Dementia has become a pressing health issue, with numbers steadily increasing. Vascular injury is the second most common cause of dementia after Alzheimer disease (AD) and a defining feature of vascular cognitive impairment (VCI), which encompasses the full range from vascular dementia (VaD) to mild cognitive impairment of vascular origin.1,2

There are various manifestations of vascular brain injury, including silent or covert brain infarcts, white matter lesions, and clinically overt strokes, all of which may contribute to cognitive decline. Cerebral small vessel disease has been recognized as the most common etiology of VCI, but there are multiple vascular causes and mechanisms that share major risk factors and may run in parallel. Adding to this complexity, vascular pathology frequently coincides with neurodegenerative pathology and disentangling the contribution of individual pathologies to cognitive decline is notoriously difficult even with advanced diagnostic tools. This is reflected by current classification schemes, which distinguish between probable and possible VaD and probable and possible vascular mild cognitive impairment.3 However, there have been various sets of diagnostic criteria in the past, which must be kept in mind when interpreting the results from epidemiological studies and randomized controlled trials (RCT).

Regardless of these methodological challenges, vascular brain injury represents an increasingly recognized target for prevention of cognitive decline and dementia. There are various modifiable factors that have been associated with VCI or VaD in clinical and epidemiological studies (Figure 1), although in many cases the causal relationships are not fully established and evidence for a preventive effect of strategies to control these factors is mostly weak.

Here, we review potential targets for prevention with a focus on longitudinal observational studies and RCT, provide an overview on current recommendations by health care professionals from the American Heart Association/American Stroke Association, summarize some of the ongoing trials, and discuss future challenges and opportunities. A fully referenced version and methodological details of this review are provided in the online-only Data Supplement.

Potential Targets for Prevention:
Lifestyle Factors

Education
Low educational level is associated with an increased risk of cognitive impairment and dementia, but the factors underlying this relationship are still discussed. Until now, there is no convincing evidence that education protects individuals from development of vascular or neurodegenerative brain pathology. Instead, education seems to attenuate the impact of pathology on the clinical expression of dementia.3 The impact of cognitive lifestyle during middle and late life and of structured cognitive intervention programs on the manifestation of dementia remains insufficiently explored.

Smoking
Smoking is associated with cognitive decline4 and a significantly increased risk of VaD, AD, and unspecified dementia (Figure 1).4,5 Current smoking has been found to be associated with deficits in specific cognitive domains, including psychomotor speed, flexibility, and memory,4 but the mechanisms connecting smoking and cognitive decline are still debated. Cigarette smoking is associated with reduced microstructural integrity of the cerebral white matter,7 and there is some evidence that smoking cessation protects against these changes. However, there are insufficient data from intervention studies to conclude on the effects of smoking cessation on cognition.8 Based on currently available evidence, the latest American Heart Association/American Stroke Association guidelines issue a class IIa/A evidence for smoking cessation in people at risk for VCI (Table 1).

Diet
Observational studies show promise for protection against cognitive decline and dementia through a number of dietary components. The most consistent evidence exists for dietary intakes of the antioxidant vitamin E, fish, n-3 fatty acids, a high ratio of polyunsaturated to saturated fats, and B vitamins, particularly B12 and folate.9 These components are prominent in the Mediterranean diet that is high in fruits,
vegetables, fish, whole grains, nuts, and monounsaturated oils, and is low in high-fat dairy and meat.

Several prospective studies found that adherence to a Mediterranean diet is associated with a lower risk of cognitive decline\textsuperscript{10,11} and AD, although there are few data for VCI and VaD. Studies of E vitamins and B vitamins suggest that low basal vitamin status is critical, whereas persons with adequate status probably do not benefit from supplementary intake of vitamins.\textsuperscript{12}

In general, RCT have failed to demonstrate a benefit from dietary supplementation. However, this may relate to methodological limitations such as the inclusion of subjects with normal vitamin status,\textsuperscript{12} supplementation through other sources, and short follow-up (Table 2). Against this background, a Mediterranean-type diet may be reasonable (Table 1).\textsuperscript{2}

**Homocysteine and Hyperhomocysteinemia**

Elevated concentrations of plasma total homocysteine may cause vascular damage.\textsuperscript{13} They are associated with lower cognitive performance\textsuperscript{14} and an increased risk of AD and dementia, although it is still debated whether this link is causal.\textsuperscript{15}

The levels of total homocysteine can be lowered by \( \approx 20\% \) with oral supplementation of specific B vitamins, marking it a potentially modifiable risk factor. However, several RCT have failed to show any obvious benefits of homocysteine-lowering therapy on cognitive performance. This might relate to limitations in study design such as the inclusion of subjects with normal homocysteine levels\textsuperscript{12} and too short follow-up (Table 2). Also, there are no trials with AD or VaD as an end point. However, it currently is not recommended to administer B vitamins for the prevention of VCI (Table 1).

