Individually modifiable risk factors to ameliorate cognitive aging: a systematic review and meta-analysis

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Key words: COGNITION, COGNITIVE ACTIVITY, COGNITIVE AGING, DEHYDROEPIANDROSTERONE, FOLATE, GINKGO BILOBA, MENOPAUSAL HORMONE THERAPY, ISOFLAVONES, MEDITERRANEAN DIET, MEMORY, META-ANALYSIS, MINDFULNESS, OMEGA-3 FATTY ACIDS, PHYSICAL EXERCISE, SOCIAL ENGAGEMENT, SYSTEMATIC REVIEW, TAI CHI, VITAMIN B12, VITAMIN D

ABSTRACT

A number of health and lifestyle factors are thought to contribute to cognitive decline associated with age but cannot be easily modified by the individual patient. We identified 12 individually modifiable interventions that can be implemented during midlife or later with the potential to ameliorate cognitive aging. For ten of these, we used PubMed databases for a systematic review of long-duration (at least 6 months), randomized, controlled trials in midlife and older adults without dementia or mild cognitive impairment with objective measures of neuropsychological performance. Using network meta-analysis, we performed a quantitative synthesis for global cognition (primary outcome) and episodic memory (secondary outcome). Of 1038 publications identified by our search strategy, 24 eligible trials were included in the network meta-analysis. Results suggested that the Mediterranean diet supplemented by olive oil and tai chi exercise may improve global cognition, and the Mediterranean diet plus olive oil and soy isoflavone supplements may improve memory. Effect sizes were no more than small (standardized mean differences 0.11–0.22). Cognitive training may have cognitive benefit as well. Most individually modifiable risk factors have not yet been adequately studied. We conclude that some interventions that can be self-initiated by healthy midlife and older adults may ameliorate cognitive aging.

INTRODUCTION

Each of us is responsible for our own health, and many aspects of healthy aging are under our direct control. With good reason, we are admonished to stop smoking, exercise regularly, and use sun screen. Concerns with memory and cognitive abilities are increasingly common in midlife and older adulthood. For cognitive aging, advice abounds, but it is less certain what the individual can do to maintain or improve mental abilities. The purpose of this systematic review is to evaluate evidence on (a) common, modifiable risk factors for (b) cognitive aging that are (c) largely under the individual's personal control and (d) can be implemented in midlife or later.

We do not focus directly on factors linked to the risk of dementia. Interventions that might prevent cognitive aging are not necessarily identical to those that might reduce risk of Alzheimer's disease or another dementia. There are, however, shared risk factors. Moreover, an intervention that ameliorates cognitive aging would be expected at the same time to reduce the likelihood of dementia by augmenting cognitive reserve, improving brain health, or both[1]. Cognitive reserve is enhanced by increasing the capacity, efficiency or redundancy of brain areas and neural pathways used when a cognitive task is performed[2]. Educational attainment, for example, is associated with reduced risk of dementia[3]. Brain health might be boosted by improved microcirculation, reduced oxidative

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REVIEW

DOI: 10.3109/13697137.2015.1078106

Received 24-07-2015
Accepted 28-07-2015

stress, enhanced glymphatic clearance of toxic metabolites, and other mechanisms.

Cognitive aging, mild cognitive impairment, and dementia

Cognitive abilities change over the life span, and performances on many – but not all – cognitive tasks show decline during midlife and older adulthood. The most severe form of cognitive deterioration is dementia, also referred to as major neurocognitive impairment. Dementia is caused by specific brain pathologies, such as the neuritic plaques and neurofibrillary tangles of Alzheimer's disease or cerebral infarction characteristic of dementia due to cerebral vascular disease. In most instances, dementia is preceded by a stage of milder decline (mild cognitive impairment, or MCI)[4], where the overall pathological burden is less severe than in dementia.

Cognitive aging represents decline in the absence of specific dementia pathologies. The underlying physiological processes are poorly characterized but are not thought to eventuate in dementia, absent co-existing dementia pathologies. Cognitive aging and MCI, however, are not always easily distinguished, and by the tenth decade of life some degree of dementia pathology is near-universal.

Midlife and beyond

Our analyses focus on interventions that can be implemented in midlife or later, a time when cognitive concerns are heightened, and presumably before there is evidence of pathological decline indicative of MCI or dementia. We include men as well as women because – apart from hormonal exposures – many modifiable risk factors pertain to both sexes, and many clinical trials still do not report separate outcomes for women and men.

For women, midlife is conceptualized to begin with the menopausal transition, as the reproductive phase of a woman's life draws to a close. Natural menopause, defined retrospectively after 12 months of amenorrhea[5], occurs at a median age of 51 years, and menstrual cycle irregularity characteristic of the menopausal transition begins on average about 4 years before. For men, where reductions in gonadal testosterone occur gradually throughout adult life[6], midlife might somewhat arbitrarily be said to begin at age 50. For women and men, midlife continues up until age 65 years, the traditional threshold for older adulthood.

Individually modifiable risk factors

In their exhaustive report on preventing Alzheimer's disease, MCI, and cognitive decline, Williams and colleagues[7] tackled a broad range of exposures and interventions. A number of factors identified in their analyses are of public health import yet do not offer meaningful opportunities for at-risk individuals at midlife or older.

This dilemma is especially true for medical conditions. Important disorders considered by Williams and colleagues, such as diabetes mellitus, hypertension, hyperlipidemia, and depression, require treatment regardless of how the illness might – or might not – impact cognitive aging. For most prescription drugs, options for individual patients are similarly limited. Side-effect profiles and personal preference can help guide selection, but the decision whether or not to treat is usually not open to debate. Cigarette smoking can be viewed analogously. This lifestyle factor is strongly associated with cardiovascular disease, stroke, lung cancer, and overall mortality. Public health exhortations to stop smoking will be largely unaffected by cognitive considerations. The individual smoker already knows she should stop.

