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Best Evidence Summaries of Topics in Mental Healthcare

BEST *in* MH *clinical question-answering service*

Question

"In adults with dementia, how effective are vitamins, minerals and food stuffs, compared to any other intervention/treatment as usual, for slowing the progression of dementia, or for improving dementia-related symptoms?"

Clarification of question using PICO structure

Patients:	Adults with dementia
Intervention:	Vitamins, minerals, and food stuffs
Comparator:	Any other intervention/treatment as usual
Outcome:	Slowing the progression of dementia, or improving dementia-related symptoms

Clinical and research implications

Overall, the available evidence suggested that neither vitamin E, vitamin B (single or combination interventions), or either of the multi-vitamin supplements assessed had any significant effect on the clinical outcomes of patients with mild to moderate AD. There was some, inconsistent evidence to suggest that omega 3 supplementation, particularly in combination with lipoic acid, may have some small positive effects on measures of cognitive function and activities of daily living; the potential effects of omega 3 supplementation may warrant further research.

What does the evidence say?

Number of included studies/reviews (number of participants)

We identified two systematic reviews,[1,2] and ten randomised controlled trials (RCTs)[3,4,6-12,14] that reported data relevant to this evidence summary. Three further studies were excluded, as they did not match the PICO criteria specified for this summary.[5,13,15] Both systematic reviews included only RCTs. All RCTs included in this summary used a placebo-controlled design. One systematic review that included two relevant studies,1 and five additional RCTs[6-9,12] assessed the effects of vitamin E and/or other antioxidants on a range of measures of cognitive function, dementia severity and activities of daily living (ADL); study durations were generally short (12-18 weeks), but one study[6] reported mean follow-up of approximately 2.5 years. One systematic review, which included three relevant studies,[2] assessed the effects of folic acid with or without vitamin B12 on cognitive function and ADL, one additional RCT assessed the effects of high dose vitamin B supplementation over 18 weeks on cognitive function (ADAS-cog) and time to a composite negative end-point,[3] and one further study assessed the effects of vitamin B6, vitamin B12 and folic acid over 26 weeks on cognitive function and ADL.[14] Three RCTs evaluated multi-vitamin supplements: One study assessed the effects of a multi-vitamin intervention, which included thiamine, riboflavin, nicotinamide, vitamin B6 and vitamin C, over 6 weeks on cognitive and behavioural function;[4] two studies assessed the effects of a specific product (Souvenaid) on cognitive function, ADL and quality of life (QoL).[10,11] All studies included in this summary were conducted in people with mild, or mild to moderate dementia; no study included participants with other types of dementia.

Main Findings

The systematic review of vitamin E found no convincing evidence of an effect on dementia symptoms/cognitive function.[1] One additional trial of vitamin E + lipoic acid + vitamin C found that this intervention had no significant effects on cognitive function or ADL.[8] A trial of vitamin E, with or without memantine, versus placebo, found that vitamin E was associated with a slower decline in ADCS-ADL than placebo, however, as there was no difference between either Memantine + vitamin E and placebo, or between memantine and placebo, and no differences between any of the groups on any other outcome measure (cognitive function, dependency, or neuropsychiatric) , it seems likely that this observation was artifactural.[6] One study, assessing docsohexanoic acid supplementation, found no significant effects on the rate of cognitive decline, dementia symptoms, ADL, Neurpsychiatric Inventory, or QoL.[9] The evidence on omega 3 supplementation was inconsistent: one study found that omega 3 alone had no significant effect on neuropsychiatric symptoms, depressive symptoms, care-giver burden or ADL;[7] a second study found that omega 3, with or without lipoic acid, had a small positive effect on measures of ADL and the same study also reported that omega 3 + lipoic acid reduced decline in cognitive function (MMSE) compared to placebo (omeg 3 alone had no significant effect).[12] The results of the second systematic review,[2] and

two RCTs[3,14] indicated that none of the vitamin B-base interventions assessed had a significant effect on cognitive function or ADL outcomes. One study of multi-vitamin supplementation (thiamine, riboflavin, nicotinamide, vitamin B6 and vitamin C) found no significant treatment effects on cognitive or behavioural functions measures.[4] The authors of the two studies of Souvenaid reported that this intervention improves memory, however, this statement was not supported by their data.[10,11]

Authors Conclusions

Farina 2012 – There was no convincing evidence that vitamin E is of benefit in the treatment of AD or MCI. Future trials assessing vitamin E treatment in AD should not be restricted to alpha-tocopherol.

Malouf 2008 - The small number of studies which have been done provide no consistent evidence either way that folic acid, with or without vitamin B12, has a beneficial effect on cognitive function of unselected healthy or cognitively impaired older people. In a preliminary study, folic acid was associated with improvement in the response of people with Alzheimer's disease to cholinesterase inhibitors. More studies are needed on this important issue.

Aisen 2008 - This regimen of high dose B vitamin supplements does not slow cognitive decline in individuals with mild to moderate AD.

Burnes 1989 - Supplementation did not prevent an increase in either cognitive impairment or behavioural disturbance.

Dysken 2014 - Among patients with mild to moderate AD, 2000 IU/d of alpha tocopherol compared with placebo resulted in slower functional decline. There were no significant differences in the groups receiving memantine alone or memantine plus alpha tocopherol. These findings suggest benefit of alpha tocopherol in mild to moderate AD by slowing functional decline and decreasing caregiver burden.

