleagues (18), which was a small study population, the short period of intervention or the use of the Mini-Mental State Examination as primary outcome might explain the lack of effect. Galduroz and Carlini (15) investigated apparently healthy, elderly volunteers who were not screened for vitamin deficiencies. This might explain why they did not find any significant alteration in cognitive functioning. The only factor that might explain the lack of effect in the study by Nolan and colleagues (17) is that the study was insufficiently powered, because they included only 10 patients. None of the suggested factors completely explains the difference in effectiveness of the studies.

Galduroz and Carlini (15) used guarana, which was not completely free of adverse effects, because four volunteers
Table 2. Randomized, Double-Blind, Placebo-Controlled, Intervention Trials (Parallel or Cross-Over) on the Effect of Multinutrient Food Supplements on Cognitive Functioning

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Study Population</th>
<th>Age (y)</th>
<th>Intervention</th>
<th>Duration</th>
<th>Outcome Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Jong et al., 2001</td>
<td>130</td>
<td>Free-living frail elderly</td>
<td>≥70 years mean = 78 y</td>
<td>Multiple micronutrient enriched foods*, or placebo</td>
<td>Daily for 17 weeks</td>
<td>2 neuropsychological tests (block-transfer test and reaction time test)</td>
<td>No significant effect of the enriched foods was observed on the 2 neuropsychological tests</td>
</tr>
<tr>
<td>Hogarth et al., 1996</td>
<td>87</td>
<td>Elderly medical in-patients</td>
<td>Mean = 83.2 y (energy) Mean = 84.3 y (vitamin) Mean = 81.8 y (E-vit) Mean = 81.3 y (placebo)</td>
<td>750 ml energy (540 kcal) (n = 22), multivitamin supplementation† (n = 20), both energy and vitamin (n = 24)‡ or placebo (n = 21)</td>
<td>4 weeks</td>
<td>Hodkinson’s abbreviated mental test score (MTS)</td>
<td>No significant differences in mental test score between the groups for energy and vitamin supplementation</td>
</tr>
<tr>
<td>Bryan et al., 2002</td>
<td>211</td>
<td>Healthy younger, middle-aged, and older women</td>
<td>20–30 y (n = 56) 45–55 y (n = 80) 65–92 y (n = 75)</td>
<td>750 µg of folate, 15 µg of vitamin B12, 75 mg of vitamin B6, or a placebo</td>
<td>Daily for 5 weeks</td>
<td>Alternate forms of standardized tests of cognitive processing resources, memory, executive function, verbal ability, and self-report mood measures</td>
<td>Significant positive effect on some measures of memory performance only, and no effect on mood</td>
</tr>
<tr>
<td>Chandra, 2001</td>
<td>86</td>
<td>Apparently healthy, independently living elderly subjects</td>
<td>≥65 y Mean = 75 y (supplement) Mean = 74 y (placebo)</td>
<td>Supplement of trace elements and vitamins† (n = 45) or a placebo (n = 41)</td>
<td>Daily for 1 y</td>
<td>Cognitive function consisting of immediate and long-term memory, abstract thinking, problem-solving ability, and attention</td>
<td>Significant improvement in all cognitive tests (p &lt; .001 to .05) except long-term memory recall (p &gt; .1)</td>
</tr>
</tbody>
</table>