Williams and colleagues[7] also discuss social factors associated with cognitive health. Some, however, cannot be addressed by middle-age and older adults. One's early childhood environment is not modifiable in adulthood. Most critical decisions on education or occupation are made well before midlife. Marital status can change at any age but would seem difficult to modify on the basis of cognitive concerns.

The midlife or older adult, however, has direct control over many lifestyle practices and nutritional factors. In addition, menopausal hormone therapy (MHT) is a notable exception to the non-discretionary nature of prescription drugs. For its most common indication – the treatment of moderate to severe vasomotor symptoms – its use *is* often viewed as discretionary. There are alternative forms of pharmacologic and non-pharmacologic therapies[8], which are often recommended in preference to MHT. A woman's informed decision is increasingly the critical factor in whether MHT is prescribed.

Risk factor selection

Based on these considerations, we identified 12 individually modifiable factors. For ten of these, we undertook a systematic review and quantitative synthesis. For two others, we relied on recently published meta-analyses (Table 1). Each selected intervention can be implemented during or after midlife. For each, the key question was, 'What are the cognitive effects of the intervention?'. Because randomized, controlled trials provide the strongest evidence for causality, our systematic reviews and synthesis were based on clinical trial findings. We used other evidence, including findings from longitudinal observation and prior systematic reviews, to frame the issues and discuss our results.

METHODS

Approach

Our approach is given below and summarized in Table 2.

Table 1 Personally modifiable, midlife and older life interventions with the potential to ameliorate cognitive aging

Factor	*Classification*
B-vitamin supplements*	Nutritional supplement
Dehydroepiandrosterone	Nutritional supplement or prescription drug†
Ginkgo biloba extract	Nutritional supplement
Mediterranean diet	Dietary factors
Menopausal hormone therapy**	Prescription drug
Mindfulness	Lifestyle
Omega-3 polyunsaturated fatty acids	Dietary factor or nutritional supplement
Social engagement	Lifestyle
Soy isoflavones††	Dietary factor or nutritional supplement
Vitamin D supplements‡	Nutritional supplement
Cognitive activity and cognitive training	Lifestyle
Physical activity (aerobic exercise)	Lifestyle

*, Folic acid, vitamin B12, and/or vitamin B6, not part of a broadly construed nutritional or multivitamin supplement; †, dietary supplement in the US, controlled drug in most other countries; ‡, not part of a broadly construed nutritional or multivitamin supplement; **, oral, transdermal or parenteral, excludes topical (vaginal) formulations; ††, soy food products or soy isoflavone supplements

Evidence

Systematic searches were based on randomized, controlled trials involving a single active intervention and a placebo or presumably inactive comparator. Where blinding was feasible – for example, when the intervention was a prescription drug or nutritional supplement – we sought confirmation that participants and evaluators were blinded. Where participant blinding was not feasible – for example, tai chi exercise or the Mediterranean diet – we required blinded outcome assessment. To reduce publication bias[9], we required evaluable outcomes from at least 50 trial participants. Because we were interested in long-term, sustained cognitive benefit, we required at least 6 months between intervention initiation and outcome assessment.

Participant characteristics

Participants of eligible trials were midlife or older, recruited from a generally healthy population, and without MCI, dementia, or a specific medical disorder. We allowed at-risk populations (e.g. elevated serum concentrations of homocysteine) without end-organ disease (e.g. stroke). For samples with younger adults, the mean age had to be at least 50 years. We considered studies of women, men, and both sexes combined. Most trials included men and women; very few provided sex-specific cognitive outcome data that would allow an examination of possible interactions by sex. For hormonal interventions, we were interested in the possibility that a woman's age or temporal proximity to menopause might modify effects of the intervention. Few trials provided these data, however, and we were unable to address issues of timing in a systematic manner.

Table 2 Inclusion and exclusion criteria for systematic review

Category	*Criteria*
Study populations	Midlife and older adult women or men; drawn from a generally healthy general population; without dementia or mild cognitive impairment
Sample size	At least 50 participants with evaluable outcomes
Interventions	See text and Table 1
Duration	6 months or longer
Evaluable outcomes	Change in cognition, based on objective, quantitative neuropsychological tests*
Primary cognitive outcome	Global cognition: based on all available neuropsychological tests, including tests of episodic memory, general intelligence, and screening cognition
Secondary cognitive outcome	Episodic memory: based on tests of verbal or non-verbal learning and recall (immediate and delayed recall of supraspan information, including recognition and incidental recall)†

*, Excluded tests of 'premorbid' intelligence, such as tests of vocabulary or the pronunciation of orthographically irregular words, and tasks primarily conceptualized as non-cognitive, such as finger-tapping; †, examples are the Benton Visual Retention Test, California Verbal Learning Test, Hopkins Verbal Learning Test, and paired-associates learning. General intelligence encompassed tests of working memory, executive functioning, semantic memory, perceptual speed, and visuoconstruction. Examples of screening cognitive tests (screening cognition) are the Mini-Mental State examination and the Telephone Interview of Cognitive Status

Search strategy and data abstraction

We searched PubMed databases through May 2015 to identify eligible trials in any language, as long as an English-language abstract was available. To identify other clinical trials, we examined reference lists from acquired trials and recent meta-analyses. Medical Subject Heading (MeSH) search terms and keywords for searches are in Supplemental Table S1, to be found online at http://informahealthcare.com/doi/abs/10.3109/13697137.2015.1078106.

Using prespecified inclusion and exclusion criteria, titles and abstracts were examined for potential relevance. Neuropsychological tests were categorized as tests of memory or general intelligence or as screening cognitive tests (Table 2). Memory tests were conceptualized as representing cognitive functions mediated by the hippocampus and adjacent medial temporal lobe areas, and general intelligence tests as representing functions mediated by neocortical association cortex.

Screening cognitive tests were relative short instruments that incorporated both memory and general intelligence items. Data from published reports were summarized in evidence tables by one reviewer and verified by a second. Other studies were reviewed qualitatively.

