Epidemiologic Reviews
Vol. 30, 2008
DOI: 10.1093/epirev/mxn010
Advance Access publication September 8, 2008


# Dementia Prevention: Methodological Explanations for Inconsistent Results

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*Accepted for publication May 29, 2008.*

The prevention of neurodegenerative dementias, such as Alzheimer disease, is a growing public health concern, because of a lack of effective curative treatment options and a rising global prevalence. Various potential risk or preventive factors have been suggested by epidemiologic research, including modifiable lifestyle factors, such as social contacts, leisure activities, physical exercise, and diet, as well as some preventive pharmacologic strategies, such as hormone replacement therapy, nonsteroidal antiinflammatory drugs, and *Ginkgo biloba*. Some factors have been targeted by interventions tested in randomized controlled trials, but many of the results are in conflict with observational evidence. The aim of this paper is to review the epidemiologic data linking potential protective factors to dementia or cognitive decline and to discuss the methodological limitations that could explain conflicting results. A thorough review of the literature suggests that, even if there are consistent findings from large observational studies regarding preventive or risk factors for dementia, few randomized controlled trials have been designed specifically to prove the protective effects of interventions based on such factors on dementia incidence. Because of the multifactorial origin of dementia, it appears that multidomain interventions could be a suitable candidate for preventive interventions, but designing such trials remains very challenging for researchers.

Alzheimer disease; bias (epidemiology); cognition disorders; dementia; epidemiologic research design; primary prevention; randomized controlled trials as topic; risk factors

Abbreviations: APOE, apolipoprotein E; NSAID, nonsteroidal antiinflammatory drug; WHIMS, Women's Health Initiative Memory Study; WHISCA, Women's Health Initiative Study of Cognitive Aging; WHS, Women's Health Study.

## INTRODUCTION

Neurodegenerative dementias, such as Alzheimer disease, are a growing public health concern. The global prevalence of dementia was estimated at 24.3 million in 2001 (1) and that of Alzheimer disease was estimated at 26.55 million in 2006 (2). Over the next 40 years, the prevalence is expected to quadruple, with a particularly dramatic increase in the number of cases in developing regions (1, 2). There are currently no effective treatment options for this condition, making its prevention a priority. Prevention is feasible due to the long asymptomatic latent period of this disease. Even an intervention that delayed disease onset by just a few years could dramatically reduce the burden of this disease on society and public health-care systems (3).

To this end, there has been a recent focus on the identification of potential preventive factors for dementia, and epidemiologic research has suggested various candidates, including modifiable lifestyle factors, such as social contacts, leisure activities, physical exercise, and diet, as well as some pharmacologic strategies, such as hormone

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**TABLE 1. Search strategy**

| Study design | Included study designs* | Exclusion criteria | Databases searched | Search terms | Other sources |
|---|---|---|---|---|---|
| Longitudinal studies | Prospective longitudinal studies<br>Prospective nested case-control studies | | Medline | "Dementia" (MeSH†) OR "Alzheimer disease" (MeSH) OR "cognition disorders" (MeSH) AND "prevention" OR "risk"‡ | Reference lists of review articles; authors' own files and experience |
| Experimental studies | Randomized controlled trials | Open-label, nonrandomized, or single-blind studies; sample size, <50; duration, <3 months; use of self-reported or magnetic resonance imaging surrogate outcomes; trials with no baseline cognitive assessment | Medline | Medline‡: "cognition disorders/prevention" and "control" (MeSH) OR "dementia/prevention" and "control" (MeSH) OR "Alzheimer disease/prevention" and "control" (MeSH) OR "cognition" OR "cognitive" OR "dementia" OR "Alzheimer('s) disease" AND "prevention" AND "randomized controlled trials" | Reference lists of review articles; authors' own files and experience |
| | | | Clinicaltrials.gov | Clinicaltrials.gov: "dementia" OR "Alzheimer" OR "cognition" AND "prevention" | |

* Reviews and meta-analyses were also identified during both searches.
† MeSH, Medical Subject Headings.
‡ These common search terms were combined with specific terms for each of the risk factors assessed.

replacement therapy, nonsteroidal antiinflammatory drugs (NSAIDs), and *Ginkgo biloba*. In addition, the treatment of vascular risk factors could be important. Some of these factors have been targeted by interventions tested in randomized controlled trials, but many of the results obtained are in conflict with those obtained in observational studies. The most well-known example of this is the Women's Health Initiative Memory Study (WHIMS) (4, 5), which suggested that hormone replacement therapy may increase the risk of dementia, contrary to results of observational studies.

The aim of this article is twofold: to explore possible methodological explanations for the divergent results in dementia observational and interventional prevention studies and to consider future research perspectives. Results from recent meta-analyses, reviews, longitudinal studies, and randomized controlled trials assessing the prevention of both dementia/Alzheimer disease and cognitive decline will be included.

## SEARCH STRATEGY

Recent studies (published in the last 15 years) were identified by using the search strategy outlined in table 1.

## SUMMARY OF FINDINGS FROM PROSPECTIVE LONGITUDINAL STUDIES AND RANDOMIZED CONTROLLED TRIALS

The associations among lifestyle, pharmacologic, and vascular risk or protective factors identified in longitudinal and experimental studies are described below and summarized in table 2.

### Nutrition

*Meta-analyses or reviews.* Two reviews (6, 7) studied nutritional factors and dementia or cognitive decline. The first in 2004 (7) noted that, while there was some evidence to suggest that antioxidants, homocysteine-related vitamins, and fatty acids are related to Alzheimer disease, it was not possible at that time to generate specific dietary recommendations for Alzheimer disease prevention because of a lack of large observational studies or randomized controlled trials. The second in 2007 (6) concluded that, despite some conflicting evidence, folate and vitamin $B_{12}$ seem to have a protective role on cognitive decline and dementia and that a balanced combination of several antioxidants may be required for prevention of cognitive decline or dementia.

Two Cochrane reviews (8, 9) found no evidence for a beneficial effect on cognition of folic acid with or without vitamin $B_{12}$, in healthy or cognitively impaired older people, or of vitamin $B_6$ supplementation in older people with or without vitamin $B_6$ deficiency.

Finally, a meta-analysis of randomized controlled trials for cognitive and noncognitive disorders underlined that supplements containing high doses of beta-carotene, vitamin A, and vitamin E could increase the risk of all-cause mortality (10).

*Prospective longitudinal studies.* Homocysteine. Six studies, conducted mainly in elderly populations aged 65 or more years, found increased homocysteine levels to be associated with an increased risk of dementia/Alzheimer disease (11–13) or cognitive decline (14–16), one of which found this association to be modified by vitamin $B_{12}$ (11). However, four studies found no association between homocysteine and dementia (17) or cognitive decline (18–21).

Vitamins $B_6$ and $B_{12}$ and folate. Eight studies have found increased intake or serum concentrations of vitamin $B_6$ (16, 22), vitamin $B_{12}$ (16, 21, 23, 24), or folate (12, 16, 22–26) in mid- or late life to have a beneficial effect on dementia/Alzheimer disease incidence or cognitive decline. Nine studies found no relation between vitamin $B_6$ (26, 27), vitamin $B_{12}$ (12, 19, 20, 22, 26–29), or folate (19–21, 27, 29) and dementia/Alzheimer disease or cognitive decline, and one (24) found that increased dietary folate intake was associated with increased cognitive decline.

Antioxidants. Fourteen studies, focusing mostly on populations aged 65 or more years, have suggested that vitamin E (30–33), vitamin C (30, 33), combined vitamins E and C (33–37), flavonoids (30, 38, 39), beta-carotene (30, 33, 40), or overall antioxidant intake (41), as well as serum selenium concentrations (42, 43), may be associated with reduced dementia/Alzheimer disease incidence or reduced cognitive decline. Five studies found no association between vitamin E (37, 44, 45), vitamin C (22, 37, 44–46), flavonoids (44), or beta-carotene (22, 31, 44–46) and dementia/Alzheimer disease or cognitive decline. Results are sometimes conflicting between dietary intakes and supplements and may be dependent on the status of the ε4 type of apolipoprotein E (APOE) (31).

Fat intake. Moderate intake of polyunsaturated fatty acids was related to a lower risk of dementia in one study (47), and another (48) found high polyunsaturated fatty acid intake to be associated with better cognitive performance. Two studies found borderline significant relations between high polyunsaturated fatty acid intake and Alzheimer disease (49) or mild cognitive impairment (50). Higher intakes of monounsaturated fatty acids were associated with better cognitive performance in one study (48) and marginally associated with a decreased Alzheimer disease risk in another (49). One study found no association between a low intake of monounsaturated fatty acid or n-3 or n-6 polyunsaturated fatty acid and dementia (51). High plasma phosphatidylcholine docosahexaenoic acid was also associated with a lower risk of all-cause dementia, but not Alzheimer disease, in one study (52) and less cognitive decline in two other studies (53, 54).

Dietary patterns. One study suggested that a diverse diet may reduce the risk of dementia (55), and a second found a decreased risk of Alzheimer disease in subjects following a Mediterranean-style diet (56). Increased fish consumption was associated with a decreased risk of dementia in four studies (55, 57–59), but in one (57) this relation became borderline significant when education was controlled for. Two further studies found higher fish consumption to be related to lower cognitive decline (60, 61).

*Experimental studies (table 3).* Homocysteine-lowering vitamins. Seven randomized controlled trials have tested the effects of homocysteine-lowering vitamins (vitamin $B_6$, vitamin $B_{12}$, and/or folic acid) on cognitive performance or cognitive decline (62–68). Five (64–68) found no difference between placebo and active treatment groups, and one (62) found significant effects of 1-month vitamin $B_{12}$, vitamin $B_6$, and folate supplementation on some measures of memory performance but not on other cognitive measures. The Folic Acid and Carotid Intima-media Thickness (FACIT) Study (63) found 3-year folic acid supplementation to beneficially affect global cognitive function and the specific cognitive domains of memory and information processing.

Antioxidants. The Women's Health Study (WHS) (69) found no benefits of vitamin E on cognition after 9.6 years of supplementation.

Multivitamins. Two randomized controlled trials (70, 71) found no effect of multivitamin supplementation (including antioxidants and homocysteine-lowering vitamins) on cognitive performance, although one (70) found some benefits in one cognitive domain for the eldest participants and those at increased risk of micronutrient deficiency.

*Limitations.* In the domain of nutrition, various doses of vitamins were used in randomized controlled trials. For example, folate supplements ranged from 200 μg (70) to 2,500 μg (67) per day. The lowest dose used was lower than the US Recommended Daily Allowance (RDA) (400 μg/day). In the Folic Acid and Carotid Intima-media Thickness Study (63), which found folate supplementation to have beneficial effects on cognitive decline, 800 μg were given daily to elderly individuals with raised homocysteine concentrations. Two trials (66, 67) used higher doses of folate but detected no cognitive benefits. A longitudinal study (26) found those in the highest quintile of folate intake ($\geq$487.9 μg) to have a lower risk of developing Alzheimer disease than those in the lowest quintile ($\leq$292.9 μg), but it is unlikely that those in the highest quintile had intakes as high as those used in some randomized controlled trials. The form of vitamins may also be important. Vitamin E exists in several different forms, more than one of which may be required for a protective effect on cognition (32). In the WHS, a supplement containing only the alpha-tocopherol form was used, and no effect was observed on cognition (69).