Notes: *Supplement contains ~100% of the Dutch RDA of the vitamins D, E, thiamine, riboflavin, B6, folic acid, B12, and C, and ~25–100% of the Dutch RDA of calcium, magnesium, zinc, iron, and iodine. †Supplement contains vitamins A (8000 U), B1 (15 mg), B2 (15 mg), B3 (50 mg), B6 (10 mg), and C (500 mg). ‡Supplement contains vitamin A (400 RE), β-carotene (16 mg), thiamine (2.2 mg), riboflavin (1.5 mg), niacin (16 mg), vitamin B6 (3.0 mg), folate (400 µg), vitamin B12 (4.0 µg), vitamin C (80 mg), vitamin D (4.0 µg), vitamin E (44 mg), iron (16 mg), zinc (14 mg), copper (1.4 mg), selenium (20 µg), and iodine (0.2 mg).
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Study Population</th>
<th>Age (y)</th>
<th>Intervention</th>
<th>Duration</th>
<th>Outcome Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seal et al., 2002</td>
<td>31</td>
<td>Inpatients with serum vitamin B12 levels between 100 and 150 pmol/L, without pernicious anemia, other malabsorption disorders, or progressive neurological or terminal illness</td>
<td>Mean = 81.4 y</td>
<td>Oral cyanocobalamin 10 μg (n = 10) and 50 μg (n = 10) or placebo (n = 11)</td>
<td>Daily for 4 weeks</td>
<td>MMSE</td>
<td>There were no significant changes in MMSE</td>
</tr>
<tr>
<td>Galduroz and Carlia, 1996</td>
<td>45</td>
<td>Normal, elderly volunteers</td>
<td>Mean = 65 y</td>
<td>500 mg brown sugar (placebo) (n = 15), 12.5 mg caffeine (n = 15), and 500 mg guarana (Paullinia cupana is a Brazilian plant) (n = 15)</td>
<td>21 weeks</td>
<td>Cognitive evaluation (Digital Span, free recall, Digital Symbol, cancellation tests, Mosaic test)</td>
<td>No significant cognitive alterations in these volunteers</td>
</tr>
<tr>
<td>Nolan et al., 1991</td>
<td>10</td>
<td>Patients with probable or possible Alzheimer’s disease (NINCDS-ADRDA criteria)</td>
<td>Mean = 76.3 y</td>
<td>Thiamine at 3 g/d or (lactose) placebo</td>
<td>1 year</td>
<td>MMSE, CERAD neuropsychological battery</td>
<td>No significant differences were found between the placebo and thiamine groups at any point during the study; in both groups, overall means for the MMSE, verbal learning, and naming scores decreased significantly over the 12-month study period</td>
</tr>
<tr>
<td>Sano et al., 1997</td>
<td>341</td>
<td>Patients with probable Alzheimer’s disease of moderate severity (CDR = 2)</td>
<td>Mean = 72.7 y (S)</td>
<td>Selegiline (10 mg a day) (n = 84), alpha-tocopherol (vitamin E, 200 IU a day) (n = 87), both selegiline and alpha-tocopherol (n = 85), or placebo (n = 85)</td>
<td>Daily for 2 years</td>
<td>Time to the occurrence of any of the following: death, institutionalization, loss of the ability to perform basic activities of daily living, or severe dementia (defined as a CDR of 3)</td>
<td>In patients with moderately severe impairment from Alzheimer’s disease, treatment with selegiline or alpha-tocopherol slows the progression of disease</td>
</tr>
<tr>
<td>Barak et al., 1996*</td>
<td>11</td>
<td>Hospitalized Alzheimer patients</td>
<td>Mean = 81.6 y</td>
<td>6 g of inositol or dextrose</td>
<td>Daily for 4 weeks</td>
<td>CAMCOG scores</td>
<td>Language and orientation improved significantly more on inositol than on placebo</td>
</tr>
<tr>
<td>Meador et al., 1993*</td>
<td>18</td>
<td>Patients with probable Alzheimer’s disease</td>
<td>Mean = 71 y</td>
<td>3 g/day thiamine administered orally or placebo</td>
<td>4 weeks</td>
<td>ADAS, MMSE, CGIC</td>
<td>Thiamine may have a mild beneficial effect in dementia of Alzheimer’s type</td>
</tr>
<tr>
<td>Deijen et al., 1992</td>
<td>76</td>
<td>Apparently healthy, self-supporting healthy male controls matched for age, plasma pyridoxal-5'-phosphate concentration, and intelligence score</td>
<td>70–79 y Mean = 73 y</td>
<td>20 mg pyridoxine HCL (n = 38) or placebo (n = 38)</td>
<td>Daily for 12 weeks</td>
<td>Cognitive performance</td>
<td>Positive effects of vitamin B6 supplementation were only found with respect to memory, especially concerning long-term memory</td>
</tr>
</tbody>
</table>