**Physical Activity**

Physical activity has multiple biological effects, including beneficial actions on synaptogenesis and neurogenesis,\textsuperscript{16} and, in fact, observational studies demonstrate a beneficial role of physical activity on the risk of VaD,\textsuperscript{17} AD, dementia, and cognitive decline. However, there are few data from RCT. The largest trial so far compared a 24-week home-based program of physical activity with education and usual care in 170 nondemented volunteers with subjective memory impairment. Physical activity provided a modest improvement in cognition over an 18-month follow-up period as assessed by the Alzheimer Disease Assessment Scale–Cognitive Subscale.\textsuperscript{18}

![Figure 1. Risk factors for vascular dementia (VaD), Alzheimer disease (AD), unspecified dementia, and cognitive impairment. Findings are derived from epidemiological studies. Relevant references are detailed in Supplementary Table I. VaD and AD share many risk factors, although the level of evidence varies for individual risk factors and dementia subtypes.](http://stroke.ahajournals.org/)

<table>
<thead>
<tr>
<th>Non-modifyable Risk Factors</th>
<th>age</th>
<th>genetic factors (APOE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifestyle Factors</td>
<td>education</td>
<td>smoking</td>
</tr>
<tr>
<td></td>
<td>diet</td>
<td>homocysteine</td>
</tr>
<tr>
<td></td>
<td>physical activity</td>
<td>obesity, BMI</td>
</tr>
<tr>
<td>Physiological Risk Factors</td>
<td>hypertension</td>
<td>hyperglycemia, diabetes</td>
</tr>
<tr>
<td></td>
<td>lipids, dyslipidemia</td>
<td>inflammation</td>
</tr>
<tr>
<td>Concomitant Clinical Vascular Disease</td>
<td>stroke</td>
<td>coronary artery disease</td>
</tr>
<tr>
<td></td>
<td>atrial fibrillation</td>
<td>peripheral arterial disease</td>
</tr>
<tr>
<td></td>
<td>chronic kidney disease</td>
<td>low cardiac output</td>
</tr>
<tr>
<td></td>
<td>depression</td>
<td></td>
</tr>
</tbody>
</table>
Cognitive function is a secondary outcome in the ongoing Lifestyle Interventions and Independence for Elders (LIFE) Study, which compares supervised moderate-intensity physical activity with an aging health education program in sedentary older persons. In a pilot study of that trial, group differences in cognitive scores were not significant but improvements in cognitive scores were associated with improvements in physical function. The LIFE study aims to recruit 1600 subjects and is expected to be completed in 2014.

The American Heart Association/American Stroke Association guidelines issue a class IIb/B evidence for physical activity for the prevention of cognitive impairment (Table 1). However, a number of questions remain, including the optimal type and frequency of physical activity, and the period in life when individuals benefit most.

### Table 1. Recommendations for Prevention of Vascular Cognitive Impairment (American Heart Association/American Stroke Association 2011)