Data synthesis

We focused on continuous measures of cognitive function. Categorical ratings based on cut scores are often arbitrary, of uncertain clinical relevance, and fail to take advantage of the full range of information contained within a continuous measure. Although categorical ratings such as transition to MCI are clinically meaningful, they typically involve assessment of both cognitive and non-cognitive processes. The transition also implicates specific pathological processes, such as those linked to Alzheimer's disease[10]. We were interested in cognitive decline independent of non-cognitive change and without implicit links to inferred pathologies. Our primary endpoint was global cognition derived from all neuropsychological test scores. Our secondary outcome was memory based both on verbally mediated tests of episodic memory and on tests less amenable to verbal encoding and retrieval strategies. We recognize that some interventions might have relatively isolated, domain-specific effects, or that some effects might be positive within one cognitive domain and neutral or negative in another. However, we were particularly concerned with the net benefit or harm of an intervention on overall cognitive functioning and, secondarily, on overall memory skills.

Statistical methods

We undertook a network meta-analysis to examine effects of individually modifiable risk factors on cognitive outcomes. This approach combines information from multiple trials that compare two or more interventions for a given disorder and provides indirect comparisons between interventions in different studies[11, 12]. Neuropsychological tests were identified as providing memory (secondary outcome), general intelligence or screening cognitive test outcomes (see Table 2 for examples). Our primary outcome (global cognition) used results of all tests. Within each study, effect size variances were adjusted to account for multiple comparisons and endpoints. For each activecontrol intervention, we calculated standardized mean differences (effect sizes) and adjusted standardized errors. Effect sizes of at least 0.2 but less than 0.5 are usually described as 'small'. We report nominally significant (two-tailed $p < 0.05$) standardized mean differences ≥ 0.1 as having potential clinical relevance, and describe these differences as very small (0.1 to < 0.2) or small (0.2 to < 0.5). Our initial approach used fixed-effect models, under the assumption that interventions would have comparable effects on cognitive outcomes in other populations of healthy midlife and older populations. We used a random-effects model in sensitivity analyses[13]. Statistical analyses were performed using R statistical packages (release 3.2.0) and the meta-library Netmeta[14].

RESULTS

Of the 1038 publications identified by our search strategy (see Supplementary Table S1, to be found online at http://informahealthcare.com/doi/abs/10.3109/13697137.2015.1078106), 24 eligible clinical trials were included in the network meta-analysis, with 490 treatment arms for three groups of cognitive endpoints (memory, general intelligence, screening cognition).

A funnel plot of the treatment effect versus standardized error of the treatment effect showed a balanced distribution, as evidence for absence of publication bias. Results of fixed-effect models for memory, general intelligence and screening cognition did not indicate heterogeneity among studies (Cochran Q: $p = 0.21$–0.91, $I^2 = 0.0$–8.4%, $\tau^2 < 0.001$–0.0012); results were similar for global cognition (Cochran Q: $p = 0.31$, $I^2 = 4\%$, $\tau^2 = 0.0004$). Similar findings for memory, general intelligence and screening cognition justified a general pooling of the network (Kendall rank correlation coefficient = 0.91; good internal consistency (Cronbach $\alpha = 0.89$); 73% of variance explained by the first principal component in a principal components analysis). Results from random effects models were virtually identical to those of fixed effect models (see Supplementary Tables S2 and S3, to be found online at http://informahealthcare.com/doi/abs/10.3109/13697137.2015.1078106). Some findings for the two Mediterranean diets and two mindfulness interventions (tai chi and yoga) differed significantly from each other and are described separately.

Most interventions had no significant effect on any cognitive outcome (results for global cognition and memory are shown in Figure 1). Two had significant positive effects on global cognition that were small (Mediterranean diet + olive oil: standardized mean difference 0.22, 95% CI 0.16–0.27) or very small (tai chi exercise: standardized mean difference 0.18, 95% CI 0.06–0.29). Two interventions had small (Mediterranean diet + olive oil: standardized mean difference 0.22, 95% CI 0.12–0.32) or very small (soy isoflavone supplements: standardized mean difference 0.11, 95% CI 0.04–0.17) positive effects on memory. Nominally significant differences for global cognition below our threshold for potential clinical relevance were noted for MHT (negative: standardized mean difference -0.03, 95% CI -0.05 to -0.01), soy isoflavones (positive: standardized mean difference 0.04, 95% CI 0.002–0.08) and the Mediterranean diet + nuts (positive: standardized mean difference 0.08, 95% CI 0.03–014).

DISCUSSION

B-vitamins

There is an intriguing relation between homocysteine, B-vitamins, and cognitive impairment. Homocysteine is a sulfur-containing