The duration of follow-up in the longitudinal studies was generally 3 or more years, but only two randomized controlled trials (63, 69) were of similar length. The duration of both supplementation and follow-up may affect the observed effects on cognition in randomized controlled trials, but the WHS did not observe any cognitive benefits after more than 9 years of vitamin E supplementation.

In nutritional interventions, particular attention could be paid to the sensitivity of subjects to the intervention. A trial of vitamin supplementation may be more beneficial in those with poor nutritional status than in those who already have sufficient intakes. One (63) of four trials (63, 64, 66, 68) targeting persons with a particular nutritional deficiency was able to demonstrate an effect on cognitive function. Participants in dementia prevention randomized controlled trials may be in good health or may already be receiving nutritional fortification through public health measures, and they may not be those at most risk of cognitive impairment (72).

Nutrient intakes were found to be related to dementia incidence in some longitudinal studies, but none of the randomized controlled trials used dementia incidence as an outcome.

In addition, interactions between different micro- and macronutrients should be considered, especially in terms of food groups or dietary patterns (55, 56).

The analysis of the associations between consumption of nutrients and cognition is complex, and it is unlikely that one nutrient alone will play a major role. From a public

**TABLE 2. Summary of associations between risk/preventive factors and dementia or cognitive outcomes in longitudinal and experimental studies**

| Factor and association | Study design and outcome | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Longitudinal studies | | | | Experimental studies | | | |
| | Dementia/ Alzheimer disease | | Cognitive impairment or decline | | Dementia/ Alzheimer disease | | Cognitive impairment or decline | |
| | No. of studies | Reference no(s). | No. of studies | Reference no(s). | No. of studies | Reference no(s). | No. of studies | Reference no(s). |
| | | | | *Nutrition* | | | | |
| High homocysteine concentration | | | | | | | | |
| Increased risk | 2 | 11, 13 | 1 | 15 | | | | |
| Increased risk in subgroup analysis | 1 | 12 | 1 | 14 | | | | |
| Increased risk for certain outcomes only | | | 1 | 16 | | | | |
| No association | 1 | 17 | 4 | 18–21 | | | | |
| Decreased risk | | | | | | | | |
| Decreased risk in subgroup analysis | | | | | | | | |
| Decreased risk for certain outcomes only | | | | | | | | |
| Other | | | | | | | | |
| Total no. of studies | 4 | | 7 | | | | | |
| High intake or serum concentration of homocysteine-lowering vitamins | | | | | | | | |
| Increased risk | | | 1 | 24 | | | | |
| Increased risk in subgroup analysis | | | | | | | | |
| Increased risk for certain outcomes only | | | | | | | | |
| No association | | | | | | | | |
| $B_6$ | 1 | 27 | 4 | 19–21, 29 | | | 2 | 64, 66 |
| $B_9$ | 1 | 27 | 3 | 19, 20, 29 | | | 2 | 65, 67 |
| $B_{12}$ | 4 | 12, 22, 27, 28 | | | | | | |
| Decreased risk | | | | | | | | |
| $B_9$ | 2 | 22, 26 | | | | | 2 | 62, 63 |
| Decreased risk in subgroup analysis | | | | | | | | |
| $B_{12}$ | | | 1 | 24 | | | | |
| Decreased risk for certain outcomes only (vitamins $B_6$, $B_9$, $B_{12}$) | | | 1 | 16 | | | | |
| Other | | | | | | | | |
| Low levels of vitamin $B_9$ associated with an increased risk | 1 | 12 | 1 | 25 | | | | |
| Low levels of vitamins $B_9$ and $B_{12}$ associated with an increased risk | 1 | 23 | | | | | | |
| High concentration of holotranscobalamin (marker of reduced vitamin $B_{12}$) associated with more rapid cognitive decline) | 1 | 21 | | | | | | |
| Total no. of studies | 9 | | 8 | | | | | |
| High intake or serum concentration of antioxidants | | | | | | | | |
| Increased risk | | | | | | | | |
| Increased risk in subgroup analysis | | | | | | | | |
| Increased risk for certain outcomes only | | | | | | | | |
| No association | 4 | 22, 31, 37, 38 | 1 | 46 | | | 1 | 69 |
| Decreased risk | 4 | 30, 32, 37, 38 | 6 | 31, 32, 34, 35, 39, 41 | | | | |

**Table continues**

**TABLE 2. Continued**

| Factor and association | Study design and outcome | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Longitudinal studies | | | | Experimental studies | | | |
| | Dementia/ Alzheimer disease | | Cognitive impairment or decline | | Dementia/ Alzheimer disease | | Cognitive impairment or decline | |
| | No. of studies | Reference no(s). | No. of studies | Reference no(s). | No. of studies | Reference no(s). | No. of studies | Reference no(s). |
| Decreased risk in subgroup analysis | | | | | | | | |
| Vitamin E | 1 | 31 | | | | | | |
| Vitamins E and C | 1 | 36 | | | | | | |
| High beta-carotene | | | 1 | 40 | | | | |
| Decreased risk for certain outcomes only | | | | | | | | |
| Other | | | | | | | | |
| Lower intakes of vitamin C and vitamin E associated with acceleration of cognitive decline | | | 1 | 33 | | | | |
| Decline in selenium associated with cognitive decline | | | 2 | 42, 43 | | | | |
| Total no. of studies | 10 | | 11 | | | | 1 | |
| High intake of fatty acids | | | | | | | | |
| Increased risk | 2 | 30, 59 | 1 | 58 | | | | |
| Increased risk in subgroup analysis | | | | | | | | |
| Increased risk for certain outcomes only | | | | | | | | |
| No association | | | 1 | 58 | | | | |
| Decreased risk | 2 | 49, 52 | 3 | 48, 50, 61 | | | | |
| Decreased risk in subgroup analysis | 1 | 47 | | | | | | |
| Decreased risk for certain outcomes only | | | 2 | 53, 54 | | | | |
| Other | | | | | | | | |
| Total no. of studies | 5 | | 7 | | | | | |
| *Social engagement and cognitive, physical, and leisure activities* | | | | | | | | |
| High level of social engagement in late life | | | | | | | | |
| Increased risk | | | | | | | | |
| Increased risk in subgroup analysis | | | | | | | | |
| Increased risk for certain outcomes only | | | | | | | | |
| No association | | | 3 | 92–94 | | | | |
| Decreased risk | 7 | 76–82 | 6 | 83–86, 88, 89 | | | | |
| Decreased risk in subgroup analysis | | | | | | | | |
| Decreased risk for certain outcomes only | | | 1 | 87 | | | | |
| Decreased risk for certain types of exposure only | | | 2 | 90, 91 | | | | |
| Other | | | | | | | | |
| Total no. of studies | 7 | | 12 | | | | | |
| Cognitive activities or training in late life | | | | | | | | |
| Increased risk | | | | | | | | |
| Increased risk in subgroup analysis | | | | | | | | |
| Increased risk for certain outcomes only | | | | | | | | |
| No association | | | | | | | | |
| Decreased risk | 7 | 76–78, 95–98 | 6 | 92, 93, 97–100 | | | 2 | 131, 132 |
| Decreased risk for certain types of exposure and certain outcomes only | | | | | | | 1 | 133 |

**Table continues**

**TABLE 2. Continued**

| Factor and association | Study design and outcome | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Longitudinal studies | | | | Experimental studies | | | |
| | Dementia/ Alzheimer disease | | Cognitive impairment or decline | | Dementia/ Alzheimer disease | | Cognitive impairment or decline | |
| | No. of studies | Reference no(s). | No. of studies | Reference no(s). | No. of studies | Reference no(s). | No. of studies | Reference no(s). |
| Decreased risk for certain outcomes only | | | 1 | 87 | | | | |
| Other | | | | | | | | |
| Total no. of studies | 7 | | 7 | | | | 3 | |
| Physical activities or exercise in late life | | | | | | | | |
| Increased risk | | | | | | | | |
| Increased risk in subgroup analysis | | | | | | | | |
| Increased risk for certain outcomes only | | | | | | | | |
| No association | 6 | 78, 96, 97, 116, 117, 122 | 4 | 92, 118–120 | | | | |
| Decreased risk | 5 | 76, 77, 101, 102, 104 | 9 | 87, 104, 108–111, 113–115 | | | | |
| Decreased risk in subgroup analysis | 4 | 95, 103, 105, 121 | 1 | 112 | | | | |
| Decreased risk for certain outcomes only | 1 | 107 | | | | | | |
| Other (details) | | | 1 | 106 | | | | |
| Total no. of studies | 16 | | 15 | | | | | |
| High no. of leisure activities in late life | | | | | | | | |
| Increased risk | | | | | | | | |
| Increased risk in subgroup analysis | | | | | | | | |
| Increased risk for certain outcomes only | | | | | | | | |
| No association | | | | | | | | |
| Decreased risk | 1 | 77 | 4 | 94, 111, 123, 124 | | | | |
| Other | | | | | | | | |
| Total no. of studies | 1 | | 4 | | | | | |
| | | | | *Hormone replacement therapy* | | | | |
| Use of unspecified hormone replacement therapy or estrogen with or without progestin in postmenopausal women | | | | | | | | |
| Increased risk | | | | | | | | |
| Increased risk in subgroup analysis | | | | | | | | |
| Increased risk for certain outcomes only | | | | | | | | |
| No association | | | 4 | 157–160 | | | | |
| Decreased risk | 1 | 154 | 1 | 155 | | | | |
| Decreased risk in subgroup analysis | | | | | | | | |
| Decreased risk for some outcomes only | | | 1 | 156 | 1 | 4 | | |
| Other | | | | | | | | |
| Total no. of studies | 1 | | 6 | | 1 | | | |
| Use of estrogen in postmenopausal women | | | | | | | | |
| Increased risk | | | | | 1 | 4 | | |
| Increased risk in subgroup analysis | | | | | | | | |
| Increased risk for certain outcomes only | | | | | | | | |
| No association | | | | | | | 3 | 161, 163, 167 |
| | | | | | | | +3* | 162, 164, 166 |