**Notes:** *Cross-over study. MMSE = Mini-Mental State Examination; NINCDS = National Institute of Neurological and Communicative Disorders and Stroke; ADRDA = Alzheimer’s Disease and Related Disorders Association; CERAD = Consortium to Establish a Registry for Alzheimer’s Disease; CDR = Clinical Dementia Rating; CAMCOG = Cambridge Cognitive Examination; ADAS = Alzheimer’s Disease Assessment Scale; CGIC = Clinical Global Impression of Change.
Table 4. Randomized, Double-Blind, Placebo-Controlled, Intervention Trials (Parallel or Cross-Over) on the Effect of ALCAR on Cognitive Functioning

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Study Population Age (y)</th>
<th>Intervention Duration</th>
<th>Outcome Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>No sign. effect</td>
<td></td>
<td></td>
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<tr>
<td>Thal et al., 2000</td>
<td>197</td>
<td>Subjects with a diagnosis of probable Alzheimer’s disease (NINCDS-ADRDA criteria) MMSE 12–26</td>
<td>45–65 y Mean = 58 y</td>
<td>3 g/day acetyl-L-carnitine (ALCAR) (n = 95) or placebo (n = 102) Daily for 1 year</td>
<td>Primary outcome measures were the Alzheimer’s Disease Assessment Scale (ADAS) Cognitive Component and the Clinical Dementia Rating Scale. Secondary measures included the ADAS Non-Cognitive Subscale, the MMSE, an Activities of Daily Living Scale (ADL), and a Clinician-Based Impression of Change (CIBIC). There were no significant differences between the treatment groups on the change from baseline to endpoint in the intent-to-treat analysis.</td>
</tr>
<tr>
<td>Thal et al., 1996</td>
<td>419</td>
<td>Subjects with mild to moderate probable Alzheimer’s disease (NINCDS-ADRDA criteria) MMSE 13–26</td>
<td>&gt;50 y Mean = 71 y (placebo), Mean = 72 y (ALCAR)</td>
<td>3 g/day of ALCAR (n = 207) or placebo (n = 212) Daily for 1 year</td>
<td>ADAS cognitive component and the Clinical Dementia Rating Scale. Overall, both ALCAR- and placebo-treated patients declined at the same rate on primary measures during the trial.</td>
</tr>
<tr>
<td>Rai et al., 1990</td>
<td>36</td>
<td>Patients with dementia of the Alzheimer type</td>
<td>&gt;60 y Mean = 79.0 y</td>
<td>1 g acetyl-L-carnitine twice daily and placebo 6 months</td>
<td>Battery of neuropsychological tests. Trends for greater improvement in the ALCAR group in relation to the Names Learning Test and a computerized Digit Recall Test, both related to aspects of short-term memory. Statistically significant effects after 12 weeks of treatment on the physician’s clinical global impression, not on digital symbol substitution test.</td>
</tr>
<tr>
<td>Herrmann et al., 1990</td>
<td>187</td>
<td>Elderly outpatients with a clinical diagnosis of mild to moderate cognitive decline</td>
<td>60–80 y Mean = 70.8 y Mean = 71.3 y (ALC)</td>
<td>1.5 g/day acetyl-L-carnitine (n = 94) or placebo (n = 93) 12 weeks</td>
<td>Clinical global impression and Digital symbol substitution test. ALC slows the progression of Alzheimer’s disease in younger subjects (&lt;65 y).</td>
</tr>
<tr>
<td>Brooks et al., 1998</td>
<td>334</td>
<td>Subjects diagnosed with probable Alzheimer’s disease by NINCDS-ADRDA criteria</td>
<td>Mean = 70.8 y Mean = 71.3 y (ALC)</td>
<td>3 g/day acetyl-L-carnitine (ALC) (n = 165) or placebo (n = 169) Daily for 1 year</td>
<td>Cognitive subscale of ADAS. Acetyl levocarnitine group demonstrated significantly less deterioration in timed cancellation tasks and Digit Span (forward) and a trend toward less deterioration in a timed verbal fluency task.</td>
</tr>
<tr>
<td>Sano et al., 1992</td>
<td>27</td>
<td>Mild to moderately demented patients with probable Alzheimer’s disease (NINCDS-ADRDA criteria)</td>
<td>60–80 y Mean = 71.2 y (placebo) Mean = 67.6 y (ALH)</td>
<td>Acetyl levocarnitine hydrochloride (2.5 g/d for 3 months followed by 3 g/d for 3 months) (n = 13) or placebo (n = 14) 6 months</td>
<td>Tests of memory, attention, language, visuospatial, and constructive abilities. Treated group showed a slower rate of deterioration in 13 of the 14 outcome measures, reaching statistical significance for the Blessed Dementia Scale, logical intelligence, verbal critical abilities, long-term verbal memory, and selective attention.</td>
</tr>
<tr>
<td>Spagnoli et al., 1991</td>
<td>130</td>
<td>Patients with a clinical diagnosis of Alzheimer’s disease</td>
<td>&gt;40 y Mean = 75.7 y Mean = 74.7 y (placebo)</td>
<td>Acetyl-L-carnitine 2 g/day (n = 63) or placebo (n = 67) 1 year</td>
<td>14 outcome measures to assess functional and cognitive impairment.</td>
</tr>
</tbody>
</table>