Freund-Levi 2008 - Supplementation with omega 3 in patients with mild to moderate AD did not result in marked effects on neuropsychiatric symptoms except for possible positive effects on depressive symptoms (assessed by MADRS) in non-APOEomega4 carriers and agitation symptoms (assessed by NPI) in APOEomega4 carriers.

Galasko 2012 - Antioxidants did not influence CSF biomarkers related to amyloid or tau pathology. Lowering of CSF F2-isoprostane levels in the E/C/ALA group suggests reduction of oxidative stress in the brain. However, this treatment raised the caution of faster cognitive decline, which would need careful assessment if longer-term clinical trials are conducted.

Quinn 2010 - Supplementation with DHA compared with placebo did not slow the rate of cognitive and functional decline in patients with mild to moderate Alzheimer disease.

Scheltens 2010 - Supplementation with a medical food including phosphatide precursors and cofactors for 12 weeks improved memory (delayed verbal recall) in mild AD patients. This proof-of-concept study justifies further clinical trials.

Scheltens 2012 - This study confirms that Souvenaid is well tolerated and improves memory performance.

Shinto 2014 – The combination of ω-3+LA slowed cognitive and functional decline in AD over 12 months. Because the results were generated from a small sample size, further evaluation of the combination of omega-3 fatty acids plus alpha-lipoic acid as a potential treatment in AD is warranted.

Sun 2007 - In this population of patients with mild to moderate AD in Taiwan, a multivitamin supplement containing vitamins B6 and B12 and folic acid for 26 weeks decreased homocysteine concentrations. No statistically significant beneficial effects on cognition or ADL function were found between multivitamin and placebo at 26 weeks.

Reliability of conclusions/Strength of evidence

The systematic review evidence included in this summary was derived from two Cochrane reviews, which were of generally good methodological quality, but which focussed on two narrowly defined interventions. The additional RCTs identified were generally poorly reported with respect to randomisation and allocation concealment procedures and were classified as at high risk of bias due to missing data for a substantial proportion of participants and/or selective reporting of outcomes.

What do guidelines say?

Neither National Institute for Health and Care Excellence (NICE) nor Scottish Intercollegiate Guidelines Network (SIGN) guidelines make recommendations regarding the treatment or slowing down of dementia-related symptoms in adults with dementia.

The evidence included in this summary does not support the formulation of new guidance in this area.

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SRs

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RCTs

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Results

Systematic Reviews

Author (year)	Search Date	Inclusion criteria	Number of included studies	Summary of results	Risk of bias
Farina et al. (2012)	06/2012	*Participants*: Participants diagnosed with probable AD according to internationally accepted diagnostic criteria (e.g., DSM-IV; NINCDS-ADRDA; ICD 10). The review also included trial, in people with MCI, on prevention of progression to AD *Intervention*: Any dosage of vitamin E or any of its constituent tocopherols or tocotrienols. Co-administration of another drug was allowed, if the same drug was also taken by the control group. *Comparator*: Placebo. *Outcome*: Primary outcomes (AD studies): cognitive function, adverse events, death. Secondary outcomes (AD studies): global measures of severity and deterioration, behavioural disturbance, mood, activities of daily living, quality of life, permanent physical disability, institutionalisation. *Study design*: RCTs	3 (2 relevant studies conducted in people with probable AD); n = 398	This systematic review aimed to assess the efficacy of vitamin E for the treatment of AD and prevention of progression of MCI to dementia. This evidence summary includes only the evidence relating to the treatment of AD. Two randomised, placebo controlled trials assessed the effects of vitamin E supplementation. One trial assessed the effects of 2000 IU/day in people with moderate dementia severity, who were living at home, and assessed outcomes over two years. The second study assessed the effects of 800 IU/day in people with mild to severe dementia (mild n=25, moderate n=26, severe n=6), and assessed outcomes over 6 months. The first study found that fewer participants in the vitamin E group reached a negative composite end point (death, institutionalisation, change to a Clinical	The review questions were clearly stated and appropriate inclusion criteria were defined. Five bibliographic databases, as well as grey literature sources were searched for relevant studies. The review process included measures to minimise error and/or bias (involvement of more than one reviewer) throughout.

				Dementia Rating (CDR) of three, or loss of two basic activities of daily living) within two years: OR 0.49 (95% CI 0.29 to 0.96). However, these data were for participants who completed the study only (155/341), i.e. more than 50% of participants were excluded from the analysis. The second study compared cognitive outcomes, baseline to six months, and between the placebo group, vitamin E responders (decrease in blood glutathione disulphide levels of >10 nmol/mL after six months), and vitamin E non-responders. There were no statistically significant differences between the vitamin E responders and the placebo group on clock drawing test, Mini Mental State Examination (MMSE), or Blessed Dementia Scale (BDS).	The methodological quality of included studies was assessed using the Cochrane risk of bias tool. Studies were appropriately summarised using a narrative synthesis.
Malouf et al. (2008)	10/2007	*Participants*: Any type of dementia, diagnosed using accepted criteria (e.g., DSM-IV; NINCDS-ADRDA; ICD 10). The review also prevention of dementia studies, in healthy older people. *Intervention*: Folic acid with or without vitamin B12 at any dose and by any route of administration. *Comparator*: Placebo. *Outcome*: Primary outcome: cognitive	8 (3 relevant, conducted in people with dementia); n = 235	This systematic review aimed to assess the effects of folic acid supplementation, with or without vitamin B12, on elderly healthy or demented people, in preventing cognitive impairment or retarding its progress. This evidence summary includes only the evidence relating to the treatment of dementia. Three randomised, placebo controlled trials	The review questions were clearly stated and appropriate inclusion criteria were defined. Six bibliographic databases, as well as grey literature