<table>
<thead>
<tr>
<th>Target</th>
<th>Target Population</th>
<th>Recommendation</th>
<th>Recommendation Class and Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lifestyle</strong></td>
<td>General</td>
<td>Mediterranean-type dietary pattern has been associated with less cognitive decline in several studies and may be reasonable</td>
<td>IIb; B</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vitamin supplementation is not proven to improve cognitive function, even if homocysteine levels have been positively influenced, and its usefulness is not well-established</td>
<td>IIb; B</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Physical activity might be considered for the prevention of cognitive impairment</td>
<td>IIb; B</td>
</tr>
<tr>
<td></td>
<td>People at risk for VCI</td>
<td>Smoking cessation is reasonable</td>
<td>Ila; A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The following lifestyle interventions may be reasonable:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>moderation of alcohol intake;</td>
<td>IIb; B</td>
</tr>
<tr>
<td></td>
<td></td>
<td>weight control; and</td>
<td>IIb; B</td>
</tr>
<tr>
<td></td>
<td></td>
<td>physical activity</td>
<td>IIb; B</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The use of antioxidants and B vitamins is not beneficial, based on current evidence</td>
<td>III; A</td>
</tr>
<tr>
<td><strong>Blood pressure</strong></td>
<td>Middle-aged and young elderly</td>
<td>There is reasonable evidence that lowering blood pressure can be useful for the prevention of late-life dementia</td>
<td>IIa; B</td>
</tr>
<tr>
<td></td>
<td>People age ≥80 y</td>
<td>The usefulness of lowering blood pressure for the prevention of dementia is not well-established</td>
<td>IIb; B</td>
</tr>
<tr>
<td></td>
<td>People at risk for VCI</td>
<td>Treatment of hypertension is recommended</td>
<td>I; A</td>
</tr>
<tr>
<td></td>
<td>Patients with stroke</td>
<td>Lowering blood pressure is effective for reducing the risk of poststroke dementia</td>
<td>I; B</td>
</tr>
<tr>
<td><strong>Hyperglycemia/diabetes</strong></td>
<td>General</td>
<td>The effectiveness of treating diabetes/hyperglycemia for the prevention of dementia is not well-established</td>
<td>IIb; C</td>
</tr>
<tr>
<td></td>
<td>People at risk for VCI</td>
<td>Treatment of hyperglycemia may be reasonable</td>
<td>IIb; B</td>
</tr>
<tr>
<td><strong>Hyperlipidemia</strong></td>
<td>General</td>
<td>The usefulness of treatment of hyperlipidemia for prevention of dementia is uncertain</td>
<td>IIb; C</td>
</tr>
<tr>
<td><strong>Hypercholesterolemia</strong></td>
<td>People at risk for VCI</td>
<td>Treatment of hypercholesterolemia may be reasonable</td>
<td>IIb; B</td>
</tr>
<tr>
<td><strong>Inflammation</strong></td>
<td>People at risk for VCI</td>
<td>It is uncertain whether treatment of inflammation will reduce the risk of VCI</td>
<td>IIb; C</td>
</tr>
<tr>
<td><strong>Antiaggregants</strong></td>
<td>General</td>
<td>The effectiveness of antiaggregant therapy for VCI is not well-established</td>
<td>IIb; B</td>
</tr>
</tbody>
</table>

VCI indicates vascular cognitive impairment.


*Ratings relate to studies cited and in the Supplementary material. For information on how to apply classification of recommendation and level of evidence, see Supplementary Table IV.

Obesity and Body Mass Index

Overweight and obesity measured by the body mass index are established risk factors for dementia, although disentangling the impact of obesity from other components of the metabolic syndrome such as hypertension and insulin resistance is challenging. Body mass index has a U-shape relationship with dementia in that both being underweight and overweight in midlife are associated with an increased risk of dementia, AD, and VaD. A study from Northern California found that central obesity increased the risk of dementia independent of body mass index and of diabetes and cardiovascular comorbidities.

Until now, there are no interventional studies examining the effect of targeted weight loss on cognitive trajectories. Nevertheless, weight control may be reasonable to prevent VCI (Table 1). There is some evidence that body mass index...
measured in late life has an inverse association with risk of dementia, but a number of factors including methodological aspects might explain this “obesity paradox.”

Physiological Risk Factors

Hypertension

There is strong evidence that long-standing hypertension in midlife increases the risk of cognitive impairment and dementia in late life, whereas the association between hypertension in late life and dementia is less consistent. Blood pressure (BP) values frequently decline in late life, and this decline has been reported to be stronger in subjects with dementia than in nondemented subjects. A J-shape or U-shape relation with late-life cognitive decline has been found for systolic BP (SBP) and, to a lesser degree, for diastolic BP. However, the mechanisms underlying these relationships are still debated. As demonstrated by a recent meta-analysis, hypertension is associated with an increased risk of incident VaD (odds ratio, 1.59; 95% confidence interval, 1.29–1.95), whereas the relationship is less clear for AD. Among subjects not using antihypertensive medication in the Honolulu Asia Aging Study, 27% of late-life dementia cases were attributable to midlife SBP levels ≥120 mm Hg. Despite conclusive evidence for the role of hypertension, there is considerable uncertainty regarding the efficacy of antihypertensive treatment for lowering the risk of dementia.