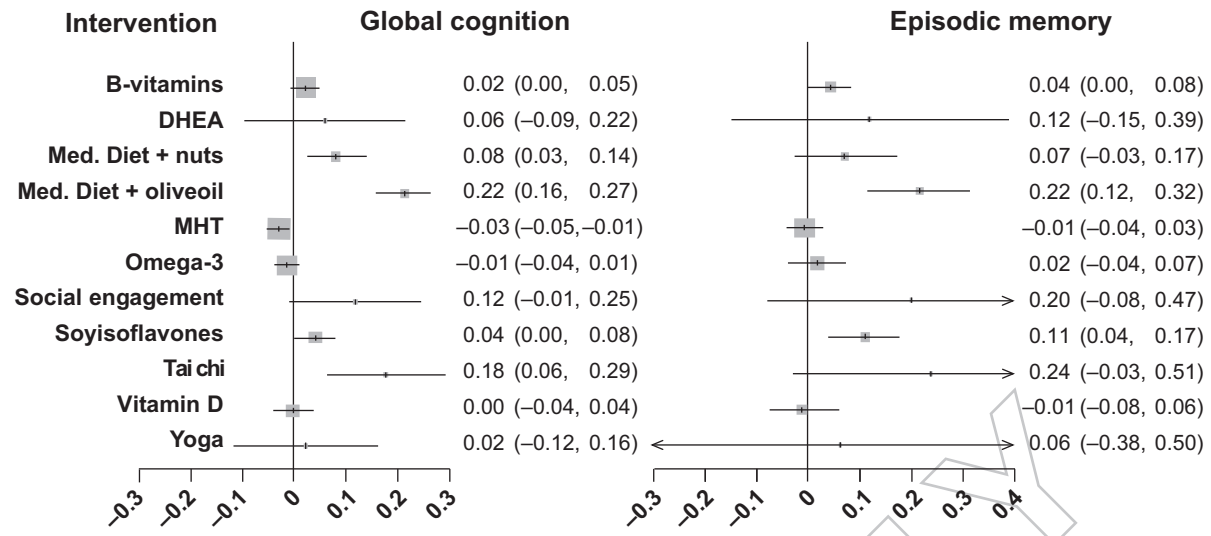

Figure 1 Results of the network meta-analysis. Fixed-effects model. Weighted standardized mean differences and 95% confidence intervals by intervention for primary (global cognition) and secondary (episodic memory) outcomes. DHEA, dehydroepiandrosterone; Med. Diet, Mediterranean diet; MHT, menopausal hormone therapy; Omega-3, omega-3 fatty acids

amino acid derived from methionine. Circulating levels increase with age, and higher homocysteine levels are associated with several important disorders, including coronary heart disease and Alzheimer's disease. Vitamin B12 (cobalamin), folic acid (vitamin B9), and vitamin B6 (pyridoxine) are cofactors in the conversion of methionine to homocysteine. Lower blood levels of folic acid and vitamin B12 are associated with Alzheimer's disease[15], and B-vitamin supplements reduce homocysteine levels[16].

Despite some encouraging findings – for example, less brain atrophy in MCI patients treated with folate and vitamin B12[17] – cognitive endpoints in randomized trials have often been null, both for dementia patients and for adults with normal cognition[18].

Four clinical trials met our search criteria, conducted over periods of 2 or 3 years[19–22]. Each was limited to older adults; participants in three trials were preselected on the basis of elevated plasma homocysteine. The active interventions were folate (400–2000 μg; four trials) plus vitamin B12 (400 or 500 μg; three trials) and vitamin B6 (10 or 25 mg; two trials). The B-vitamin interventions effectively lowered homocysteine levels. One trial reported improved memory and other cognitive skills with folate supplements[19], and three reported no cognitive effect of B-vitamin intervention[20–22]. Our meta-analysis indicated no benefit for global cognition or memory.

Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) is a weakly androgenic steroid secreted by the adrenal cortex. Small quantities are also produced within the brain. It is an intermediary in the biosynthesis of androgens and estrogens. DHEA or its sulfate ester has been hyped as a superhormone and as an anti-aging hormone. It is the most abundant circulating steroid, and levels in women and men decline dramatically with age. Interest in DHEA is particularly keen in the US, where it is classified as a dietary supplement and can be purchased over the counter. In most countries, it is available only by prescription, including the UK where it is regulated as a Class C drug.

A Cochrane review concluded that evidence did not support a beneficial effect of DHEA supplementation on cognitive function of middle-age or older adults without dementia[23]. One clinical trial met our search criteria. In this 12-month US study, 225 midlife and older men and women were randomized to DHEA 50 mg daily or placebo[24]. Consistent with the interpretation of study authors, we identified no cognitive benefit.

Ginkgo biloba

Ginkgo biloba is extracted from leaves of the *Ginkgo biloba* tree, described as a living fossil unrelated to other extant tree species. The extract is marketed as a dietary supplement, often with claims that it boosts memory. It has been tested in patients with MCI and dementia, as well as cognitive aging. Smaller trials found Ginkgo biloba extract promising in stabilizing or slowing decline in cognitively impaired patients with neuropsychiatric symptoms[25]. However, very large clinical trials in the US and France found no evidence that Ginkgo biloba reduced the incidence of dementia over a 5- or 6-year period[26,27].

Fewer studies have assessed the effects of Ginkgo biloba on cognitive aging. Cognitive decline was assessed as a secondary outcome in the Ginkgo Evaluation of Memory trial[27]. The study enrolled over 3000 community-dwelling adults aged

72 years and older. The study cohort included patients with MCI as well as cognitively normal participants. When compared to placebo, Ginkgo biloba extract over 6 years did not reduce declines in memory or other cognitive functions[28]. One clinical trial would have otherwise met our eligibility criteria, except that data were not in a form that we could extract for quantitative analysis. This 42-month US study of 118 cognitively normal participants over 84 years of age found no significant difference in memory decline between participants allocated to Ginkgo biloba or placebo[29].

Mediterranean diet

The Mediterranean diet holds promise as a palatable approach to the remediation of cognitive aging. There is no one specific Mediterranean diet. Rather, the diet reflects traditional patterns of food consumption in Greece, southern Italy, Spain, and Portugal. Characteristics include relatively large proportions of fish and relatively low proportions of meat; unsaturated fatty acids such as those found in olive oil; legumes, fruits, vegetables, and unprocessed cereal grains; moderate amounts of cheese, yogurt, and other dairy products; and moderate quantities of wine. Observational research suggests that higher adherence to a Mediterranean diet is associated with lower risks of MCI and Alzheimer's disease[30]. In the Nurses' Health Study, long-term adherence to a Mediterranean diet was associated with moderately better cognition but was unrelated to cognitive change[31].

One clinical trial met our search criteria. This was a multisite study of over 1000 Spanish participants aged 55–80 years with diabetes or other cardiovascular risk factors. Participants were randomized to one of two versions of the Mediterranean diet (supplemented with extra virgin olive oil (Mediterranean diet + olive oil) or mixed nuts (Mediterranean diet + nuts)) or to a low-fat diet control diet. At the Navarra study site, cognitive function was screened 6.5 years after randomization[32], with detailed testing on a subset of participants[33]. At the Barcelona site, neuropsychological tests were administered at baseline and about 4 years later[34]. Substantial numbers of participants were lost to follow-up or excluded. Compared to the low-fat diet, both Mediterranean diets were reported to improve aspects of cognitive function. Our meta-analysis suggested better global cognition and memory with the Mediterranean diet + olive oil.