		measurements. Secondary outcome: blood folate levels; serum or plasma levels of total homocysteine; mood changes. *Study design*: RCTs		assessed effectiveness in people with dementia. One trial compared 2mg/d of folic acid + 1 mg/d of vitamin B12 to placebo, in people with a DSM-IV diagnosis of dementia. This study found no significant differences, in cognitive function (MMSE, ADAS-COG) or activities of daily living (BADL), between the intervention and placebo groups at 12 weeks. A second trial compared 1mg/d folic acid to placebo in people with a diagnosis of AD. This study found no significant differences, in cognitive function (MMSE, DDST), between the intervention and placebo groups at six weeks. However, folic acid was associated with an improvement on the Instrumental Activities of Daily Living Social Behaviour Subscale (IADL/SB); mean difference 4.01 (95% CI 0.50 to 7.52). No data were extracted from the third small trial (10 mg/d folic acid versus placebo, 11 people with dementia).	sources were searched for relevant studies. The study selection, but not the data extraction process included measures to minimise error and/or bias (involvement of more than one reviewer). The methodological quality of included studies was assessed using Cochrane criteria. Studies were appropriately summarised using a narrative synthesis.

RCTs

Author (year)	Inclusion criteria	Number of participants	Summary of results	Risk of bias
Aisen et al. (2008)	*Participants*: Individuals with probable AD. Inclusion criteria: aged greater than 50, with Mini-Mental State Examination (MMSE) score between 14-26. Exclusion criteria: having levels of vitamin B12 or folate below normal, or renal insufficiency; use of anticholinergic, sedative, anti-Parkinson or anti-AD drugs within two months prior to enrolment. *Intervention*: Folic acid 5mg, vitamin B12 1mg, vitamin B6 25mg, administered once daily. *Comparator*: Placebo tablet of identical appearance. *Outcome*: Primary outcome: 18 month change score on the Alzheimer's Disease Assessment Scale (ADAS-cog), which measures memory, attention, language, orientation, and praxis. Secondary outcomes: cognition (MMSE; Clinical Dementia Rating sum of boxes, CDR-SOB), activities of daily living (Alzheimer's Disease Cooperative Study Activities of Daily Living scale, ADCS-ADL), neuropsychiatric symptoms (Neuropsychiatric Inventory, NPI), quality of life (Quality of Life-AD, QOL-AD), time to	n = 409 (intervention group = 240; placebo group = 169).	This study aimed to assess the efficacy and safety of vitamin B for the treatment of AD. All study participants had mild to moderate AD. The mean age of study participants was 76.3±8.0 years and 56% were female. There were no significant differences in baseline demographic or socioeconomic characteristics, or in biochemical or psychological measures, between the two study groups. Dropout rates were similar between the intervention and control groups. There was no between group difference in the rate of change in ADAS-cog over 18 months: placebo =0.372 points/month, active= 0.401 points/month, p=0.52, 95% CI of rate difference −0.06 to 0.12. Time to the first of five possible endpoints (death, institutionalization, increase in global CDR score, 15 point decline on the ADCS-ADL scale, or 4 point decline on ADAS-cog) did not differ between the groups: HR 0.99 (95% CI: 0.78 to 1.21).	The randomisation process used a permuted block design with a block size of 5 (3 active, 2 placebo); no further details were reported. No details of allocation concealment were reported. The study was a double-blind design and a placebo tablet of identical appearance to the intervention

	attainment of significant endpoints (4-point decline from baseline ADAS-cog score, death, institutionalization, 1 stage worsening on the global CDR scale, 15 point decline on the ADCS-ADL).			was used. The primary analysis was ITT. Change from baseline data were reported for both groups for all specified outcomes, but between group comparisons were only reported for rate of change of ADAS-cog and time to endpoint.
Burns et al. (1989)	*Participants*: Individuals with dementia. Exclusion criteria: serious physical or mental illness that could prevent completion of the study *Intervention*: Vitamin tablets: thiamine, 100mg; riboflavin, 10 mg; nicotinamide, 400 mg; vitamin B6, 10 mg; ascorbic acid,	n = 19 (active group = 10; placebo group = 9)	This trial did not report a clear objective, but appeared to focus primarily on the use of multi-vitamin supplementation to improve nutritional outcomes. Seventeen of the 19 included participants were female. Data were only reported for the 15 participants who completed the study. The mean age of participants who complete the	No details of randomisation or allocation concealment were reported.