**Table continues**

**TABLE 2. Continued**

| Factor and association | Study design and outcome | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Longitudinal studies | | | | Experimental studies | | | |
| | Dementia/ Alzheimer disease | | Cognitive impairment or decline | | Dementia/ Alzheimer disease | | Cognitive impairment or decline | |
| | No. of studies | Reference no(s). | No. of studies | Reference no(s). | No. of studies | Reference no(s). | No. of studies | Reference no(s). |
| Decreased risk | 3 | 146–148 | 1 | 150 | | | | |
| Decreased risk in subgroup analysis | | | 1 | 151 | | | | |
| Decreased risk for some outcomes only | | | 2 | 149, 152 | | | | |
| Other (trends for increased risk in long-term users for certain outcomes only) | | | 1 | 153 | | | | |
| Total no. of studies | 3 | | 5 | | 1 | | 6 | |
| Use of estrogen and progestin in postmenopausal women | | | | | | | | |
| Increased risk | | | 1 | 150 | 1 | 4 | | |
| Increased risk in subgroup analysis | | | | | | | | |
| Increased risk for certain outcomes only | | | 1 | 153 | | | | |
| Inconsistent results (detrimental effect for certain cognitive domains, beneficial effects on others) | | | | | | | 1 | 165 |
| No association | | | | | | | | |
| Decreased risk | | | | | | | | |
| Decreased risk in subgroup analysis | | | | | | | | |
| Decreased risk for some outcomes only | | | 1 | 152 | | | | |
| Other | | | | | | | | |
| Total no. of studies | | | 3 | | 1 | | 1 | |
| | | | | *Nonsteroidal antiinflammatory drugs* | | | | |
| Use of all types of NSAIDs† or unspecified NSAIDs | | | | | | | | |
| Increased risk | | | | | | | | |
| Increased risk in subgroup analysis | | | | | | | | |
| Increased risk for certain outcomes only | | | | | | | | |
| No association | 1 | 181 | | | | | | |
| Decreased risk | | | | | | | | |
| Decreased risk in subgroup analysis | | | 1 | 189 | | | | |
| Decreased risk for some outcomes only | | | | | | | | |
| Other (decreased risk but did not remain in sensitivity analysis) | 1 | 104 | | | | | | |
| Total no. of studies | 2 | | 1 | | | | | |
| Use of aspirin | | | | | | | | |
| Increased risk | | | | | | | | |
| Increased risk in subgroup analysis | 1 | 188 | | | | | | |
| Increased risk for certain outcomes only | | | | | | | | |
| No association | 3 | 179, 182, 187 | 2 | 184, 185 | | | 1 | 191 |
| Decreased risk | 1 | 178 | | | | | | |
| Decreased risk in subgroup analysis | | | | | | | | |
| Decreased risk for some outcomes only | | | 1 | 180 | | | | |
| Decreased risk in sensitivity analysis | 1 | 186 | | | | | | |
| Other | | | | | | | | |
| Total no. of studies | 6 | | 3 | | | | 1 | |

**Table continues**

**TABLE 2. Continued**

| Factor and association | Study design and outcome | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Longitudinal studies | | | | Experimental studies | | | |
| | Dementia/ Alzheimer disease | | Cognitive impairment or decline | | Dementia/ Alzheimer disease | | Cognitive impairment or decline | |
| | No. of studies | Reference no(s). | No. of studies | Reference no(s). | No. of studies | Reference no(s). | No. of studies | Reference no(s). |
| Use of nonaspirin NSAIDs | | | | | | | | |
| Increased risk | | | | | | | | |
| Increased risk in subgroup analysis | | | | | | | | |
| Increased risk for certain outcomes only | | | | | | | | |
| Increased risk in sensitivity analysis | | | | | 1 | 190 | | |
| No association | 2 | 182, 188 | 3 | 180, 183, 184 | | | | |
| Decreased risk | 3 | 178, 186, 187 | | | | | | |
| Decreased risk in subgroup analysis | 1 | 179 | | | | | | |
| Decreased risk for some outcomes only | | | | | | | | |
| Other | | | | | | | | |
| Total no. of studies | 6 | | 3 | | | | | |
| | | | | *Ginkgo biloba* | | | | |
| *Ginkgo biloba* supplementation | | | | | | | | |
| Increased risk | | | | | | | | |
| Increased risk in subgroup analysis | | | | | | | | |
| Increased risk for certain outcomes only | | | | | | | | |
| No association | 1 | 199 | | | | | 2 | 201, 202 |
| Decreased risk | | | | | | | | |
| Decreased risk in subgroup analysis | | | | | | | | |
| Decreased risk for some outcomes only | | | | | | | 1 | 200 |
| Other | | | | | | | | |
| Total no. of studies | 1 | | | | | | 3 | |
| | | | | *Blood pressure* | | | | |
| High blood pressure in midlife | | | | | | | | |
| Increased risk | 4 | 236–239 | 1 | 240 | | | | |
| Increased risk in subgroup analysis | | | | | | | | |
| Increased risk for certain outcomes only | 1 | 122 | 2 | 242, 244 | | | | |
| Increased risk for certain exposures only | | | 3 | 241, 243, 245 | | | | |
| No association | | | 1 | 246 | | | | |
| Decreased risk | | | | | | | | |
| Decreased risk in subgroup analysis | | | | | | | | |
| Decreased risk for certain outcomes only | | | | | | | | |
| Other | | | | | | | | |
| Total no. of studies | 5 | | 7 | | | | | |
| High blood pressure in late life | | | | | | | | |
| Increased risk | 1 | 211 | 4 | 82, 213, 216, 219 | | | | |
| Increased risk in subgroup analysis | 1 | 209 | 2 | 214, 218 | | | | |
| Increased risk for certain outcomes only | 3 | 107, 210, 212 | | | | | | |
| Increased risk for certain exposure measures (i.e., SBP† or DBP†) only | | | 3 | 215, 217, 220 | | | | |
| No association | 5 | 104, 230–233 | 2 | 234, 235 | | | | |
| Decreased risk | 2 | 221, 223 | 1 | 224 | | | | |

**Table continues**

**TABLE 2. Continued**

| Factor and association | Study design and outcome | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Longitudinal studies | | | | Experimental studies | | | |
| | Dementia/ Alzheimer disease | | Cognitive impairment or decline | | Dementia/ Alzheimer disease | | Cognitive impairment or decline | |
| | No. of studies | Reference no(s). | No. of studies | Reference no(s). | No. of studies | Reference no(s). | No. of studies | Reference no(s). |
| Decreased risk in subgroup analysis | 1 | 222 | | | | | | |
| Other | | | | | | | | |
| U-shaped relation between late-life blood pressure and dementia/ cognitive decline | 1 | 228 | 3 | 225–227 | | | | |
| High SBP and low DBP associated with an increased risk | 1 | 229 | | | | | | |
| Low DBP associated with an increased risk | | | | | | | | |
| Total no. of studies | 15 | | 15 | | | | | |
| Use of antihypertensive medication | | | | | | | | |
| Increased risk | | | | | | | | |
| Increased risk in subgroup analysis | | | | | | | | |
| Increased risk for certain outcomes only | | | | | | | | |
| No association | 3 | 104, 221, 250 | | | 1 | 253 | 3 | 253–255 |
| Decreased risk | 3 | 228, 247, 248 | | | 2 | 251, 252 | | |
| Decreased risk in subgroup analysis | | | | | | | | |
| Decreased risk for certain outcomes only | 1 | 249 | | | | | | |
| Other | | | | | | | | |
| Total no. of studies | 7 | | | | 3 | | 3 | |
| | | | | *Diabetes* | | | | |
| Diabetes in midlife | | | | | | | | |
| Increased risk | 2 | 122, 285 | | | | | | |
| Increased risk in subgroup analysis | | | | | | | | |
| Increased risk for certain outcomes only | | | | | | | | |
| No association | 1 | 277 | | | | | | |
| Decreased risk | | | | | | | | |
| Decreased risk in subgroup analysis | | | | | | | | |
| Decreased risk for certain outcomes only | | | | | | | | |
| Other | | | | | | | | |
| Total no. of studies | 3 | | | | | | | |
| Diabetes in late life | | | | | | | | |
| Increased risk | 6 | 231, 263, 280, 281, 283, 284 | 4 | 267, 269, 271, 273 | | | | |
| Increased risk in subgroup analysis | 2 | 276, 279 | | | | | | |
| Increased risk for certain outcomes only | | | 10 | 215, 242, 263–266, 268, 270, 274, 275 | | | | |
| No association | 6 | 107, 267, 270, 282, 286, 287 | 2 | 218, 272 | | | | |
| Decreased risk | | | | | | | | |
| Decreased risk in subgroup analysis | | | | | | | | |
| Decreased risk for certain outcomes only | | | | | | | | |
| Other | | | | | | | | |
| Total no. of studies | 14 | | 16 | | | | | |
| Treatment of diabetes | | | | | | | | |

**Table continues**

**TABLE 2. Continued**

| Factor and association | Study design and outcome | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Longitudinal studies | | | | Experimental studies | | | |
| | Dementia/ Alzheimer disease | | Cognitive impairment or decline | | Dementia/ Alzheimer disease | | Cognitive impairment or decline | |
| | No. of studies | Reference no(s). | No. of studies | Reference no(s). | No. of studies | Reference no(s). | No. of studies | Reference no(s). |
| Increased risk | 2 | 282, 283 | | | | | | |
| Increased risk in subgroup analysis | | | 1 | 264 | | | | |
| Increased risk for certain outcomes only | | | | | | | | |
| No association | | | | | | | | |
| Decreased risk | | | | | | | | |
| Decreased risk in subgroup analysis | | | | | | | | |
| Decreased risk for certain outcomes only | | | | | | | | |
| Other (increased for regimen or insulin treatment, similar risk for oral hypoglycemic drugs) | | | 1 | 269 | | | | |
| Total no. of studies | 2 | | 2 | | | | | |

* Estrogen with or without progestin according to hysterectomy status.
† NSAID, nonsteroidal antiinflammatory drug; SBP, systolic blood pressure; DBP, diastolic blood pressure.

health perspective, it is important to assess in more depth the associations among groups of nutrients or particular dietary habits that may have an impact on cognition.

### Social contacts, leisure activities, and physical exercise

*Meta-analyses or reviews.* Three reviews have assessed the effects of social and mental lifestyle factors and/or physical exercise on dementia and cognitive decline (73–75). The first (73) concluded that an active and socially integrated lifestyle in the elderly might protect against dementia, although it was suggested that the effects of social, mental, and physical lifestyle components may act through common pathways. The other two reviews (74, 75) noted some benefits of physical activity on cognition in the elderly, mainly based on longitudinal studies, but found little evidence to suggest a link with dementia/Alzheimer disease, because of a lack of randomized controlled trials in this area.

*Prospective longitudinal studies.* Social contacts and social engagement. Fourteen studies have found an inverse relation between the level of late-life social contacts or engagement and the risk of dementia/Alzheimer disease (76–82) or cognitive decline (83–89). Midlife social engagement was assessed by one of these studies (82) but was not found to be related to dementia risk.

Two studies (90, 91) found only certain measures of social engagement to be associated with better cognitive function, and four studies found no association between participation in social activities (92, 93) or social network or support measures (91, 94) and cognition.