Menopausal hormone therapy

After menopause, the depletion of ovarian follicles leads to permanent reductions in circulating levels of estrogens and progesterone, although small amounts continue to be made within the brain. These hormonal changes can affect neural processes concerned with cognition and pathological processes linked to Alzheimer's disease.

Cognitive complaints are common during midlife, and the menopausal transition may represent a time of cognitive vulnerability[35]. It is controversial whether MHT, a systemic estrogen with or without a progestational agent, benefits or harms cognitive abilities[36]. A related controversy concerns MHT effects on Alzheimer's disease. Clinical trial evidence from the Women's Health Initiative (WHI) indicates that MHT increases dementia risk in women after age 65 years and older, whereas observational data link MHT use at younger ages to reduced Alzheimer risk[37–39].

We identified six eligible trials for review and quantitative synthesis. All involved women aged 60 years and older. The MHT formulation in most trials was conjugated estrogens 0.625 mg/day with or without medroxyprogesterone acetate[40–45]; other formulations were low-dose transdermal estradiol 0.014 mg/day[46] and oral estradiol 1 mg/day and norethindrone[47]. Most comparisons with placebo were nil. In single studies, differences favored placebo on a screening cognitive test[40] and a test of verbal memory[42] and favored MHT on a non-verbal memory test[42]. Our meta-analysis of the six trials suggested no clinically meaningful effect of MHT compared to placebo on global cognition or memory, with nominal effects on global cognition (standardized mean difference -0.03) that favored placebo.

Few clinical trials of MHT have included younger postmenopausal women, and none met our inclusion criteria. Small clinical trials in surgically menopausal women suggest short-term cognitive benefit of MHT when started at the time of oophorectomy[36]. A large 4-month trial of recently menopausal women with cognitive complaints found no cognitive benefit of conjugated estrogens 0.625 mg/day plus medroxyprogesterone acetate in women aged 45–55 years[48]. A three-arm trial published too late to be included in our systematic review provides results from 693 younger postmenopausal women, mean age 53 years. Women were allocated to conjugated estrogens 0.45 mg/day and oral micronized progesterone, to transdermal estradiol 0.05 mg/day and micronized progesterone, or to placebo[49]. Cognitive outcomes at nearly 3 years did not differ significantly among treatment groups. The timing hypothesis is examined more directly in a large, recently completed randomized trial that includes both younger and older postmenopausal women randomized to oral estradiol with or without micronized progesterone, vaginal gel or placebo[50]; these findings are not yet published.

Mindfulness

Mindfulness is a mental state characterized by the focus of attention on the present moment. The attentional spotlight often includes bodily sensations – for example, proprioceptive sensations related to breathing or posture – as well as stimuli arising from the external environment. Mindfulness is intentional, non-analytical, and non-judgmental. It is an important component of meditation and mind-body practices such as yoga, tai chi, and qi gong. Mindfulness interventions have been most studied in relation to psychological stress, anxiety, and depression. Some investigators have examined cognitive outcomes as well. A recent meta-analysis of tai chi

trials concluded that tai chi improves executive cognitive functions[51].

Our systematic search focused on meditation, yoga, tai chi, and qi gong. We identified three eligible trials. A 6-month trial of Hatha yoga found no cognitive benefit compared to wait-list controls[52]. In contrast, tai chi exercises performed for 6 months (US)[53] or 40 weeks (Shanghai, China)[54] improved several neuropsychological measures. The Shanghai investigators reported significant increases in brain volume in the tai chi group compared to the no-intervention control[54]. Our meta-analysis indicates that tai chi exercise improves global cognition.

Omega-3 polyunsaturated fatty acids

Low rates of cardiovascular disease among the Inuit of Greenland are associated with high dietary intakes of fish. This observation led to studies on health effects of omega-3 fatty acids. These are n-3 long-chain polyunsaturated fatty acids, where n-3 refers to the location of the last carbon–carbon double bond, three carbons from the end of the fatty acid backbone. Two, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), are obtained primarily from certain fatty fish and their oils. The brain contains large amounts of DHA, an important component of nerve cell membranes. A Cochrane review found no clear role for omega-3 fatty acids in modifying dementia risk and no clear benefit of omega-3 supplementation on cognitive abilities in healthy older adults[55].

Three clinical trials met our search criteria. Active interventions were capsule supplements of EPA-DHA or ethyl-esters of n-3 polyunsaturated fatty acids[56–58]. The largest – a multinational trial targeting midlife and older adults with mild diabetes, abnormal fasting glucose levels, or impaired glucose tolerance – followed several thousand participants for a median of 6.2 years[56]. None of the studies reported cognitive benefit compared to placebo, and our meta-analysis confirmed the absence of cognitive effect.

Social engagement

Social engagement is postulated to reduce risk for cognitive aging and dementia. Social engagement has been variously assessed – usually by self-report – from marital status, number of people within a household, size of social network, or participation in social activities. Observational findings on social engagement and cognition are inconsistent[7].

Clinical trials that assess social engagement typically use a design that introduces other activities at the same time. For example, a pilot trial of volunteer service in elementary school settings provided participants with not only new social networks but also with new cognitive challenges and enhanced physical activity[59]. This multimodal approach is quite reasonable but makes it difficult to discern the contribution of social engagement *per se*.

One trial met our search criteria, the 40-week clinical trial conducted in Shanghai, China, referred to above, which included a social interaction arm and a no-intervention control[54]. Social interaction occurred within an 'extremely lively' discussion group that met for 1 hour, three times weekly under the direction of a group leader. We did not find a significant effect of social engagement on cognitive outcomes.