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Table 4. Randomized, Double-Blind, Placebo-Controlled, Intervention Trials (Parallel or Cross-Over) on the Effect of ALCAR on Cognitive Functioning (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Study Population</th>
<th>Age (y)</th>
<th>Intervention</th>
<th>Duration</th>
<th>Outcome Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrigo et al., 1990*</td>
<td>12</td>
<td>Elderly subjects with chronic cerebral lesions</td>
<td>58–65 y Mean = 61.1 y</td>
<td>1.5 g/day acetyl-L-carnitine or placebo</td>
<td>Daily for 4 weeks</td>
<td>Mini-Mental Test, STAI memory for numbers, memory for words, non-verbal performance, motor performance</td>
<td>Significant differences between drug and placebo were found in memory (number and word tests) and in responses to simple stimuli and the performance of the maze test</td>
</tr>
<tr>
<td>Passeri et al., 1990</td>
<td>60</td>
<td>Elderly suffering from mild mental impairment</td>
<td>&gt;65 y Mean = 75.1 y (placebo) Mean = 74.0 y (ALCAR)</td>
<td>2 g/day acetyl-L-carnitine &lt;i&gt;(n = 30)&lt;/i&gt; or placebo &lt;i&gt;(n = 30)&lt;/i&gt;</td>
<td>12 weeks</td>
<td>Complete battery of rating scales and psychometric tests</td>
<td>Acetyl-L-carnitine-treated patients showed statistically significant improvement in the behavioral scales, in the memory tests, in the attention barrage test, and in the Verbal Fluency test</td>
</tr>
<tr>
<td>Bonavita, 1986</td>
<td>40</td>
<td>Patients showing neuropsychic signs and/or symptoms of slight-medium intensity, which were consistent with clinical identification of the senile brain</td>
<td>&gt;65 y 66–85 y Mean = 74.3 y</td>
<td>1 g/day L-acetylcarnitine or placebo</td>
<td>6 weeks</td>
<td>Mental parameters of the senile brain</td>
<td>Short-term, intensive L-acetylcarnitine treatment can determine a significant improvement of the main mental parameters of the senile brain</td>
</tr>
</tbody>
</table>

*Cross-over study. NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; MMSE = Mini-Mental State Examination.
A weakness of all the reviews concerning the effectiveness of treatment is publication bias as a result of the selective nonpublication of null or negative trials. For this systematic review, we performed a MEDLINE search of the literature. We used carefully determined key words and selection criteria to define our topic. We used the criteria at different stages in the selection procedure of articles for our review. In addition to the MEDLINE search, we manually checked the references of selected articles and some reviews on nutritional supplements and cognitive functioning to yield the best possible literature search.