Cognitive activities in late life. Twelve studies have demonstrated a relation between increased participation in cognitive activities in late life and a decreased risk of dementia (76–78, 95), Alzheimer disease (95–98), vascular dementia (95), or cognitive decline or impairment (87, 92, 93, 97, 99, 100). No studies were identified that failed to find an association between cognitive activities and outcomes, although the positive effects in one of the above-mentioned studies (87) were seen only in some specific cognitive domains.

Physical exercise. An increased frequency or intensity of physical exercise or activities in late life was associated with a decreased risk of dementia/Alzheimer disease (76, 77, 95, 101–107) or cognitive decline/impairment in 19 studies (87, 104, 108–115). However, nine studies found no association with dementia/Alzheimer disease (78, 96, 97, 116, 117) or cognitive decline/impairment (92, 118–120). Two studies examined the effects of midlife physical exercise on the risk of dementia in late life and found conflicting results (121, 122).

Leisure activity. Five studies found that high levels of leisure activities decreased the risk of dementia (77) or cognitive function (94, 111, 123) or decline (124), and one study (117) found the individual activities of traveling, odd jobs, knitting, and gardening to be associated with a reduced risk of dementia. Contrastingly, two studies (99, 125) did not find any of the individual everyday activities assessed (including social, experimental, and developmental activities) to be associated with cognition, although overall domain scores remained associated with the development of cognitive impairment in one study (99). Other studies (77, 93–95) have also assessed the effects of individual activities, in addition to activity domains, but there are no consistent results. Furthermore, two studies noted that the beneficial effects of cognitive, social, and physical activities on dementia (76) or cognitive decline (87) were greatest when older persons had high levels of participation in activities

in two or more domains. Again, some results were confined to only some of the cognitive domains tested (87, 123).

*Experimental studies (table 4).* Cognitive training. There has been much research into the effects of cognitive training on cognition but often with major methodological limitations, such as a lack of randomization or blinding (126, 127), small sample sizes (128), or short follow-up (129, 130).

Three recent methodologically sound randomized controlled trials (131–133) have considered the effects of cognitive training on cognitive function in the elderly; two were relatively small scale with short follow-up periods (131, 133). In the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) Study (132), 2,832 participants received a 6-week intervention (focused on memory, reasoning, and speed of processing) and were followed up for 5 years. All trials found cognitive training to have some beneficial effects on cognition, especially in the cognitive domains directly related to the intervention, and these effects were found to last up to 5 years in this study, which also found some effects on everyday functioning (132).

Physical exercise. Few trials have assessed the efficacy of standardized physical exercise on cognitive outcomes (134). Oken et al. (135) assessed the effects of a 6-month yoga intervention on cognition and quality of life in healthy seniors. Despite improving physical and quality-of-life measures, this intervention did not affect cognitive outcomes. Kramer et al. (136) compared two exercise interventions (aerobic vs. anaerobic) in the elderly and found after 6 months a substantial improvement in a specific domain (executive control tasks) in participants in the aerobic group, although other cognitive domains remained equivalent between groups.

*Limitations.* Exposure definition and measurement vary greatly among studies (73): Some used quantitative measures of numbers of social contacts or activities (77, 94, 111, 117), while others attempted to gauge their frequency or intensity (78, 95, 97) or satisfaction with social interactions (80). Several studies simultaneously assessed the effects of different types of leisure activities on dementia or cognitive decline, often grouping them into categories of ''social,'' ''physical,'' or ''intellectual'' activities (77, 78, 87, 92, 93, 95, 99). However, some activities may be associated with all three domains (e.g., traveling, going to the theater/concerts, engaging in family/charity work), making it difficult to distinguish the effects of each domain. One study (76) rated the mental, social, and physical components of each activity and then compiled domain scores, meaning that one activity could contribute to more than one domain. These researchers found that all three component scores were related to dementia risk and that the most beneficial effect was present for subjects with high scores in several components. Thus, it is hard to distinguish the effects of different exposures. Consequently, it may be hard to develop interventions concerning leisure activities on the basis of the longitudinal evidence gained so far. No randomized controlled trials have tested the effects of social engagement interventions on cognition and, although there have been various studies of cognitive training interventions, many were not methodologically sound randomized controlled trials. The randomized controlled trials described above all found some positive effects on cognition, but it is not clear if the improvements are beneficial in real-life situations, or if they affect dementia incidence.

For physical exercise, it is important to distinguish between aerobic and anaerobic exercise. The trial by Kramer et al. (136) found aerobic, but not anaerobic, exercise to improve executive function. Consistently, the yoga intervention, considered as anaerobic exercise, had no effect on cognition (135). In both studies, the duration of intervention and follow-up may have been too short to demonstrate any effect. Participants in the yoga study were healthy seniors, but exercise may be more beneficial in less healthy subjects. The participants in both trials were highly motivated to volunteer for an exercise intervention and probably differed from those who did not take part.

The frequency of exercise interventions may be important. The yoga intervention was carried out only once a week, but it may have had greater effects on cognitive function if it was carried out more often (135). It is not clear which specific aspects of cognitive function may be most affected by physical activity (137).

The window of exposure is important, even if the two longitudinal studies that assessed the effect of physical exercise in midlife report contradictory results (121, 122). The methodology was relatively similar, but the opposing results could be explained by differential adjustment for potential confounders or by the type of activity concerned. In one study (121), only leisure activities were assessed, while in the other, work-related physical activity was also considered (122). The ''well-being'' effect provided by leisure activities, suggested by certain authors as a mechanism explaining the beneficial effect of physical exercise on cognition, could explain the different results.

There remain several uncertainties in the domain of physical exercise, including how long exercise effects last after cessation of training or how much exercise is needed to reinstate previously observed benefits (137).

In conclusion, the results of longitudinal studies, many of which came from well-established, population-based cohort studies focused on aging, are largely concordant and suggest an inverse relation between the level of social contacts or engagement or of social, cognitive, or physical activities and the risk of dementia or cognitive decline. Although there is limited evidence from experimental studies, a mentally, physically, and socially active lifestyle is to be recommended in late life, because even if the cognitive benefits have not yet been entirely elucidated, at the very least, this lifestyle should bring about improved quality of life and overall health.

### Hormone replacement therapy

*Meta-analyses or reviews.* Various reviews and meta-analyses have assessed the effects of hormone replacement therapy on dementia and cognition (138–145), although most were conducted before the latest published randomized controlled trials. Meta-analyses differ in the type and characteristics of included studies. Two meta-analyses found inconsistent results (139, 141) while others reported decreased risks, but most showed statistical heterogeneity

**TABLE 3. Randomized controlled prevention trials of nutritional factors**

| First author, year (reference no.) | Trial name* | Intervention | Subjects | Sample size calculation† | No. | Length of follow-up | Cognitive outcome(s) | Scales or criteria | Intention to treat‡ | Results |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | *Vitamins* | | | | |
| Eussen, 2006 (64) | | Vitamin $B_{12}$ (1,000 μg) vs. vitamin $B_{12}$ (1,000 μg) + folic acid (400 μg) vs. placebo | Free-living elderly and older persons living in care-facility homes; ≥70 years, mild vitamin $B_{12}$ deficiency | N | 195 | 6 months | Change in cognitive function | MMSE,§ GDS,§ CDR§ | N | Neither supplementation with vitamin $B_{12}$ alone nor that in combination with folic acid was accompanied by any improvement in cognitive function. |
| Durga, 2007 (63) | FACIT | Folic acid (800 μg) vs. placebo | Men and postmenopausal women; 50–70 years; raised plasma total homocysteine (13–26 μmol/liter) | | 818 | 3 years | Change in cognitive performance | Word learning test, concept shifting test, Stroop color-word test, VFT,§ letter digit substitution test | Y | Change in memory, information-processing speed, and sensorimotor speed were significantly better in the folic acid group than in the placebo group. |
| McMahon, 2006 (66) | | Folate (1,000 μg) + vitamin $B_6$ (10 mg) + vitamin $B_{12}$ (500 μg) vs. placebo | >65 years; plasma homocysteine concentration of at least 13 μmol/liter; no suspected dementia or depression | | 276 | 2 years | Change in cognitive performance | MMSE, RAVLT,§ COWAT,§ category VFT, TMT,§ National Adult Reading Test | | No significant differences were present between the vitamin and placebo groups in cognition test scores. |
| Stott, 2005 (67) | | Folic acid (2.5 mg), vitamin $B_{12}$ (500 μg), vitamin $B_6$ (25 mg), and riboflavin (25 mg) (alone or in combination) vs. placebo | ≥65 years; ischemic vascular disease; MMSE (≥19); red blood cell folate (≥280 ng/ml); and vitamin $B_{12}$ (≥250 pg/ml) | | 185 | 1 year | Change in cognitive function | TICS,§ LDC§ | Y | Oral folic acid + vitamin $B_{12}$ was not associated with statistically significant beneficial effects on cognitive function over the short or medium term. |
| Lewerin, 2005 (65) | | Cyanocobalamin (0.5 mg) + folic acid (0.8 mg) + vitamin $B_6$ (3 mg) vs. placebo | Community-dwelling subjects; mean age, 76 (SD,§ 4) years | | 209 | 4 months | Change in cognitive performance | Digit span forwards and backwards, identical forms, visual reproduction, synonyms, block design, digit symbol, Thurstone's Picture Memory Test, figure classification | | No difference between groups was noted. |
| Bryan, 2002 (62) | | Folate (750 μg) vs. vitamin $B_{12}$ (15 μg) vs. vitamin $B_6$ (75 mg) vs. placebo | 20–92 years, healthy women | | 211 | 1 month | Change in cognitive function and mood | Boxes test, Digit Symbol Coding-120s, symbol search, digit span backward, letter number sequencing, RAVLT (IR§ + DR§), digit symbol coding-symbol recall, activity recall, the Stroop test, self-ordered pointing task, uses for common objects, TMT, VFT, excluded letter fluency, WAIS-III§ vocabulary, spot the word test | | Supplementation had a significant positive effect on some measures of memory performance only and no effect on mood. Dietary status was associated with speed of processing, recall and recognition, and verbal ability. |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Kang, 2006 (69) | WHS—cognitive substudy | Vitamin E (600 IU on alternate days) vs. placebo | ≥65 years, women | 6,377 | Up to 10 years (4 years of cognitive follow-up) | Change in cognitive performance | Three repeated assessments by telephone at 2-year intervals: TICS, a telephone adaptation of the MMSE; East Boston Memory Test (IR + DR); delayed recall of the TICS 10-word list, category fluency | | There was no difference in global score between the vitamin E and placebo groups 5.6 years and 9.6 years after randomization. The mean cognitive change over time was also similar in the vitamin E group compared with the placebo group for the global score. |
| | | | *Antioxidants* | | | | | | |
| | | | *Multivitamins* | | | | | | |
| Wolters, 2005 (71) | | Multivitamins—vitamin C (150 mg), magnesium (50 mg), vitamin E (36 mg), pantothenic acid (16 mg), beta-carotene (9 mg), pyridoxine (3.4 mg), riboflavin (3.2 mg), thiamine (2.4 mg), folic acid (400 μg), biotin (200 μg), selenium (60 μg), cobalamin (9 μg)—vs. placebo | ≥60 years, healthy, free-living women | 220 | 6 months | Change in cognitive performance | Symbol search test, WAIS-III, and the pattern-recognition test. Intelligence as assessed by the KAI§ | | Vitamin supplementation had no effect on cognitive performance after 6 months. |
| McNeill, 2007 (70) | MAVIS | Vitamin and mineral supplement—vitamin A (800 μg), vitamin C (60 mg), vitamin D (5 μg), vitamin E (10 mg), thiamin (1.4 mg), riboflavin (1.6 mg), niacin (18 mg), pantothenic acid (6 mg), pyridoxine (2 mg), vitamin $B_{12}$ (1 μg), folic acid (200 μg), iron (14 mg), iodine (150 μg), copper (0.75 mg), zinc (15 mg), and manganese (1 mg)—vs. placebo | ≥65 years | 910 | 1 year | Change in cognitive function | Digit span forward and verbal fluency | Y | Supplementation had no effect on cognitive function. |
| Toole, 2004 (68) | VISP | High-dose vitamins—pyridoxine (25 mg), cobalamin (0.4 g), and folic acid (2.5 mg)—vs. low-dose vitamins—pyridoxine (200 μg), obalamin (6 μg), and folic acid (20 μg) | ≥35 years, raised homocysteine level, nondisabling ischemic stroke; no severe cognitive impairment or refractory depression | 3,680 | 2 years | Change in cognitive function | MMSE | Y | No difference between groups was present. |