Soy isoflavones

Isoflavones are plant-derived diphenolic compounds structurally similar to estrogens. They are sometimes classified as selective estrogen receptor modulators, since biological effects can be estrogenic or antiestrogenic in the brain and in other tissues. Soy, the major dietary source of isoflavones, is a staple of traditional diets in some Asian countries. Soy isoflavones have been investigated in relation to breast cancer, prostate cancer, cardiovascular disease, menopausal vasomotor symptoms, osteoporosis, and other health outcomes. Observational studies in countries where soy dietary consumption is relatively low generally report no associations with cognition. Some investigations in populations with higher levels of consumption report adverse associations[60,61]. Cognitive effects of different soy products might differ[61].

Four clinical trials, all involving healthy postmenopausal women, met our search criteria: two from the US[62,63], one from Hong Kong[64], and one from the Netherlands[65]. Sample sizes ranged from 53 to 313, with follow-up times of 6 to 30 months. The active interventions were 80–110 mg daily of soy-derived isoflavone supplements. Where specified, supplements contained genistein, daidzein, and glycitein in the approximate ratio found in soy.

Most comparisons between treatment groups did not differ. One trial reported better category fluency in the isoflavone group[62] and one trial reported worse performance on a working memory task and better performance on a visual memory task[63]. The largest, longest trial found no treatment effect on a composite neuropsychological measure of global cognition but better performance in the isoflavone group on a composite measure of visual memory[63]. In this trial, treatment group comparisons on composite neuropsychological measures did not differ between women less than age 60 years compared to women aged 60 and above. In secondary analyses, there was an inverse association between the level of endogenous exposure (measured by urinary isoflavonoids) and performance on neuropsychological tests of general intelligence (but not memory)[66]. Our meta-analysis indicated that soy isoflavone supplements improve memory but have no effect on global cognition.

Vitamin D

Vitamin D refers to several related fat-soluble steroid derivatives, including vitamin D3 (1,25-dihydroxycholecalciferol, or 1,25-dihydroxyvitamin D) and vitamin D2 (ergocalciferol).

Few foods contain vitamin D, and vitamin D deficiency is common in many areas of the world[67]. Dietary vitamin D3 is obtained from fish oils and fortified dairy products. The major natural source comes from conversion of 7-hydroxycholesterol to cholecalciferol in the skin in the presence of sunlight (ultraviolet B). Cholecalciferol is converted in the liver to 25-hydroxyvitamin D, which in turn is converted in the kidneys to vitamin D3, the biologically active form. Vitamin D3 crosses the blood–brain barrier and is locally synthesized in the brain from 25-hydroxyvitamin D. Cell-specific gene regulation occurs through interactions with the vitamin D receptor, a member of the steroid/thyroid hormone receptor superfamily. The receptor is widely distributed in the brain and other tissues.

Serum levels of 25-hydroxyvitamin D are lower in Alzheimer's disease patients than healthy older adults[68], and lower levels are associated with poorer cognitive function and increased Alzheimer risk[69]. An Institute of Medicine report, however, found insufficient support for vitamin D benefit beyond recognized roles in calcium metabolism and bone health[70].

One clinical trial met our search criteria[71]. This was a secondary analysis from the WHI trial of calcium and vitamin D (400 IU vitamin D3 daily) versus placebo. Many participants were simultaneously enrolled in the memory study component of the WHI MHT trial. Over a mean follow-up of more than 7 years, average scores on a screening cognitive test did not differ between treatment groups, nor did other neuropsychological test scores in a subgroup included in an ancillary analysis[71]. Our meta-analysis showed no cognitive effect of vitamin D.

Cognitive and physical activities

We did not undertake systematic reviews of cognitive activity and physical activity because these lifestyle interventions have been widely publicized, and recent meta-analyses provide a basis for interpretation and conclusions.

Cognitive activity and cognitive training

Use-dependent neural plasticity forms the basis of learning, memory, and skill acquisition. Engaging in cognitively stimulating activity has the potential to ameliorate cognitive abilities diminished by aging. The Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial provides partial support for the mantra, 'use it or lose it'. This large-scale randomized trial in community-dwelling older adults used interventions focused on memory, reasoning, or processing speed[72]. Comparisons were to a no-intervention control. Training occurred in group sessions over a period of about 5 weeks, and booster sessions were provided to a subset of participants. At 2 years, each active intervention improved cognitive skills within the targeted domain but not other cognitive domains[72]. Effects of the reasoning and processing speed interventions could still be detected 10 years later[73]. Training had no effect on everyday functioning at 2 years, but at 10 years self-reported functioning had declined less in cognitive training groups compared to the no-intervention group[72,73].

A recent systematic review identified 31 randomized trials of cognitive training or mental stimulation involving older adults without known existing cognitive impairment[74]. Compared to no intervention, cognitive training significantly improved performance on several memory measures (face-name recall, immediate recall, and paired associates learning, but not delayed recall). Compared to active controls, cognitive training improved performance on tasks involving memory (recognition) and other cognitive abilities (working memory, processing speed, and overall cognitive functioning). Similar findings were reported in a preceding meta-analysis[75].

Aerobic physical activity

Aerobic exercise is thought to maintain brain health indirectly through cardiovascular benefit and directly through effects on cerebral flow, neurogenesis, increased production of brain-derived neurotrophic factor, and other mechanisms. A robust animal literature supports a role for aerobic activity in maintaining cognitive function and reducing brain pathology in animal models of Alzheimer's disease. The observational literature extends these findings to humans, showing inverse associations between regular physical exercise and cognitive decline, MCI, and Alzheimer's disease[7,76,77]. Aerobic exercise (walking) compared to stretching exercise is reported to increase the size of the anterior hippocampus[78].

A Cochrane Collaboration review assessed cognitive effects of aerobic exercise in 12 randomized trials[79]. Participants were aged 55 years and older. No intervention exceeded 6 months. There were three 6-month trials, two with at least 50 participants[52,80]. The first trial randomly assigned sedentary, healthy older adults to an aerobic (walking) or anaerobic (toning and stretching) intervention, with structured classes that met three times weekly[80]. Executive control processes improved in the walking group. The second was a three-armed trial that included walking (one class weekly plus home exercise) and a wait-list control[52]. Cognitive function at trial completion did not differ between groups. In a 40-week trial not included in the Cochrane review, cognitive outcomes did not differ between participants in a thrice-weekly walking group and a no-intervention comparison group[54]. The Cochrane meta-analysis reported no evidence for cognitive benefit when aerobic exercise was compared to an active intervention (eight trials including 506 participants) or to no intervention at all (six trials, 296 participants)[79]. Improved cardiorespiratory fitness was not associated with cognitive improvement. The authors concluded that aerobic exercise, including activities that

improve cardiovascular fitness, provides no cognitive benefit in healthy older adults.