	200 mg. All daily for 6 weeks. *Comparator*: Placebo. *Outcome*: Various nutritional and biochemical outcomes; cognition (30 point Mental state score); 36 point behavioural disturbance score.		study was 81±5.3 years. There were no significant baseline differences in behavioural, cognitive, or nutritional measures, between the intervention and control groups. Vitamin supplementation did not improve cognitive function or behavioural disturbance. Participants in the vitamin supplementation group showed a small increase in behavioural disturbance during the study (mean change 3.8±2.6). There were no significant changes in behavioural disturbance score in the placebo group and no significant changes in cognitive function in either group.	The trial was described as double-blind Four of 19 participants were excluded from the analyses. Data were reported for all specified outcomes.
Dysken et al. (2014)	*Participants*: Individuals with probable AD of mild to moderate severity. Inclusion criteria: MMSE score between 12 and 26; currently taking an acetylcholinesterase Inhibitor. *Intervention*: (1) Alpha tocopherol (1000 IU twice daily), a fat-soluble vitamin and antioxidant, and memantine (10mg twice a day). *Comparator*: (2) Alpha tocopherol (1000 IU twice daily), and a placebo for memantine; (3) A placebo for alpha tocopherol, and memantine (10mg twice a day); (4) placebo. *Outcome*: Primary outcomes: ADCS-ADL.	n = 613 (group 1, vitamin E + memantine = 154; group 2, vitamin E + placebo = 152; group 3, memantine + placebo = 155; group 4, placebo = 152)	This study aimed to assess the effectiveness of vitamin E memantine, or both, in slowing the progression of mild to moderate AD in people taking acetylcholinesterase inhibitors. Study participants were veterans (97% male), with a mean age of 78.8±7.1 years. Baseline demographic, socioeconomic and clinical characteristics were similar across the treatment groups. The 2 most commonly prescribed AChEIs were donepezil (65%) and galantamine (32%). Over a mean follow-up duration of 2.77±1.22 years, vitamin E was associated with a slower decline (ADCS-ADL) than placebo: mean difference in change 3.15 (95% CI: 0.92 to 5.39). This was interpreted as representing a delay in clinical progression of 19% per year compared to placebo. However,	Participants were randomized centrally by the coordinating Centre; no further details reported. No details of allocation concealment were reported.

	Secondary outcomes: Cognition (MMSE; ADAS-COG) neuropsychiatric symptoms (NPI) time caregivers spend assisting the patient (Caregiver Activity Survey, CAS); functional dependence (Dependence Scale, DS); adverse events and serious adverse events.		neither the memantine + vitamin E group or the memenatine + placebo groups were significantly different from placebo. There were no significant treatment effects, for any of the active interventions, on any other outcome measure.	The trial was described as double-blind 52 Participants were excluded from the analyses due to lack of any follow-up data Data were reported for all specified outcomes.
Freund-Levi et al. (2008)	*Participants*: Individuals with probable AD according to DSM-IV criteria. Inclusion criteria: MMSE between 15-30, living at home, treated with a stable dose of acetylcholine esterase inhibitors for at least 3 months prior to enrolment. Exclusion criteria: being treated with NSAID, history of alcohol abuse, suffering from a concomitant serious disease, and not having a carer. *Intervention*: Omega-3 for 6 months (four 1-gram capsules a day) *Comparator*: Placebo for 6 months (four	n = 204 (active group, omega 3 = 103; placebo group = 101).	This study aimed to assess the effects of omega 3 supplementation on behavioural symptoms and activities of daily living, in people with mild to moderate AD, and to explore possible associations of effects with APOE genotype. There were 14 dropouts from the omega 3 group and 16 from the placebo group; data were only reported for participants who completed the study. The mean age of participants who completed the study was approximately 73 years, and 52% were female. Baseline demographic and clinical characteristics were similar across the two study groups.	Participants were randomised, using sealed envelopes, in blocks of four; no further details were reported. The study was described as double blind.

	capsules a day). *Outcome*: Neuropsychiatric symptoms (NPI) depressive symptoms (Montgomery Asberg Depression Rating Scale, MADRS); caregiver burden (Caregiver Burden Scale, CBS), activities of daily living (Disability Assessment for Dementia Scale, DAD).		There were no significant treatment effects on any outcome measure assessed (NPI, MARDS, CBS, or DADS) or on any of the 12 domains of the NPI, at 6 or 12 months. The authors stated that there were significant positive treatment effects on the agitation domain of the NPI and on MARDS scores, for APOEomega4 carriers, but full data were not reported (p values only).	Data were only reported for participants who completed the study (total of 30 dropouts excluded). Data were reported for all specified outcomes.
Galasko et al. (2012)	*Participants*: Individuals with probable AD. Inclusion criteria: MMSE scores between 16-30; aged between 50-85; with a carer; neuroimaging result within the last 24 months consistent with AD but lacking evidence of significant vascular disease or other intracranial disease processes; stable anti-AD treatment with a cholinesterase inhibitor, memantine, or both, for at least 3 months. Exclusion criteria: diagnosis of dementia other than AD, a neurological disorder or major psychiatric disorder, or drug or alcohol abuse/dependence; having contraindications to lumbar puncture were	n = 78 (26 in each arm)	This study primarily aimed to assess the effects of antioxidant supplementation on CSF biomarkers. However, data were also reported on patient-relevant outcome measures. The mean age of study participants was approximately 72 years and 46% were female. Baseline demographic, socioeconomic and clinical characteristics were similar across the three study groups. The MMSE scores showed a greater decline in the intervention 1 (vitamin supplement) group than in the placebo group (no numerical data reported). There were no differences between groups in changes in ADCS-ADL total scores, or in scores for subscales of basic or	No details of randomisation or allocation concealment were reported. The study was described as double blind. 18 Participants who did not complete the