* FACIT, Folic Acid and Carotid Intima-media Thickness; WHS, Women's Health Study; MAVIS, Mineral and Vitamin Intervention Study; VISP, Vitamin Intervention for Stroke Prevention.

† Sample size calculation based on cognitive outcome (Y, based on cognitive outcome *or* post hoc calculation demonstrated sufficient power; N, no sample size calculation *or* sample size calculation not based on cognitive outcome).

‡ Intention to treat: Y, yes; N, no.

§ MMSE, Mini-Mental State Examination; GDS, Geriatric Depression Scale; CDR, Clinical Dementia Rating [Scale]; VFT, Verbal Fluency Test; RAVLT, Rey Auditory-Verbal Learning Test; COWAT, Controlled Oral Word Association Test; TMT, Trail-making Test; TICS, Telephone Interview for Cognitive Status; LDC, Letter Digit Coding; SD, standard deviation; IR, immediate recall; DR, delayed recall; WAIS-III, Wechsler Adult Intelligence Scale III; KAI, Kurztest für Allgemeine Intelligenz.

**TABLE 4. Randomized controlled prevention trials of cognitive activities and physical exercise**

| First author, year (reference no.) | Trial name* | Intervention | Subjects | Sample size calculation† | No. | Length of follow-up | Cognitive outcome(s) | Scales or criteria | Intention to treat‡ | Results |
|---|---|---|---|---|---|---|---|---|---|---|
| Mahncke, 2006 (131) | | Experimental memory training program vs. active control activity vs. no-contact control group | ≥60 years; MMSE,§ >24; mean age, 64 years | N | 182 | 3 months | Changes in neuropsychological function | MMSE | Y | Significant memory enhancement in experimental group. No significant change in matched active and no-contact controls |
| Valentijn, 2005 (133) | | Collective or individual memory training vs. control (waiting list) | Healthy individuals aged ≥55 years with subjective memory complaints; MMSE, ≥24 | | 139 | | Objective and subjective memory functioning | Objective measures: Visual Verbal Learning Test; short story test<br>Subjective measures: abridged Metamemory in Adulthood Questionnaire; Cognitive Failure Questionnaire | Y | Participants in the collective memory training group, but not the individual memory training group (who received the same intervention but individually), reported more stability in memory functioning (certain scales of a subjective memory measure) and showed positive effects in objective memory functioning (one out of two tests) |
| Willis, 2006 (132) | ACTIVE | Cognitive training interventions (memory vs. reasoning vs. speed) vs. control | ≥65 years; MMSE, >22; no functional impairment | | 2,832 | 5 years | Cognitive and functional performance | Cognitive outcomes (reasoning, memory, attention speed) and functional outcomes (ADL,§ IADL, problem solving, speed processing) | Y | Reasoning training resulted in less functional decline in self-reported IADL.§ Compared with the control group, cognitive training participants had improved cognitive abilities specific to the abilities trained that continued 5 years after the initiation of the intervention. |
| Oken, 2006 (135) | | Yoga (one class/week) vs. aerobic exercise (one class/week) vs. waiting list control | 65–85 years; no underlying medical conditions that could impair cognition | | 135 | 6 months | Change in cognitive function | Battery of cognitive measures focused on attention and alertness (i.e., the Stroop test and a quantitative electroencephalogram measure of alertness) | | No difference between groups |
| Kramer, 1999 (136) | | Aerobic exercise (walking) vs. anaerobic exercise (stretching and toning) | 60–75 years; previously sedentary | | 124 | | Change in cognitive function (pre- and postexercise) | Tasks requiring executive control (task switching, response compatibility, and stopping) | Y | Aerobic trials showed substantial improvements in performance on tasks requiring executive control compared with anaerobically trained subjects. |

* ACTIVE, Advanced Cognitive Training for Independent and Vital Elderly.

† Sample size calculation based on cognitive outcome (Y, based on cognitive outcome *or* post hoc calculation demonstrated sufficient power; N, no sample size calculation *or* sample size calculation not based on cognitive outcome).

‡ Intention to treat: Y, yes; N, no.

§ MMSE, Mini-Mental State Examination; IADL, Instrumental Activities of Daily Living; ADL, Activities of Daily Living.

(138, 141, 144) and were based on studies of poor quality (138, 139, 141, 144). It was noted that results of longitudinal studies often suggested a protective effect of hormone replacement therapy (138, 144), while earlier randomized controlled trials were inconclusive. The most recent meta-analysis (140), conducted according to Cochrane guidelines, analyzed 16 randomized controlled trials including the recent WHIMS trial. It showed ''with good evidence'' no improvement in cognition and a potential deleterious effect of some hormone replacement therapy regimens.

*Prospective longitudinal studies.* Seven studies have suggested that current or previous estrogen use alone may be associated with a decreased risk of dementia (146–148) or cognitive decline (149, 150), although in some cases effects were limited to only some specific cognitive domains or to subjects with the *APOE*E4* genotype (149, 151, 152). In two of them, an increased duration of estrogen was associated with decreased risk of dementia (147, 148). One study (153) found a trend for cognitive decline in long-term users of estrogen alone.

Past or present use of estrogen plus progestin or unspecified ''hormone replacement therapy'' was associated with a decreased risk of dementia (154) or cognitive decline (155) in four studies, although the relation was sometimes confined to certain cognitive domains (152, 156). Four studies found no clear relation between hormone replacement therapy and cognitive decline (157–160), while two (150, 153) found an increased risk of cognitive decline in long-term users.

*Experimental studies (table 5).* Eight randomized controlled trials (4, 5, 144, 161–166) studied the effects of hormone replacement therapy on dementia or cognitive decline in postmenopausal women. Participants were aged 65 or more years in all except two studies (163, 164). WHIMS (4, 5) was by far the largest study with 6,500 women treated with estrogen alone (WHI-ERT), estrogen plus progestin (WHI-PERT), or placebo for more than 5 years. The Women's Health Initiative Study of Cognitive Aging (WHISCA) (165), an ancillary study of WHIMS, assessed cognitive decline in the WHI-PERT arm. The other trials involved less than 500 subjects, with shorter follow-up (from 3 months to 3 years). The type of menopause (natural or surgical) was usually not stated. This can affect the type of hormone replacement therapy and the characteristics of the women, who may differ in terms of age, and therefore prognosis for cognitive decline. The type of hormone replacement therapy (estrogen alone (4, 161, 163, 167), estrogen with or without progestin according to hysterectomy (162, 164, 166), or estrogen plus progestin (5, 165)), route of administration (mainly oral), and dose used (e.g., between 0.01 and 2 mg of estrogen daily) were variable.

Six randomized controlled trials found no association between cognition and estrogen replacement therapy with or without progestin according to hysterectomy status (161–164, 166, 167).

The three studies based on the same trial found no protective effect of hormone replacement therapy: Estrogen plus progestin was associated with an increased risk of probable dementia (5) and decline in some cognitive functions (165), and estrogen alone (4) was associated with an increased risk of the combined mild cognitive impairment-dementia endpoint.

*Limitations.* There has been much discussion of the conflicting results of longitudinal and experimental evidence (138, 139, 168–171). Exposure definition and measurement varied greatly between longitudinal studies with lack of precision (ever/never use or past/current/never use) and assessment at one or two time points only.

Longitudinal studies cannot control for the type and dose of hormone replacement therapy, so regimen variations could explain the discrepancies observed. For example, the type of estrogen (conjugated equine estrogen) used in WHIMS may have more deleterious cognitive effects than estradiol, which is usually assessed in longitudinal studies (168).

In summary, estrogen alone or hormone replacement therapy cannot be recommended for cognitive improvement in older postmenopausal women without cognitive impairment, because the risks (notably cardiovascular disease and stroke) outweigh the potential cognitive benefits (172).

### Aspirin and other NSAIDs

*Meta-analyses or reviews.* Three meta-analyses of observational studies (cohort and nonprospective) were identified (173–175). Two assessed NSAIDs and aspirin (173, 174), and one assessed nonaspirin NSAIDs (175). The outcomes were Alzheimer disease alone (175), dementia/Alzheimer disease (174), and Alzheimer disease and any cognitive impairment (173). Some had more stringent inclusion criteria (175) than others (174). Only one (175) assessed the quality of the studies included, and two showed statistical heterogeneity (173, 174).

Etminan et al. (174) concluded that only nonaspirin NSAIDs, especially with long-term use, could decrease the risk of Alzheimer disease. These results should be taken with caution because of potential confounding (176) and heterogeneity. de Craen et al. (173) assessed 25 studies (21 of which studied Alzheimer disease, 10 prospectively) and reported conflicting results according to study design. Beneficial effects were attributed to bias. Szekely et al. (175) assessed 11 studies (including four prospective studies) and concluded that nonaspirin NSAIDs may prevent or delay the onset of Alzheimer disease, especially with long-term use.

A review of observational studies (177) concluded that long-term use of NSAIDs could significantly reduce the risk of dementia.

*Prospective longitudinal studies.* The use of NSAIDs (104, 178, 179) or aspirin (178, 180) was associated with a decreased risk of dementia or cognitive decline in four studies, although associations were restricted to some domains and age groups (180) or those with an *APOE*E4* allele (179) and, in one case, the relation did not persist after sensitivity analyses (104).