Observational Studies

Published data suggest some preventive effect of antihypertensive treatment when administered to younger people. Specifically, several studies found an association between the use of BP-lowering drugs and risk of AD, which was more pronounced when patients were followed-up for extended time periods. The Rotterdam study and the Honolulu Asia Aging Study presented data on VaD. Antihypertensive treatment was associated with a reduced risk of VaD in both studies. However, hazard ratios varied between studies and there was no clear effect of the duration of follow-up.

The preventive effects of antihypertensive drugs on the risk of stroke differ depending on drug classes independently of effects on mean BP. Data on dementia are much less consistent. Most observational studies found no differences between individual classes of antihypertensive drugs with regard to risk of dementia. Two studies reported a stronger effect of diuretics, especially potassium-sparing diuretics. Other studies found a stronger protective effect for angiotensin receptor blockers and angiotensin-converting enzyme inhibitors. However, these observations may, in part, relate to limitations in study design. Two studies reported data for VaD but again there was no consistent finding regarding the effects of specific drug classes.
**Table 3. Ongoing Preventive Trials***

<table>
<thead>
<tr>
<th>Trial (Name; Trial Reference)</th>
<th>Population Characteristic</th>
<th>Intervention (N=Estimated Enrollment)</th>
<th>End Points</th>
<th>Follow-up (Planned)</th>
<th>Results Expected</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single-component interventions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPRINT (Systolic Blood Pressure Intervention Trial; NCT01206062)</td>
<td>≥55 y</td>
<td>Intensive blood pressure (SBP &lt;120 mm Hg) vs standard arm (SBP &lt;140 mm Hg); N=9250</td>
<td>Secondary end point: dementia, decline in cognitive function</td>
<td>6 y</td>
<td>2018</td>
</tr>
<tr>
<td>ASPREE (Aspirin in reducing events in the Elderly; NCT01035853)</td>
<td>≥70 y</td>
<td>100 mg enteric-coated aspirin vs placebo; N=19000</td>
<td>Primary end point: death from any cause or incident dementia or persistent physical disability</td>
<td>Every 3–6 mo</td>
<td>2016</td>
</tr>
<tr>
<td>SPS3 (Secondary prevention of small subcortical strokes trial; NCT00059306)</td>
<td>≥30 y, diagnosis of small subcortical ischemic stroke or subcortical transient ischemic attack</td>
<td>Aspirin+clopidogrel vs aspirin+placebo; N=3000</td>
<td>Secondary outcome: cognitive decline</td>
<td>4 y</td>
<td>2012</td>
</tr>
<tr>
<td>NICE (Efficacy and safety study of nimodipine to prevent mild cognitive impairment after acute ischemic strokes; NCT01220622)</td>
<td>30–80 y, diagnosis of acute cerebral infarction</td>
<td>30 mg nimodipine for 6 mo; N=656</td>
<td>Primary end point: cognitive function, assessment with ADAS-cog and MMSE at 6 mo; secondary outcome: VaD diagnosed by NINDS-AIREN</td>
<td>6 mo</td>
<td>2012</td>
</tr>
<tr>
<td><strong>Multicomponent interventions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FINGER (Finnish Geriatric Intervention Study to Prevent cognitive Impairment and disability; NCT01041989)</td>
<td>60–77 y, dementia risk score ≥6 points</td>
<td>Multidomain lifestyle counseling including nutritional guidance, increased physical activity, cognitive training, increased social activity, and intensive monitoring of vascular and metabolic risk factors; N=1200</td>
<td>Primary outcome: neuropsychological test battery, Stroop, and trail-making tests</td>
<td>2 y</td>
<td>2013</td>
</tr>
<tr>
<td>ASPIS (Austrian Polyintervention Study to Prevent Cognitive Decline After Ischemic Stroke; NCT01109836)</td>
<td>60–77 y, diagnosis of ischemic stroke</td>
<td>Intensive control and motivation for better compliance with medication, regular blood pressure measurements, diet changes, and physical activity vs standard stroke care; N=200</td>
<td>Primary outcome: cognitive decline (neuropsychological tests and ADAS-cog)</td>
<td>2 y</td>
<td>2014</td>
</tr>
<tr>
<td>PreDIVA (Prevention of Dementia by Intensive Vascular Care)63</td>
<td>70–78 y, nondemented subjects</td>
<td>Intensive vascular care comprises visiting a practice nurse every 4 mo to assess vascular risk factors, including hypertension, hypercholesterolemia, diabetes, overweight, smoking, and level of physical exercise; intervention: lifestyle and medical; N=3700</td>
<td>Primary outcome: dementia and disability</td>
<td>6 y</td>
<td>not specified</td>
</tr>
<tr>
<td>PODCAST (Prevention Of Decline in Cognition After Stroke Trial; ISRCTN85562386)</td>
<td>&gt;70 y, diagnosis of ischemic stroke</td>
<td>Intensive blood pressure (SBP &lt;125 mm Hg) and/or lipid-lowering (LDL &lt;2.0 mmol/L) vs moderate blood pressure (SBP &lt;140 mm Hg) and LDL ( &lt;3.0 mmol/L); N=3400</td>
<td>Primary outcome: cognition (Addenbrooke Cognitive Examination); secondary outcome: dementia (AD, VaD), cognition (MMSE, trail making, stroop)</td>
<td>8 y</td>
<td>2018</td>
</tr>
</tbody>
</table>