	excluded; medical factors or conditions that could increase systemic oxidative stress. *Intervention*: (1) Vitamin E (800 IU/d) plus vitamin C (500 mg/d) plus alpha-lipoic acid (900 mg/d). For 16 weeks. *Comparator*: (2) co-enzyme Q (CoQ; 400 mg/d; (3) placebo. Both for 16 weeks. *Outcome*: Change in cognition (MMSE) and activities of daily living (ADCS-ADL).		instrumental ADL, although there were trends toward greater decline in the intervention 1 (vitamin supplement) group (no numerical data reported).	study were excluded from the analyses. No numerical data were reported for clinical outcomes.
Quinn et al. (2010)	*Participants*: Individuals with probable AD. Inclusion criteria: MMSE score between 14-26; medically stable; consumed on average no more than 200 mg/d of Docosahexaenoic acid (DHA); not taking DHA or omega-3 fatty acid supplements. Exclusion criteria: taking medication with anticholinergic effects or sedatives or receiving any other treatment for AD. *Intervention*: DHA, 1g twice a day. *Comparator*: Placebo *Outcome*: Primary outcomes: ADAS-cog; Clinical Dementia Rating (CDR). Secondary outcomes: ADCS-ADL, NPI, QoL-AD.	n=402 (active, DHA, group = 238; placebo group = 164)	This study aimed to assess whether supplementation with docosahexaenoic acid (DHA) slows cognitive and functional decline in people with AD. The mean age of study participants was 76±8.7 years and 52% were female. Baseline demographic, socioeconomic and clinical characteristics were similar across the two study groups, with the exception that there were more females in the placebo group (60%) than in the DHA group (47%). DHA supplementation had no significant effect on the rate of change of ADAS-cog: The mean rate of change in ADAS-cog score over 18 months was 8.27 points (95% CI: 6.72 to 9.82 points) for the placebo group compared with 7.98 points (95% CI: 6.51 to 9.45 points) for the DHA group. Similarly, DHA supplementation had no effect on the rate of change of CDR: the mean rate of change over 18 months was 2.93 (95% CI: 2.44 to 3.42) for the placebo group compared with 2.87 (95% CI: 2.44 to 3.30) for the DHA group.	Randomisation used a centralised, interactive, voice response system. No details of allocation concealment were reported. The study was described as double blind. 107 Participants did not

			Secondary outcome measures (ADCS-ADL, NPI and MMSE) also showed no significant differences in rate of decline over 18 months, between the DHA and placebo groups.	complete the study. The primary analyses were ITT. No data were reported for QoL-AD.
Scheltens et al. (2010)	*Participants*: Individuals with probable AD according to NINCDS-ADRDA criteria. Inclusion criteria: MMSE score between 20-26; aged 50 years or over; current outpatient status; drug naïve; Geriatric Depression Scale score of 4 or below; having a carer. Exclusion criteria: neurological diseases other than AD; previous use of cholinesterase inhibitors, N-methyl-D-aspartate-receptor antagonists or other AD medications; use of antidepressants, sleeping tablets, tranquillizers, or lipid-lowering medications; use of antipsychotics, antiepileptics, ginko biloba, or intake of >200% RDA of vitamins B, C, or E within 1 month before baseline. *Intervention*: Souvenaid (125 mL tetrapackages), containing a specific	n = 225 (active group = 113; placebo group = 112)	This study aimed to assess the effects of a specific medical food supplement (Souvenaid) on cognitive function in people with mild AD. Daily dose of the supplement , Souvenaid, contained the following components: EPA 300 mg; DHA 1200 mg; phospholipids 106 mg; choline 400 mg; uridine monophosphate 625 mg; vitamin E (alpha-TE) 40 mg; vitamin C 80 mg; selenium 60 µg; vitamin B12 3 µg; vitamin B6 1 mg; folic acid 400 µg. The mean age of study participants was 73.7 years, 50% were male and the mean baseline MMSE score was 23.9. Baseline demographic, socioeconomic and clinical characteristics were similar across the two study groups. At 12-weeks, 40% of patients in the intervention group showed an improvement in WMS-r delayed recall, compared to 24 % in the control group. However, the mean change	Randomisation was computer generated, separately for each study centre. No information on allocation concealment was reported. All study staff and patients were blinded to the products given.

	formulation of nutrients, vitamins, minerals, trace elements, and macronutrients, taken once a day at breakfast. *Comparator*: Placebo. *Outcome*: Primary outcomes: Wechsler Memory Scale-Revised (WMS-R); ADAS-cog. Secondary oucomes: MMSE; Clinician Interview-Based Impression of Change plus Caregiver Input (CIBIC-plus) NPI; ADCS-ADL; QOL-AD.		in WMS-r delayed recall (numerical values not reported) was comparable between groups and there was no between group difference in the number of patients experiencing improvements in WMS-r immediate recall. There were also no significant between group differences in the co-primary outcome ADAS-cog, or in any of the secondary outcome measures, at 12 weeks. Only safety outcomes were reported at 24 weeks. It should be noted that the study was fully funded by the manufacturer of Souvenaid and that data collection and analyses were undertaken by the manufacturer.	Participants who had taken at least one dose of the study medication and had at least one post-baseline assessment were included in the 12-week analyses (212/225) Three change from baseline outcomes, including the co-primary outcome WMS-r, were presented only as percentages of participants declined, improved and un-changed,