However, six studies found no clear association between NSAIDs (181–184) or aspirin (182, 184–187) and dementia or cognitive decline, and one (188) found the use of aspirin to increase the risk of dementia in *APOE*E4*-negative individuals. Four studies found increased duration of NSAID use (178, 186, 187, 189) to be associated with a lower risk of

**TABLE 5. Randomized controlled prevention trials of hormone replacement therapy**

| First author, year (reference no.) | Trial name* | Intervention | Subjects | Sample size calculation† | No. | Length of follow-up | Cognitive outcome(s) | Scales or criteria | Intention to treat‡ | Results |
|---|---|---|---|---|---|---|---|---|---|---|
| Shumaker, 2004 (4) | WHIMS; WHI-ERT | Oral CEE§ (0.625 mg) vs. placebo | Community-dwelling postmenopausal women aged 65–79 years | Y | 2,947 | Mean, 5.4 years | Dementia incidence (primary outcome); MCI incidence; cognitive function | Dementia: DSM-IV§; cognitive function: CERAD§ neurologic battery (poor performance defined as <10th percentile based on CERAD norms on at least one test) | Y | Estrogen therapy alone (WHI-ERT) did not reduce dementia or MCI§ incidence and increased the risk for both endpoints combined. |
| Shumaker, 2003 (5) | WHIMS; WHI-PERT | Oral CEE (0.625 mg) + MPA§ (2.5 mg) vs. placebo | Community-dwelling postmenopausal women aged 65–79 years | Y | 4,532 | Mean, 4.2 years | Dementia incidence (primary outcome); MCI incidence; cognitive function | Cognitive function: CERAD neurologic battery (poor performance defined as <10th percentile based on CERAD norms on at least one test) | Y | Estrogen plus progestin (WHI-PERT) increased the risk for probable dementia for the combined endpoint and did not prevent MCI. |
| Resnick, 2006 (165) | WHISCA | Oral CEE (0.625 mg) + MPA (2.5 mg) vs. placebo | Community-dwelling postmenopausal women aged 65–79 years | Y | 1,416 | Mean, 1.35 year | Change in specific cognitive functions | MMSE§; logical memory (IR§ + DR§); Benton Visual Retention Test; CVLT§ digit span forward and backward; brief visuospatial memory test (IR + DR); word list memory; word list recall; TMT B§; modified Boston Naming Test; VFT§ | N | Inconsistent results: detrimental effects on some aspects (verbal memory, CVLT) of memory; beneficial effect on figural memory (BVLT§); and no effect on the seven remaining tests |
| Almeida, 2006 (161) | | Oral estradiol (0.5–2 mg); gradual escalation and then deescalation vs. placebo | Community-dwelling, hysterectomized women aged ≥70 years: MMSE, >24 | N | 115 | 20 weeks | Change in cognitive function | CAMCOG§; block design; memory for faces (IR + DR); CVLT (IR + DR); VFT | Y | No significant differences on cognition |
| Viscoli, 2005 (164) | WEST Ancillary Study | 17β-estradiol (1 mg) or 17β-estradiol (1 mg) + progestin (5 mg) for 12 days/year for women without hysterectomy vs. placebo | Postmenopausal women aged >44 years with a recent nondisabling ischemic stroke or transient ischemic attack and without recurrent stroke: mean age, 70 years | N | 461 | Average, 3 years | Cognitive decline; change in cognitive function | MMSE-modified Boston Naming Test; Digit Span; Word List Generation Disk; Spatial Recognition; Delayed Naming | Y | No significant effects on cognitive measures |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Yaffe, 2006 (167) | Ultra-low-dose estradiol patch (0.014 mg) vs. placebo | Women at least 5 years beyond menopause: mean age, 67 years; intact uterus; normal bone density for age; various exclusion criteria | Y | 471 | 2 years | Change in cognitive function | 3MSE§ logical memory (IR + DR); brief visuospatial memory test (IR + DR); word list; memory word list; recall trails B test; modified Boston Naming Test; VFT | N | No improvement on cognition |
| Binder, 2001 (162) | Oral conjugated estrogens (0.625 mg) or oral conjugated estrogens (0.625 mg) + trimonthly MPA (5 mg/day for 13 days every third month) for women without hysterectomy vs. placebo | Community-dwelling women aged ≥75 years, free of depression (current participation in an aerobic program) | N | 67 | 9 months | Change in cognitive function | VFT; Weschler's paired-associate learning and 20-minute delayed-recall TMT A&B, cancellation, random letter, random-form tests | N | No improvement in cognitive performance |
| Polo-Kantola, 1998 (163) | Transdermal estrogen (gel: 2.5 g if <56 years of age or patch: 50 μg if aged ≥56 years) vs. placebo<br>Cross-over design | Postmenopausal women aged 47–65 years, with previous hysterectomy<br>Various exclusion criteria (e.g., neurologic, cardiovascular, endocrinologic or mental disease, malignancies, heavy smokers, psychoactive medication) | N | 68 | 3 months | Cognitive performance | Cognispeed; paced auditory serial addition test; digit span; digit symbol; Benton Visual Retention Test | N | Estrogen replacement therapy was not superior to placebo in any tests of cognitive performance. |
| Greenspan, 2005 (166) | Oral CEE (0.625 mg) or oral CEE (0.625 mg) + MPA (2.5 mg) for women without hysterectomy vs. placebo<br>Factorial design | Community-dwelling women aged >65 years; mean age, 71.3 years | N | 373 | 3 years | Change in cognitive function | MMSE | Y | No improvement in cognitive change |

* WHIMS, Women's Health Initiative Memory Study; WHI-ERT, WHIMS estrogen-only arm; WHI-PERT, WHIMS estrogen + progestin arm; WHISCA, Women's Health Initiative Study of Cognitive Aging; WEST, Women's Estrogen for Stroke Trial.

† Sample size calculation based on cognitive outcome (Y, based on cognitive outcome *or* post hoc calculation demonstrated sufficient power; N, no sample size calculation *or* sample size calculation not based on cognitive outcome).

‡ Intention to treat: Y, yes; N, no.

§ CEE, conjugated equine estrogen; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders,* 4th Edition; CERAD, Consortium to Establish a Registry for Alzheimer Disease; MCI, mild cognitive impairment; MPA, medroxyprogesterone acetate; MMSE, Mini-Mental State Examination; IR, immediate recall; DR, delayed recall; CVLT, California Verbal Learning Test; BVLT, Brief Visuo-Spatial Learning Test; TMT A&B, Trail-making Test, parts A and B; VFT, Verbal Fluency Test; CAMCOG, the cognitive and self-contained part of the Cambridge Examination for Mental Disorders of the Elderly; 3MSE, Modified Mini-Mental State Examination.

dementia or cognitive decline, although in one, the association was restricted to *APOE*E4*-positive individuals (189). Contrastingly, one study (179) found no relation with duration of use.

Certain studies using the ''lag time'' method (i.e., excluded exposure data from 1–2 years before diagnosis) found a beneficial effect in people exposed before this 2-year period (178, 186, 187), but others did not (179).

*Experimental studies (table 6).* Two randomized controlled trials tested the effects of NSAIDs (190) or aspirin (191) on dementia or cognitive decline. In the Alzheimer Disease Antiinflammatory Prevention Trial (ADAPT) Study (190), specifically designed as a dementia primary prevention trial but prematurely terminated because of safety concerns, celecoxib and naproxen showed trends for increased risks of Alzheimer disease compared with placebo. The WHS cognitive cohort (191) involved 6,377 women aged over 65 years who were treated with low-dose aspirin or placebo for 9.6 years on average. Active treatment had no effect on cognitive performance or decline at either cognitive assessment.

*Limitations.* The findings of positive observational studies could result from bias (e.g., recall, prescription (192), or publication (173) bias). However, some longitudinal studies still found a protective effect after making particular attempts to reduce bias (e.g., exposure determined from extensive national pharmacy databases (187)).

Only two randomized controlled trials have assessed the effects of NSAIDs on cognition. The Alzheimer Disease Antiinflammatory Prevention Trial Study (190) found an increased risk of dementia among subjects receiving NSAIDs, but few dementia events were observed in the shortened follow-up period, making it difficult to draw conclusions. Participants may not have benefited from NSAID treatment because of their relatively high age ($\geq$70 years).

The WHS found no effect of aspirin on cognitive decline, despite a relatively long follow-up period. It assessed cognitive decline rather than Alzheimer disease incidence, but most longitudinal studies on aspirin found little evidence for a beneficial effect on cognitive decline (180, 184, 185, 189). Although it was not specifically designed to assess cognitive outcomes, this trial had sufficient power to detect a significant effect on cognitive decline.

The aspirin dose used in the WHS may not have been strong enough to provide an antiinflammatory effect on cognition, although one longitudinal study (180) found low-dose aspirin to protect against memory decline.

The type of NSAID is important. Although it is difficult to determine which specific NSAIDs are associated with the cognitive benefits seen in some longitudinal studies, they are probably not those used in the randomized controlled trials. Furthermore, the randomized controlled trial treatments are not those thought to have the greatest effects on the 42-amino-acid form of amyloid beta protein (193–195).

Longitudinal evidence has suggested that longer-term use of NSAIDs, beginning in midlife, may be more beneficial (187). This could explain the absence of protective effects in the randomized controlled trials. Furthermore, two studies (175, 189) suggest that NSAID use in the 2 years preceding dementia onset offers no protection.

**TABLE 6. Randomized controlled prevention trials of nonsteroidal antiinflammatory agents**

| First author, year (reference no.) | Trial name* | Intervention | Subjects | Sample size calculation† | No. | Length of follow-up | Cognitive outcome(s) | Scales or criteria | Intention to treat | Results |
|---|---|---|---|---|---|---|---|---|---|---|
| ADAPT Research Group, 2007 (190) | ADAPT | Naproxen (220 mg, twice a day) or celecoxib (200 mg, twice a day) vs. placebo | Aged $\geq$70 years, no cognitive impairment, first-degree relatives with Alzheimer disease-like dementia | N | 2,528 | Planned up to 7 years but stopped after 1 year | Alzheimer disease incidence, all-cause dementia incidence, and incidence of Alzheimer disease prodromes including amnestic mild cognitive impairment | Dementia: DSM-IV,‡ NINCDS-ADRDA‡<br>Cognitive Assessment Battery | N/A‡ | Both treatments showed a trend toward increased Alzheimer disease incidence, which became statistically significant when seven prevalent cases were excluded form the analysis. However, there were very few conversion events due to the early termination of the trial. |
| Kang, 2007 (191) | WHS—cognitive substudy | Low-dose aspirin (100 mg on alternate days) vs. placebo | Women aged $\geq$65 years; mean age, 72 years | Y | 6,377 | Mean duration of treatment, 9.6 years; duration of cognitive follow-up, 4 years | Cognitive decline and change in cognitive function | Global composite score: TICS‡; East Boston Memory Test (IR‡ + DR‡); 10-words list, category fluency<br>(Substantial decline: worst 10th centile of decline) | | No overall benefit |

* ADAPT, Alzheimer Disease Antiinflammatory Prevention Trial; WHS, Women's Health Study.
† Sample size calculation based on cognitive outcome (Y, based on cognitive outcome *or* post hoc calculation demonstrated sufficient power; N, no sample size calculation *or* sample size calculation not based on cognitive outcome).
‡ DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition; N/A, not available; NINCDS-ADRDA, National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association; TICS, Telephone Interview for Cognitive Status; IR, immediate recall; DR, delayed recall.