General discussion

A number of factors under an individual's control might improve cognitive aging and – although not a focus of this review – at the same time reduce dementia risk through enhanced cognitive reserve and brain health. Unfortunately, evidence in many areas is still inadequate. This is true not only for medical and psychiatric disorders, most prescription medications, and early life exposures[7] but also for the individually modifiable factors considered in this review. Only four interventions in our meta-analysis included data from three or more clinical trials (B-vitamins, omega-3 polyunsaturated fatty acids, MHT, and soy isoflavones). Wide confidence intervals for some treatment effects (Figure 1) reflect the small number of trials and relatively small sample sizes.

Most interventions considered in our meta-analysis did not show clinically meaningful effects on global cognition or memory, and none showed effects that could be characterized as large, or even medium. Cognitive efficacy of the Mediterranean diet was supported by just one trial, with data from two study sites. It is difficult to know which components of this multifaceted nutritional intervention contributed to observed benefit. Because benefit in this dietary trial was most apparent in the arm receiving olive oil supplements, findings may not generalize to other versions of the Mediterranean diet.

Tai chi exercise also emerged as an intervention that may benefit cognitive aging. We identified only two eligible trials. We classified tai chi as a mindfulness intervention, but this Eastern exercise also involves skill learning and aerobic activity of mild-to-moderate intensity, taught in a socially engaging group setting. Beneficial effects of soy isoflavone supplements on memory (but not global cognition) and effects of cognitive training are other promising avenues for additional research. It should pointed out that isoflavone trials involved only women. High isoflavone dosages in these trials approximate levels of dietary consumption in several Asian countries but greatly exceed levels found in Western diets[81]. Our MHT results support guideline recommendations that MHT should not be used to ameliorate cognitive aging[82,83]. However, it is important to recognize that few clinical trials of MHT have included younger postmenopausal women and none has focused specifically on the largest group of women for whom MHT is indicated, namely women with moderate-to-severe vasomotor symptoms.

There are limitations to our findings. We were unable to consider all individually modifiable risk factors, and our search strategy may not have identified all eligible trials for factors that we did consider. An intervention might reduce dementia risk without necessarily improving cognitive aging. Exclusion of small trials to reduce publication bias could introduce other biases, and we did not formally evaluate trial quality. The focus on single interventions may underestimate effects of multimodal or combined approaches. Cognitive aging does not begin at midlife[84], and effects of some individually modifiable interventions may be greater if implemented at an earlier age.

We conclude that individual choices can and do affect cognitive aging. Beneficial effects, when present, are likely to be modest but are nonetheless potentially important. However, we do not make specific recommendations in the absence of stronger evidence of meaningful effectiveness. Further research, particularly on dietary factors, cognitive activity, and multimodal leisure activities such as tai chi exercise seem especially warranted.

ACKNOWLEDGEMENTS

We thank Rachael Smith and Barbara C. Henderson for assistance with data verification.

Conflict of interest Philippe Lehert, Eef Hogervorst and Victor Henderson declare no conflict of interest for this study. Paulina Villaseca has received honoraria for lectures and for acting as a member of an Advisory Board for Glaxo Smith & Kline. Pauline Maki has served as a consultant for Noven, Abbott, and Pfizer.

Source of funding Supported by National Institutes of Health grants R01AG034639 and P50AG047366.

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Supplementary materials available online

Table S1 Search terms used in PubMed searches
Table S2 Cognitive effects of individually modifiable factors, random-effects model
Table S3 Effects of individually modifiable interventions: general intelligence (non-memory) outcomes

Supplementary material for Lehert P. et al. Individually modifiable risk factors to ameliorate cognitive aging: a systematic review and meta-analysis, Climacteric. 2015; doi: 10.3109/13697137.2015.1078106.