				with a single p value for between group difference. 24-week outcome data were not reported.
Scheltens et al. (2012)	*Participants*: Individuals with probable AD according to NINCDS-ADRDA criteria. Inclusion criteria: MMSE score ≥20; aged 50 years or over; drug naïve; having a carer; recent MRI or CT showing no other possible causes of dementia. Exclusion criteria: neurological diseases other than AD; GDS score >6; previous use of cholinesterase inhibitors or N-methyl-D-aspartate-receptor antagonists within 3 months before baseline; use of antidepressants, sleeping tablets, tranquillizers, or lipid-lowering medications; use of antipsychotics, antiepileptics, ginko biloba, or intake of >200% RDA of vitamins B, C, or E within 1 month before baseline; use of omega-3 fatty acid containing supplements or regular consumption of oily fish (>twice/week) within 2 months prior to baseline; excessive alcohol intake or drug	n = 259 (active group = 130; placebo group = 129	The stated aim of this study was to confirm and extend the findings of the previous Souvenaid study (described above). It should therefore be noted that there were some differences in inclusion criteria and outcome measures between the two studies and the severity of AD in this study population appears lower. In addition the duration of this study is no longer than that of the original Souvenaid study, but 24 week data from the original study were not published. The mean age of study participants was approximately 74 years, 51% were male and the mean MMSE score was 25 (suggesting a population with very mild AD). Baseline demographic, socioeconomic and clinical characteristics were similar across the two study groups. There were no statistically significant, between-group differences in change from baseline to 24 weeks on the memory or executive function domains of the NTB. The mean (sd) change from baseline to 24 weeks, on the NTB composite score, was 0.120 (0.278) in the intervention group and 0.035 (0.286) in the control group, p = 0.035. No results were	Randomisation was computer generated, separately for each study centre. No information on allocation concealment was reported. All study staff and patients were blinded to the products given. 12 patients

	abuse; nursing home institutionalisation *Intervention*: Souvenaid (125 mL tetrapackages), containing a specific formulation of nutrients, vitamins, minerals, trace elements, and macronutrients, taken once a day at breakfast. *Comparator*: Placebo. *Outcome*: Primary outcome: memory function domain of the Neuropsychological Test Battery (NTB), which included Rey Auditory Verbal Learning Test immediate recall, delayed recall and recognition performance, and Wechsler Memory Scale-revised (WMS-r) verbal paired associates immediate and delayed recall. Secondary outcomes: executive function domain, total composite score and individual item scores of NTB; the orientation task of the ADAS-cog; Letter Digit Substitution Test.		reported for the individual tests comprising the NTB, or for other secondary outcomes. It should be noted that the study was fully funded by the manufacturer of Souvenaid and that data collection and analyses were undertaken by the manufacturer.	from the intervention group and 9 from the control group were lost to follow-up. Analyses were conducted on an ITT basis (all randomised participants were included in the efficacy analyses). No results were reported for the individual tests comprising the NTB, or for other secondary outcomes.
Shinto et al. (2014)	*Participants*: Individuals with probable AD according to NINCDS-ADRDA criteria.	n = 39 (group 1,	This study was designed to assess the effects of supplementation with omega-3 fatty acids alone (ω-3) or	Participants were

	Inclusion criteria: MMSE score 15-26; Clinical Dementia Rating Scale (CDRS) score 0.5-1.0; health status that would not interfere with ability to complete the study; having a carer. Exclusion criteria: non-AD dementia; residence in a long-term care facility; history of stroke; health conditions such as cancer, liver disease, major depressive disorder, major central nervous diseases; taking lipid-lowering medication, fish oil supplements within 30 days of enrolment; consumption greater than one 6 ounce serving per week of fish or seafood within 30 days of enrolment. *Intervention*: (1) omega-3 (containing a daily dose of 675 mg DHA, 975 mg EPA) *Comparator*: (2) omega-3 (containing a daily dose of 675 mg DHA and 975 mg Eicosapentaenoic acid) plus lipoic acid (LA; 5600 mg/day); (3) placebo. *Outcome*: Primary outcome: change in urine F2-isoprostane levels at 12 months. Secondary outcomes: change at 12 months in cognition (ADA-cog, MMSE) and activities of daily living (ADL, IADL).	omega-3 = 13; group 2, omenga 3 + lipoic acid = 13; group 3, placebo = 13)	omega-3 plus alpha lipoic acid (ω-3 +LA) compared to placebo on oxidative stress biomarkers in AD; clinical measures were included as secondary outcomes. The mean age of study participants was approximately 76 years, 44% were female and the mean baseline MMSE score was approximately 22. Baseline demographic and clinical characteristics were similar across the three study groups. Baseline F2-isoprostane (ng/mg creatinine) was significantly higher in the omega 3 group than in the other two groups. There were no statistically significant differences in the mean change in ADAS-cog, over 12 months, between the three groups. There was no statistically significant difference in the mean change in MMSE, over 12 months, between the omega 3 group (-4.3±1.3) and the placebo group (-4.6±1.4), however, patients in the omega 3 + lipoic acid group appeared to experience significantly less decline (-1.0±0.7). Activities of daily living data were inconsistent. There were no statistically significant differences in the mean change in ADL, over 12 months, between the three groups. However, both the omeg 3 group (0.7±1.0) and the omega 3 + lipoic acid group (0.9±1.1) showed significantly less deterioration in IADL than the placebo group (4.2±0.9).	randomised by a computer generated scheme that was stratified by smoking status. No details of allocation concealment were reported. The study was described as double-blind and specified that the blinding of research staff assessing outcomes was tested at 12 months. Two participants from the

				placebo group, two from the omega 3 group and one from the omega 3 + lipoic acid group did not complete the study; it was not clear whether all randomised participants were included in the analyses. Data were reported for all specified outcomes.
Sun et al. (2007)	*Participants*: Individuals with probable AD according to DSM-IV criteria. Inclusion criteria: MMSE score between 10 and 26; aged >50. Exclusion criteria included: history of epilepsy; clinically significant hepatic, renal, pulmonary, metabolic, or endocrine disturbances or significant	n = 89 (active group = 45; placebo group = 44)	This study aimed to assess the effects of oral multivitamin supplementation containing vitamins B6 and B12 and folic acid on cognitive function and serum homocysteine levels in patients with mild to moderate AD. The mean age of study participants was approximately 75 years, 51% were male and the mean baseline MMSE score	No details of the randomisation procedure or allocation concealment were