In conclusion, the risk-benefit ratio of NSAIDs is not clear, and safety concerns have been raised with some treatments. Further clinical trials are needed to establish the cognitive effects, but the treatment used must be safe.

### *Ginkgo biloba* supplementation

*Meta-analyses or reviews.* Two reviews have assessed *Ginkgo biloba* for secondary prevention (196, 197) and noted that, although some trials found protective effects, overall results were inconsistent.

*Prospective longitudinal studies.* Although other types of epidemiologic studies have provided evidence for a protective effect of *Ginkgo biloba* on cognition (198), one prospective longitudinal study reported no association between ginkgo use and dementia risk (199).

*Experimental studies (table 7).* One short-term randomized controlled trial (200) involving middle-aged subjects found a *Ginkgo biloba-Panax ginseng* combination to have positive effects on some measures of cognition, but another (201) found no effect of *Ginkgo biloba* with other supplements on cognition. A 3.5-year trial of *Ginkgo biloba* in 118 elderly persons aged 85 or more years found no significant effect on cognitive decline overall but did find a protective effect in compliant patients (202).

*Limitations.* Only one longitudinal study and three randomized controlled trials were identified. Evidence concerning the effects of *Ginkgo biloba* on the prevention of dementia or cognitive decline is therefore limited. In light of the apparent safety of this intervention, further research is merited. The results of two large ongoing prevention trials (203, 204) will provide important data.

### Hypertension

*Meta-analyses or reviews.* A comprehensive review (205) concluded that available longitudinal evidence suggests that high blood pressure in midlife is a risk factor for cognitive impairment and dementia/Alzheimer disease in late life, but that results are inconsistent for the effects of late-life blood pressure.

A Cochrane meta-analysis (206) assessed the effects of three blood pressure-lowering interventions of at least 6 months' duration on cognition in individuals without prior cerebrovascular disease. No significant effect on cognitive function or the incidence of dementia was detected, but there was heterogeneity between trials. Two other meta-analyses (207, 208) with much less stringent inclusion/exclusion criteria noted modest or borderline protective effects of antihypertensive treatment on dementia or certain cognitive domains.

*Prospective longitudinal studies.* Late-life blood pressure. Fourteen studies found increased late-life blood pressure to be associated with increased dementia (107, 209–212), mild cognitive impairment (213), or cognitive impairment/decline (83, 214–220), although in some cases the association was restricted to a certain age group (209), either systolic (209, 215, 220) or diastolic (217) blood pressure only, medicated hypertension (218), or vascular dementia but not Alzheimer disease (107, 210, 212).

Four studies, however, suggested that higher late-life blood pressure is associated with a decreased risk of dementia (221–223) or impaired cognitive function (224), and other studies have found U-shaped (225–227) or other (228, 229) relations.

Seven studies found no association between late-life blood pressure and dementia (104, 230–233) or cognition (234, 235).

Midlife blood pressure. Eleven studies found midlife hypertension to be associated with an increased risk of dementia (122, 236–239) or cognitive decline (240–245) during late life, although the relation was sometimes restricted to a certain type of dementia (vascular dementia not Alzheimer disease) (122), either systolic or diastolic blood pressure (241, 243–245), untreated hypertension (237), or older participants (242). One study (246) found no association between midlife blood pressure and late-life cognition.

Antihypertensive treatment. Three studies found use or increased duration of use of antihypertensive treatment to be associated with a decreased dementia/Alzheimer disease risk (228, 247, 248). One study found that antihypertensive treatment was associated with a decreased risk of vascular dementia but not Alzheimer disease (249), while three found no association with dementia (104, 221, 250).

*Experimental studies (table 8).* Five large-scale ($\geq$2,500 subjects) randomized controlled trials (251–255) examined the effects of antihypertensive treatment on dementia or cognitive decline in elderly subjects for at least 3 years, although not as a primary outcome. Two studies (251, 252) found that treatment reduced the risk of dementia although, in one case (251), it was associated with only reduced risks of recurrent stroke-associated dementia and cognitive decline. The other three studies found no effect on dementia or cognition.

*Limitations.* Consistent longitudinal evidence points to raised midlife blood pressure as a risk factor for dementia/Alzheimer disease or cognitive decline, but experimental studies of antihypertensive treatment were carried out in late life, perhaps missing the ideal window of exposure. Longitudinal studies present an unclear picture of the effects of late-life blood pressure. Furthermore, follow-up in the randomized controlled trials may have been too short to demonstrate an effect.

Of five randomized controlled trials, two (251, 252) were positive, but in the Perindopril Protection against Recurrent Stroke Study (PROGRESS), treatment was linked to a lower risk of only recurrent stroke-related dementia, and in the Systolic Hypertension in Europe (Syst-Eur) trial, the relation was borderline significant (256). Other randomized controlled trials failed to demonstrate any protective effects.

In the Study on Cognition and Prognosis in the Elderly (SCOPE) trial, because of ethical reasons, experimental treatment was compared with usual treatment rather than placebo as originally planned, which probably reduced the detectable between-group effects.

Different types of antihypertensive treatments may have different effects on dementia or cognition. Specifically, calcium channel blockers and angiotensin-converting enzyme inhibitors may have the greatest effects, which may be

**TABLE 7. Randomized controlled prevention trials of *Ginkgo biloba***

| First author, year (reference no.) | Intervention | Subjects | Sample size calculation* | No. | Length of follow-up | Cognitive outcome(s) | Scales or criteria | Intention to treat† | Results |
|---|---|---|---|---|---|---|---|---|---|
| Carlson, 2007 (201) | Standardized *Ginkgo biloba* extract (160 mg) + gotu kola (68 mg) + decosahexaenoic acid (180 mg) + vitamin A (300 IU) + multivitamin multimineral supplement vs. placebo (multivitamin multimineral supplement) | Aged 65–85 years and free of depression and dementia | N | 78 | 4 months | Cognitive function | Benton Visual Retention Test; controlled oral word association; judgment of line orientation; 3MSE‡; list learning; symbol digit modalities | N | No improvement in cognitive function |
| Wesnes, 2000 (200) | Standardized *Ginkgo biloba* extract (60 mg) + standardized *Panax ginseng* extract (100 mg) vs. placebo<br>Two frequency regimens (one capsule twice a day or two capsules once a day) | Healthy, middle-aged (38–66 years) persons free of depression | N | 256 | 12 weeks | Cognitive function (quality of memory index, speed of memory index, continuity of attention, power of attention) | Cognitive Drug Research computerized cognitive assessment: word presentation; word recall (IR‡ + DR‡); picture presentation; simple reaction time; digit vigilance task; choice reaction time; spatial working memory; numeric working memory; joystick tracking task; word recognition; picture recognition | N | Improvement of memory quality (+7.5%) |
| Dodge, 2008 (202) | Standardized *Ginkgo biloba* extract (240 mg) + vitamin E (40 IU) vs. placebo (vitamin E, 40 IU) | ≥85 years, no subjective memory complaints; normal memory function§; MMSE,‡ ≥24; CDR = 0; functionally independent (ADL,‡ 0); no significant depressive symptoms¶ | N | 118 | 3.5 years | 1) Mild cognitive decline<br>2) Decline in memory function | 1) Progression from CDR‡ 0 to CDR 0.5<br>2) CERAD‡ word list, delayed recall of 10 words | | *Ginkgo biloba* had no effect on cognitive or memory decline overall. In a secondary analysis, a protective effect of *Ginkgo biloba* was seen in compliant subjects. |

* Sample size calculation based on cognitive outcome (N, no sample size calculation or sample size calculation not based on cognitive outcome).

† Intention to treat: N, no.

‡ 3MSE, Modified Mini-Mental State Examination; IR, immediate recall; DR, delayed recall; CDR, Clinical Dementia Rating [Scale]; CERAD, Consortium to Establish a Registry for Alzheimer Disease; MMSE, Mini-Mental State Examination; ADL, Activities of Daily Living.

§ Defined by the education-adjusted score on the Logical Memory Subscale of the Wechsler Memory Scale-Revised.

¶ Center for Epidemiologic Studies Depression Scale score, <4.

**TABLE 8. Randomized controlled prevention trials of antihypertensive treatments**

| First author, year (reference no.) | Trial name* | Intervention | Subjects | Sample size calculation† | No. | Length of follow-up | Cognitive outcome(s) | Scales or criteria | Intention to treat‡ | Results |
|---|---|---|---|---|---|---|---|---|---|---|
| Tzourio, 2003 (251) | PROGRESS | Perindopril (4 mg) ± indapamide (2–2.5 mg) vs. placebo | History of cerebrovascular disease; mean age, 64 years | N | 6,105 | Mean, 3.9 years | Dementia<br>Cognitive decline | DSM-IV§<br>Drop of ≥3 MMSE§ points | Y | Treatment was associated with reduced risks of dementia and cognitive decline associated with recurrent stroke. |
| Forette, 1998 (252) | Syst-Eur follow-up dementia project | Nitrendipine (10–40 mg) that could be later combined with or replaced by enalapril maleate (5–20 mg) and/or hydrochlorothiazide (12.5–25 mg) vs. placebo | ≥60 years; isolated systolic hypertension; mean age, 69.9 years | N | 2,902 | Median, 3.9 years (including 2 years in open-label phase) | Dementia<br>Change in cognitive function | DSM-IIIR§<br>MMSE | Y | Long-term antihypertensive therapy reduced the risk of dementia by 55% from 7.4 to 3.3 cases per 1,000 patient years. |
| Lithell, 2003 (253) | SCOPE | Candesartan (8–16 mg) vs. placebo | 70–89 years; hypertension; MMSE, ≥24; mean age,79.4 years | N | 4,937 | 3–5 years; mean duration, 44.6 months | Dementia<br>Cognitive decline | ICD-10§<br>Drop of ≥4 MMSE points | Y | No difference between groups |
| Prince, 1996 (255) | MRC treatment trial of hypertension in older adults | Atenolol (50 mg) vs. amiloride (2.5 mg) vs. placebo | 65–74 years; hypertension; mean age, 70.4 years | N | 2,584 | 4.5 years | Cognitive performance | PALT§; TMT§ | Y | No difference between groups |
| Applegate, 1994 (254) | SHEP | Step 1 drug: chlorthalidone (12.5–25 mg); step 2 drugs: atenolol (25 mg) or reserpine (0.05 mg) vs. placebo | ≥60 years; isolated systolic hypertension; no history of myocardial infarction, stroke, or depression; mean age, 72 years | N | 4,736 | 5 years | Cognitive decline | Short CARE§ test | Y | No difference in the incidence of cognitive decline in ITT§ analysis but preventative effect in per protocol analysis |

* PROGRESS, Perindopril Protection against Recurrent Stroke Study; Syst-Eur, Systolic Hypertension in Europe; SCOPE, Study on Cognition and Prognosis in the Elderly; MRC, Medical Research Council; SHEP, Systolic Hypertension in the Elderly Program.