Supplementary Table S1 Search terms used in PubMed searches

Search category	*Search terms*
Outcomes	"memory"[MeSH Terms] OR "memory"[All Fields] OR "cognition"[MeSH Terms] OR "cognition"[All Fields] OR "cognitive"[All Fields]
Limitations	"Randomized Controlled Trial"[ptyp] AND "adult"[MeSH Terms]
Interventions[*]	
B vitamins (Vitamin B12, folic acid, vitamin B6) (79 | 4)	"vitamin b 12"[MeSH Terms] OR "vitamin b 12"[All Fields] OR ("vitamin"[All Fields] AND "b12"[All Fields]) OR "vitamin b12"[All Fields] OR "cobalamin"[All Fields]) OR "vitamin b 6"[MeSH Terms] OR "vitamin b 6"[All Fields] OR "pyridoxine"[All Fields] OR "folic acid"[MeSH Terms] OR "folate"[All Fields] OR "folic acid"[All Fields]
DHEA (38 | 1)	("dehydroepiandrosterone sulfate"[MeSH Terms] OR "dehydroepiandrosterone"[MeSH Terms] OR "dehydroepiandrosterone"[All Fields] OR "dehydroepiandrosterone sulfate"[All Fields] OR "prasterone"[All Fields] OR "dhea*"[All Fields]
Ginkgo biloba (108 | 0[†])	"ginkgo biloba"[MeSH Terms] OR ("ginkgo"[All Fields] AND "biloba"[All Fields]) OR "ginkgo biloba"[All Fields] OR ("ginkgo"[All Fields] AND "biloba"[All Fields]) OR "ginkgo biloba"[All Fields] OR "EGb 761"[All Fields]
Mediterranean diet (7 | 1[‡])	"diet, mediterranean"[MeSH Terms] OR ("diet"[All Fields] AND "mediterranean"[All Fields]) OR "mediterranean diet"[All Fields] OR ("mediterranean"[All Fields] AND "diet"[All Fields])
Menopausal hormone therapy (237 | 6[§])	"hormone replacement therapy"[MeSH Terms] OR "oestrogen"[All Fields] OR "estrogens"[Pharmacological Action] OR "estrogens"[MeSH Terms] OR "estrogens"[All Fields] OR "estrogen"[All Fields]
Mindfulness (306 | 3)	"mindfulness"[MeSH Terms] OR "mindfulness"[All Fields]) OR "tai ji"[MeSH Terms] OR "tai ji"[All Fields] OR "tai chi"[All Fields] OR ("qigong"[MeSH Terms] OR "qigong"[All Fields] OR "qi gong"[All Fields] OR "meditation"[MeSH Terms] OR "meditation"[All Fields] OR "yoga"[MeSH Terms] OR "yoga"[All Fields] OR "mind-body"[All Fields]
Omega-3 polyunsaturated fatty acids (56 | 3)	"fatty acids, omega-3"[MeSH Terms] OR "omega-3"[All Fields] OR "alpha-linolenic acid"[MeSH Terms] OR "docosahexaenoic acids"[MeSH Terms] OR "eicosapentaenoic acid"[MeSH Terms] OR "linolenic"[All Fields] OR "docosahexaenoic"[All Fields] OR "eicosapentaenoic"[All Fields] OR "n 3 polyunsaturated fatty acid"[All Fields] OR "n 3 polyunsaturated fatty acids"[All Fields]
Social engagement and social support (163 | 1)	"social"[All Fields] AND ("engagement"[All Fields] OR "participation"[All Fields] OR "activity"[All Fields])
Soy isoflavones (22 | 4)	soy[All Fields] OR "isoflavones"[MeSH Terms] OR "isoflavones"[All Fields] OR "isoflavone"[All Fields]) OR "soy foods"[MeSH Terms] OR ("soy"[All Fields] AND "foods"[All Fields]) OR "soy foods"[All Fields] OR "tofu"[All Fields]
Vitamin D (22 | 1)	"vitamin d"[MeSH Terms] OR "vitamin d"[All Fields] OR "ergocalciferols"[MeSH Terms] OR "ergocalciferols"[All Fields] OR "cholecalciferol"[MeSH Terms] OR "cholecalciferol"[All Fields]
Cognitive training and cognitive activity	Reviewed on basis of recent meta-analysis[‖]
Physical activity (aerobic exercise)	Reviewed on basis of recent meta-analysis[‖]

[*]Numbers in parentheses represent number of citations | number of eligible trials. [†]Data from one otherwise eligible trial were not in a form that could be extracted for analysis (see text). [‡]Three publications; one trial. [§]Eight publications; six trials. An additional trial published after our systematic search is described in the text. [‖]We did not undertake an independent systematic search on these topics (see text)
DHEA = dehydroepiandrosterone or dehydroepiandrosterone sulfate

Supplementary Table S2 Cognitive effects of individually modifiable interventions: random-effects model

	Global cognition		*Episodic memory*	
Intervention	*Standardized mean difference*	*95% CI*	*Standardized mean difference*	*95% CI*
B-vitamins	0.02	−0.01 to 0.05	0.04	0.00 to 0.08
Dehydroepiandrosterone	0.06	−0.10 to 0.22	0.12	−0.15 to 0.39
Mediterranean diet + mixed nuts	0.08	0.03 to 0.14	0.07	−0.03 to 0.17
Mediterranean diet + olive oil	0.22	0.16 to 0.27	0.22	0.12 to 0.32
Menopausal hormone therapy	−0.03	−0.05 to 0.00	−0.01	−0.04 to 0.03
Omega-3 fatty acids	−0.02	−0.04 to 0.01	0.02	−0.04 to 0.07
Social engagement	0.12	−0.02 to 0.25	0.20	−0.08 to 0.47
Soy isoflavones	0.04	0.00 to 0.08	0.11	0.04 to 0.17
Tai chi exercise	0.18	0.06 to 0.29	0.24	−0.03 to 0.51
Vitamin D	0.00	−0.04 to 0.04	−0.01	−0.08 to 0.06
Yoga	0.02	−0.12 to 0.17	0.06	−0.38 to 0.50

Standard mean differences and 95% confidence intervals by intervention for primary (global cognition) and secondary (episodic memory) outcomes. Estimates from fixed-effects and random-effects models are very similar

Supplementary Table S3 Effects of individually modifiable interventions: general intelligence (non-memory) outcomes

	Fixed effects model		*Random effects model*	
Intervention	*Standardized mean difference*	*95% CI*	*Standardized mean difference*	*95% CI*
B-vitamins	0.01	−0.03 to 0.04	0.00	−0.04 to 0.04
Dehydroepiandrosterone	0.09	−0.13 to 0.31	0.09	−0.14 to 0.31
Mediterranean diet + mixed nuts	0.08	0.00 to 0.15	0.08	0.00 to 0.15
Mediterranean diet + olive oil	0.21	0.14 to 0.28	0.21	0.14 to 0.29
Menopausal hormone therapy	−0.03	−0.06 to 0.01	−0.02	−0.06 to 0.02
Omega-3 fatty acids	−0.04	−0.08 to -0.01	−0.05	−0.09 to 0.00
Social engagement	0.09	−0.06 to 0.24	0.09	−0.06 to 0.24
Soy isoflavones	0.01	−0.05 to 0.06	0.01	−0.05 to 0.06
Tai chi exercise	0.14	0.01 to 0.27	0.14	0.01 to 0.27
Vitamin D	0.00	−0.06 to 0.06	0.00	−0.07 to 0.07
Yoga	0.02	−0.13 to 0.17	0.02	−0.14 to 0.17

Standard mean differences and 95% confidence intervals by intervention for general intelligence outcomes. General intelligence was not a primary or secondary outcome, and results are not interpreted in the text