We reviewed all potentially eligible articles using a checklist for randomized controlled trials by the Dutch Cochrane Centre, extended with items from the Delphi list (10) to select only trials with high-quality designs. In most excluded articles, the methodologic aspects, such as randomization, blindness of treatment, and placebo treatment, were not clearly described. As a result of the selection, we found a wide variety in participants, intervention dose and duration, and applied outcome measures in the performed trials.

Because of the wide variety in the study designs, it is difficult to draw a firm conclusion about which nutrient or combination of nutrients supplied would have a positive effect on which domain of cognitive functioning. No clear pattern emerged to explain the observed positive effects.

The clearest finding was that in the multinutrient studies that did not show positive effects, cognitive functioning was tested using simple, general tests. Conversely, significantly positive effects were found in the multinutrient studies in which functioning was specifically measured on different aspects of cognitive functioning. Martin and colleagues (30) also noted this phenomenon in their review. A possible explanation is the difference between fluid and crystallized abilities. Cognition has two aspects: one is the capacity to apply information learned during the life span (crystallized abilities) and the other reflects information-processing capacities (fluid abilities). The latter are more vulnerable to changes in nutritional status and could be influenced more by B vitamin supplementation (31). Results of intervention studies, therefore, depend in part on which of the two aspects of cognition is tested. Another aspect influencing the effect is that changes in cognitive functioning by nutrition are subtle. The outcome measures included in intervention trials should be able to detect small changes over time. The use of several different outcome measures in the studies reviewed makes it difficult to interpret the results.

Another interesting aspect of the trials reviewed is the large number of articles on ALCAR, mostly funded by Sigma-Tau Pharmaceuticals (Gaithersburg, MD). A variety of nutritional components may positively influence cognitive functioning. Table 1 lists the putative mechanisms behind these results. In this review, alpha-tocopherol, inositol, and some B vitamins (thiamine, pyridoxine, folate, and B12) had a positive effect on cognitive functioning in some studies. In other studies, vitamin B12 and thiamine did not show this positive effect. In the group of ALCAR studies, six trials found significantly positive effects but the other four did not. Thal and colleagues (23,24) suggest a possible mechanism for the effects of ALCAR. ALCAR’s most common function is to shuttle acetyl groups across the inner mitochondrial membrane to be available for oxidation, thereby participating in cellular energy production. In addition, ALCAR appears to play a role in the removal of toxic accumulations of fatty acids from mitochondria. Furthermore, ALCAR functions as a membrane-stabilizing agent. The best way to improve cognitive functioning in elderly persons might be to combine all positive effects of different nutrients, as we hypothesized in the introduction of this review. A proper supply of nutrients is probably more important for cognitive functioning than the availability of a single component.

Besides the selection of outcome measures, other factors that might explain the absence of effect are the size of the study population, the age of the participants, the presence of Alzheimer’s disease, and the dose and duration of the intervention. Because of the heterogeneity of the trials and the lack of a clear pattern of explanatory factors, it is difficult to draw a conclusion about the effectiveness of single nutrients in improving cognitive functioning or preventing impairment in elderly persons. Therefore, we conclude that additional high-quality trials are needed to cluster the results in different components of the diet and to suggest firm conclusions about single nutrients. Future trials should be conducted in patients with mild cognitive impairment, because the window of opportunity for effective intervention may be as short as 1 year from the onset of medical symptoms, as Martin and colleagues (8) suggested. The duration of administration of the nutrient should be long enough to counteract reversible damage processes to the brain. In designing a trial, researchers should keep in mind which possible nutritional mechanism underlies their study. For the outcome measures, the most ideal situation would be that researchers in the field would use one standard neuropsychological battery of sensitive tests. Comparing studies would become easier and more accurate. Finally, dose–response relationships of nutrients should be investigated to determine an optimal dose for improving cognitive functioning.

Our results suggest that nutritional supplements may improve the cognitive functioning of elderly persons and do no harm. A great opportunity exists to conduct well-designed studies to support these findings.

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