	cardiovascular disease; vascular dementia or cerebrovascular disease; use of any vitamin supplement or dementia treatment except AChEIs. *Intervention*: Multivitamin supplement for 26 weeks (including vitamin B6, B12, folic acid), alongside a cholinesterase inhibitor. *Comparator*: Placebo, alongside a cholinesterase inhibitor. *Outcome*: Cognition (MMSE, CASI, and ADAS-Cog/11) and activities of daily living (ADL Index, and IADL).		was 18.7. Baseline demographic, biochemical and clinical characteristics were similar across the two study groups. There were no statistically significant differences between the intervention and control groups, on any clinical measure (ADAS-cog/11, MMSE, CASI, ADL, or IADL), in change from baseline to 26 weeks.	reported. The study was described as double-blind. Participants who received at least one dose of study medication and had at least one post-baseline assessment were included in the analyses; in practice, all randomised participants appear to have been included. 12 patients from the intervention group and 14 from the

				placebo group did not complete the study. Data were reported for all specified outcomes.

Risk of Bias:

SRs

Author (year)	Risk of Bias				
	Inclusion criteria	Searches	Review Process	Quality assessment	Synthesis
Malouf et al. (2008)	☺	☺	☹	☺	☺
Farina et al. (2012)	☺	☺	☺	☺	☺

RCTs

Study	RISK OF BIAS					
	Random allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting
Aisen et al. (2008)	?	?	☺	☺	☺	☺
Burns et al. (1989)	?	?	☺	☺	☹	☺
Dysken et al. (2014)	?	?	☺	☺	☹	☺
Freund-Levi et al. (2008)	?	?	☺	☺	☹	☺
Galasko et al. (2012)	?	?	☺	☺	☹	☹
Quinn et al. (2010)	?	?	☺	☺	☹	☹
Scheltens et al. (2010)	☺	?	☺	☺	☹	☹
Scheltens et al. (2012)	☺	?	☺	☺	☹	☹
Shinto et al. (2014)	☺	?	☺	☺	☹	☺

Sun et al. (2007)	?	?	☺	☺	☹	☺

☺Low Risk ☹High Risk ? Unclear Risk

Search Details

Source	Search Strategy	Number of hits	Relevant evidence identified
SRs and Guidelines			
NICE	Dementia vitamin; 17 dementia mineral; 6 dementia food; 20 dementia supplement; 14	57	0
DARE	1 (Calcium OR Magnesium OR Phosphorus OR Potassium OR Chlorine OR Sodium OR Sulphur OR Iron OR Zinc OR caroten* OR riboflavin* OR selenium* OR Vitamin* OR Mineral* OR nutritio* OR food* OR feed* OR diet* OR supplement* OR (ascorbic adj1 acid) OR antioxidant*) IN DARE 6152 Delete 2 MeSH DESCRIPTOR Vitamin A EXPLODE ALL TREES 47 Delete 3 MeSH DESCRIPTOR Vitamin B 12 EXPLODE ALL TREES 28 Delete 4 MeSH DESCRIPTOR Vitamin B 6 EXPLODE ALL TREES 26 Delete 5 MeSH DESCRIPTOR Vitamin B Complex EXPLODE ALL TREES 35 Delete 6 MeSH DESCRIPTOR Vitamin D EXPLODE ALL TREES 186 Delete 7 MeSH DESCRIPTOR Vitamin E EXPLODE ALL TREES 50 Delete 8 MeSH DESCRIPTOR Vitamin K EXPLODE ALL TREES 59 Delete 9 MeSH DESCRIPTOR Ascorbic Acid EXPLODE ALL TREES 46 Delete 10 MeSH DESCRIPTOR Folic Acid EXPLODE ALL TREES 144 Delete 11 MeSH DESCRIPTOR Riboflavin EXPLODE ALL TREES 4 Delete 12 MeSH DESCRIPTOR Vitamins EXPLODE ALL TREES 123 Delete 13 MeSH DESCRIPTOR Minerals EXPLODE ALL TREES 111 Delete 14 MeSH DESCRIPTOR Dietary Supplements EXPLODE ALL TREES 689 Delete 15 MeSH DESCRIPTOR Calcium EXPLODE ALL TREES 74 Delete 16 MeSH DESCRIPTOR Zinc EXPLODE ALL TREES 54 Delete 17 MeSH DESCRIPTOR Magnesium EXPLODE ALL TREES 39 Delete	116	2