† Sample size calculation based on cognitive outcome (N, no sample size calculation or sample size calculation not based on cognitive outcome).

‡ Intention to treat: Y, yes.

§ DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition; MMSE, Mini-Mental State Examination; DSM-IIIR, *Diagnostic and Statistical Manual of Mental Disorders*, 3rd Edition-Revised; ICD-10, *International Classification of Diseases*, 10th Edition; PALT, Paired Associated Learning Test; TMT, Trail-making Test; CARE, Comprehensive Assessment and Referral Evaluation; ITT, intention-to-treat.

brought about through mechanisms other than blood pressure lowering (257, 258).

There is relatively strong evidence that hypertension in midlife is a risk factor for dementia or cognitive decline, but associations with late-life blood pressure remain unclear. There is little evidence to suggest that antihypertensive treatment in late life reduces risks of dementia or cognitive decline. Initiation of antihypertensive treatment in midlife needs to be assessed in future randomized controlled trials.

### Diabetes

*Meta-analyses or reviews.* Two reviews (259, 260) studied the relation between diabetes and cognitive decline and concluded that, compared with people without diabetes, people with diabetes have a 1.5-fold greater risk of cognitive decline.

A review of 14 longitudinal based studies (261) compared the incident risk of dementia (Alzheimer disease, vascular dementia, and mixed dementia) in diabetic and nondiabetic subjects. They concluded that there is convincing evidence that shows an increased risk of dementia in people with diabetes, but there are few details on the modulating and mediating effects of glycemic control, other vascular risk factors, and microvascular complications.

In addition, a Cochrane review (262) of the effect of type 2 diabetes treatment on cognitive decline was unable to carry out a meta-analysis of randomized controlled trials because of a lack of studies of suitable quality.

*Prospective longitudinal studies.* Sixteen studies (215, 218, 242, 263–275) have explored the link between diabetes and cognitive decline. All but two (218, 272) found that diabetic adults have more cognitive decline compared with nondiabetic adults; psychomotor efficiency, executive function, and learning and memory skills are often the most affected domains.

Seventeen studies (107, 122, 231, 263, 270, 276–286) have examined the association between diabetes and Alzheimer disease incidence. The risk of Alzheimer disease tended to be largest in the three (122, 277, 285) studies that measured the risk factor in midlife and had a long follow-up period. However, one study (277) found no association between diabetes in midlife and risk of Alzheimer disease, and six studies (107, 270, 278, 282, 286, 287) found no association between diabetes in late life and risk of Alzheimer disease. Diabetes treatment might also be a relevant factor. Two studies indicate that the risk of dementia is higher in diabetic subjects treated with insulin (282, 283).

*Experimental studies.* Five randomized controlled trials (288–292) evaluating the effect of diabetes treatment on cognitive function over short durations (<1 year) or with questionable methodology (lack of double blinding) have reported contradictory results.

There are currently no intervention trials of high methodological quality assessing cognitive decline. The Action to Control Cardiovascular Risk in Diabetes Memory in Diabetes (ACCORD-MIND) Study (293) was testing the effects of long-term glycemic control on cognitive decline and structural brain changes in patients with type 2 diabetes, but treatment has been stopped because of safety concerns (294).

*Limitations.* There is consistent longitudinal evidence to suggest that diabetes is associated with dementia and cognitive decline, although nine studies were negative. In one of these studies, subjects were 85 or more years (272). There may be a ''survivor effect,'' where individuals who reach old age, despite having multiple vascular risk factors, are survivors and might be less susceptible to the adverse effects of these risk factors.

Of the six studies finding no effect of diabetes on Alzheimer disease, five distinguished between vascular dementia and Alzheimer disease. The boundary between vascular dementia and Alzheimer disease remains controversial, so the possibility of misdiagnosis must be considered and might explain some of the negative results.

An increased risk of Alzheimer disease was seen in diabetic subjects treated by insulin (282, 283); whether these results show the severity of diabetes or an effect of insulin treatment itself is unknown.

In conclusion, diabetes is a risk factor for cognitive decline and dementia, but at this time, there are no high quality intervention studies examining the effect of metabolic control on cognition.

## COMMON METHODOLOGICAL ISSUES

Some common methodological limits could apply to various domains. The measurement of some exposures can suffer from a lack of precision: Self- or proxy-report rather than objective measures can lead to misclassification. In two studies (218, 277), diabetes was assessed only through declarative data, which may have led to an underestimation of the effect.

In longitudinal studies, exposure is often measured at one time point, and exposure variations over time are not considered. For example, few studies assessed changes in social interactions or activity participation over time, which may be especially important around the time of retirement.

The window of exposure might also be important, as some interventions may have differential effects according to the time of exposure. It has been suggested that hormone replacement therapy needs to be started around the immediate postmenopausal period for a beneficial effect (143, 168, 170, 295–297) but that randomized controlled trial participants were perhaps too old. Subjects included in nutritional randomized controlled trials were generally aged over 60 years, but nutrients may affect the neurodegenerative process at an early stage (7). One successful nutritional trial (63) was conducted in a slightly younger population, aged 50–70 years.

Observational studies often fail to take into account all potential confounding factors, such as depression or baseline cognitive performance. From this review, we can see the importance of adjusting for the presence of *APOE*E4*, but many studies did not consider this factor. We suggest that a minimum set of confounders including age, education, and baseline cognitive performance should be considered, but some studies did not adjust for all of the these factors simultaneously. Furthermore, recorded exposure variables could be a marker of unrecorded characteristics. For example,

a healthy diet or use of vitamin supplements could reflect overall healthier behavior, leading to ''healthy user'' bias (298). In addition, postmenopausal treated women may have fewer hormone replacement therapy contraindications (hypertension, diabetes, history of stroke). Controlling for such confounders diminished the effect of hormone replacement therapy on cognition (138, 153, 159). Social engagement or activity participation could also be an indicator of previous life experiences (299), such as education or socioeconomic status, but generally only education was controlled for (73).

Protopathic bias is important. A low level of exposure (e.g., social engagement or activity participation) may be indicative of a neurodegenerative process that is not yet clinically apparent. However, in several domains, all observed associations remained after controlling for baseline cognitive function or after sensitivity analysis, excluding persons who developed dementia or cognitive decline soon after exposure measurement.

Outcome definition is variable. Some studies evaluated dementia incidence (assessed using standard international criteria with or without independent validation committees). Other studies considered different aspects of cognition by using a variety of cognitive tests and definitions of impairment or decline. Thus, the comparison of studies is difficult, and some authors questionably assume that cognitive decline is a validated surrogate marker of dementia. Furthermore, the clinical relevance of cognitive decline is rarely mentioned (300). Furthermore, some hypertension studies assessed all-cause dementia, including vascular forms, and therefore were more likely to be related to hypertension or an antihypertensive drug, while others specifically assessed Alzheimer disease.

Insufficient statistical power is a frequent limitation. For example, of the 10 nutritional randomized controlled trials, only two were large scale (68, 69). Given that interventions may have relatively modest effects, randomized controlled trials need sufficient power to detect small changes on cognitive outcome measures. Ancillary studies initially designed for noncognitive outcomes could be underpowered for cognitive outcome, since dementia/Alzheimer disease incidence remains relatively low.

Attrition rates are rarely considered. In nutritional intervention, the trial with the lowest attrition rate was the only trial able to demonstrate significant benefits of supplementation (63). In the Systolic Hypertension in the Elderly Program (SHEP) Study, which found no effect of antihypertensive treatment on cognitive decline or dementia, sensitivity analyses suggested that differential dropout may have obscured potential treatment effects (301). Some other trials of antihypertensives reported high rates of dropout (255) or discontinuation of study medication (251), which could have affected results.

Concerning statistical analysis, few studies used methods that took into account variation of covariates with time, which is important with many years of follow-up. Furthermore, it is difficult to compare longitudinal studies analyzing only subjects followed for the entire study period (e.g., excluding deaths and dropouts) and studies considering unequal durations of follow-up (i.e., survival analysis) or missing value(s) (i.e., mixed models).

## MULTIPLE EXPOSURE AND MULTIDOMAIN INTERVENTIONS

Because of the multifactorial nature of Alzheimer disease, it would seem logical to initiate multidomain interventions designed to examine not only the individual effects of each intervention but also any potential synergistic effects. Several intervention trials of this nature are currently underway (302, 303).

Some specific challenges need to be underlined in designing trials involving multidomain interventions. First, surrounding the specific selection of subjects, we can imagine that subjects who agree to modify multiple lifestyle domains are likely to have a higher level of education and better overall health, meaning that it may be difficult to demonstrate an effect of the intervention. Observance in multidomain trials is difficult to assess if the intervention combines different lifestyle factors. If the intervention is based on lifestyle recommendations, it will be difficult to evaluate actual behavioral modifications precisely. In these interventions, it is impossible to maintain double-blind conditions and difficult to define an adequate control group, especially for physical exercise interventions. It is also difficult to identify the independent effects of each factor, because they may act through common mechanisms (e.g., via cardiovascular mechanisms), and there may be between-group contamination.

## CONCLUSION

In this review, many methodological explanations for divergent observational and experimental results for dementia prevention were identified.

The evidence for preventive strategies for neurodegenerative dementia remains inconsistent, especially because of the lack of randomized controlled trials assessing dementia incidence as a primary outcome. At present, it is not possible to determine any specific recommendations for pharmacologic strategies or lifestyle changes. Future epidemiologic studies must attempt as much as possible to minimize bias and confounding, in order to generate reliable hypotheses on which to base randomized controlled trials.

If it existed, a preventive strategy based on the use of a pharmacologic treatment would seem to be a relatively simple method of preventing dementia/Alzheimer disease. A good risk-benefit ratio would be imperative because of the number of subjects who will be exposed to the intervention without ever developing the disease. In the absence of such a treatment, even if it is difficult to change lifestyle habits, lifestyle factors (diet, social engagement, cognitive stimulation, physical exercise) seem the most reasonable candidates for prevention trials at the current time, in particular because of their safety. As a result of the difficulties in conducting a multidomain intervention, randomized controlled trials may not represent the ''gold standard'' in this field, and large public health interventions at the population level could be required. However, such interventions would have to be feasible, cost effective, and easily transferable in order to have a real public health impact.

## ACKNOWLEDGMENTS

Nicola Coley is supported by a CIFRE PhD studentship, which is jointly funded by the French National Association for Technical Research and Beaufour Ipsen Pharma.

Conflict of interest: none declared.

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