	18 MeSH DESCRIPTOR Phosphorous Acids EXPLODE ALL TREES 0 Delete 19 MeSH DESCRIPTOR Potassium EXPLODE ALL TREES 21 Delete 20 MeSH DESCRIPTOR Sodium EXPLODE ALL TREES 10 Delete 21 MeSH DESCRIPTOR Iron EXPLODE ALL TREES 54 Delete 22 MeSH DESCRIPTOR Food EXPLODE ALL TREES 1157 Delete 23 MeSH DESCRIPTOR Antioxidants EXPLODE ALL TREES 111 Delete 24 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 6759 Delete 25 (dement* OR alzheimer* OR (mild adj1 cognitive adj1 impairment)) IN DARE 709 Delete 26 MeSH DESCRIPTOR Alzheimer Disease EXPLODE ALL TREES 298 Delete 27 MeSH DESCRIPTOR Dementia EXPLODE ALL TREES 595 Delete 28 MeSH DESCRIPTOR Dementia, Vascular EXPLODE ALL TREES 21 Delete 29 MeSH DESCRIPTOR Dementia, Multi-Infarct EXPLODE ALL TREES 0 Delete 30 MeSH DESCRIPTOR Frontotemporal Dementia EXPLODE ALL TREES 3 Delete 31 MeSH DESCRIPTOR Lewy Body Disease EXPLODE ALL TREES 6 Delete 32 MeSH DESCRIPTOR Frontotemporal Lobar Degeneration EXPLODE ALL TREES 3 Delete 33 #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 945 Delete 34 #24 AND #33 116 Delete		
Primary studies			
CENTRAL	#1 MeSH descriptor: [Dementia] explode all trees 3831 #2 MeSH descriptor: [Vitamins] explode all trees 1665 #3 minerals 7431 #4 MeSH descriptor: [Food] explode all trees 22178 #5 #2 or #3 or #4 28765 #6 #1 and #5 80	80	12
PsycINFO	1. PsycINFO; exp DEMENTIA/; 53465 results. 2. PsycINFO; DIETARY SUPPLEMENTS/ OR VITAMIN THERAPY/ OR exp VITAMINS/; 4807 results. 3. PsycINFO; mineral*.ti,ab; 2180 results. 4. PsycINFO; FOOD/; 9584 results.	174	0

	5. PsycINFO; "food stuffs".ti,ab; 18 results. 6. PsycINFO; 2 OR 3 OR 4 OR 5; 16207 results. 7. PsycINFO; 1 AND 6; 566 results. 8. PsycINFO; CLINICAL TRIALS/; 7958 results. 9. PsycINFO; random*.ti,ab; 133909 results. 10. PsycINFO; groups.ti,ab; 374870 results. 11. PsycINFO; (double adj3 blind).ti,ab; 18156 results. 12. PsycINFO; (single adj3 blind).ti,ab; 1442 results. 13. PsycINFO; EXPERIMENTAL DESIGN/; 9288 results. 14. PsycINFO; controlled.ti,ab; 83052 results. 15. PsycINFO; (clinical adj3 study).ti,ab; 8127 results. 16. PsycINFO; trial.ti,ab; 70442 results. 17. PsycINFO; "treatment outcome clinical trial".md; 27915 results. 18. PsycINFO; 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17; 581273 results. 19. PsycINFO; 7 AND 18; 174 results.		
Embase	9. EMBASE; DIETARY SUPPLEMENTS/ OR VITAMIN THERAPY/ OR exp VITAMINS/; 502115 results. 10. EMBASE; mineral*.ti,ab; 140538 results. 11. EMBASE; FOOD/; 53473 results. 12. EMBASE; "food stuffs".ti,ab; 336 results. 13. EMBASE; 9 OR 10 OR 11 OR 12; 672326 results. 14. EMBASE; 8 AND 13; 8057 results. 15. EMBASE; exp VITAMIN/; 464378 results. 16. EMBASE; 10 OR 11 OR 12 OR 15; 636642 results. 17. EMBASE; 8 AND 16; 7510 results. 18. EMBASE; random*.ti,ab; 903966 results. 19. EMBASE; factorial*.ti,ab; 23398 results. 20. EMBASE; (crossover* OR cross-over*).ti,ab; 69965 results. 21. EMBASE; placebo*.ti,ab; 202525 results. 22. EMBASE; (doubl* ADJ blind*).ti,ab; 143754 results.	722	0

	23. EMBASE; (singl* ADJ blind*).ti,ab; 14685 results. 24. EMBASE; assign*.ti,ab; 242860 results. 25. EMBASE; allocat*.ti,ab; 85555 results. 26. EMBASE; volunteer*.ti,ab; 178196 results. 27. EMBASE; CROSSOVER PROCEDURE/; 40306 results. 28. EMBASE; DOUBLE BLIND PROCEDURE/; 115609 results. 29. EMBASE; RANDOMIZED CONTROLLED TRIAL/; 350916 results. 30. EMBASE; SINGLE BLIND PROCEDURE/; 18869 results. 31. EMBASE; 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30; 1437317 results. 32. EMBASE; 17 AND 31; 722 results.		
Medline	8. MEDLINE; exp DEMENTIA/; 123817 results. 9. MEDLINE; DIETARY SUPPLEMENTS/ OR VITAMIN THERAPY/ OR exp VITAMINS/; 290709 results. 10. MEDLINE; mineral*.ti,ab; 118047 results. 11. MEDLINE; FOOD/; 24094 results. 12. MEDLINE; "food stuffs".ti,ab; 278 results. 13. MEDLINE; 9 OR 10 OR 11 OR 12; 422560 results. 14. MEDLINE; 8 AND 13; 1753 results. 15. MEDLINE; "randomized controlled trial".pt; 389609 results. 16. MEDLINE; "controlled clinical trial".pt; 89898 results. 17. MEDLINE; randomized.ab; 309398 results. 18. MEDLINE; placebo.ab; 159909 results. 19. MEDLINE; "drug therapy".fs; 1748083 results. 20. MEDLINE; randomly.ab; 223322 results. 21. MEDLINE; trial.ab; 322179 results. 22. MEDLINE; groups.ab; 1408235 results. 23. MEDLINE; 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22; 3453594 results. 24. MEDLINE; 14 AND 23; 826 results.	826	0
Summary	**NA**	**NA**	

Disclaimer

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