Table contains data from reference 63. AD indicates Alzheimer disease; ADAS-cog, Alzheimer Disease Assessment Scale-Cognitive Subscale; LDL, low-density lipoprotein; MMSE, Mini Mental State Examination; NINDS-AIREN, National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l’Enseignement en Neurosciences; SBP, systolic blood pressure; VaD, vascular dementia; VCI, vascular cognitive impairment.

*Selection of trials targeted against established risk factors for VaD in which dementia or cognitive decline is a major end point.
RCT
Eight large RCT investigated the effect of antihypertensive treatment on incident dementia (7 studies) or cognitive decline (6 studies) (Supplementary Table III). All trials included patients at increased risk for cardiovascular events but with variable inclusion criteria. The mean age at baseline ranged from 64 to 84 years, the duration of follow-up (mean or median) ranged from 2.0 to 4.7 years, and the mean difference in SBP achieved by active treatment vs placebo ranged from 3 to 15 mm Hg (Figures 2 and 3). In all but 1 trial (PRoFESS) antihypertensive treatment reduced the incidence of stroke or a combined vascular end point. A beneficial effect on the risk of incident dementia was reported in the Syst-Eur trial (P = 0.05).36 However, there was no clear-cut effect on dementia in any of the other trials (Figure 2). Furthermore, there was no clear effect on cognitive performance except in 1 trial (PROGRESS).37

The Syst-Eur trial included patients with a BP of 160 to 219 mm Hg SBP and <95 mm Hg diastolic.36 Active treatment was initiated with nitrendipine and, if necessary, combined with or replaced by enalapril, hydrochlorothiazide, or both titrated to reduce SBP by predefined margins. The mean decrease in SBP between the active and placebo group was 8.3 mm Hg (diastolic BP, 3.8 mm Hg). The trial was stopped prematurely because of a significant benefit from treatment for lowering stroke risk. The rate of incident dementia was reduced by 50% (Figure 2), with most cases classified as AD. In an open-label extension study, the principal result was confirmed with a similar effect on mixed or VaD.38 In the PROGRESS trial, treatment with perindopril with or without the addition of indapamide was associated with a reduced incidence of dementia in the subgroup of patients with recurrent stroke (risk reduction, 34%; 95% confidence interval, 3%–55%) and in patients receiving combination therapy (risk reduction, 23%; 95% confidence interval, 0%–41%).37 However, in meta-analyses of all trials antihypertensive treatment had no significant effect on the risk of dementia, cognitive impairment,40 or cognitive decline.40 When stratifying

![Difference in reduction in SBP in the treatment group compared to the placebo group](image)

**Figure 2.** Association of reduction in systolic blood pressure with risk reduction for incident dementia in randomized trials of blood pressure-lowering treatment. Drug classes used as active treatment are marked by color and position within large boxes. Insert, Boxes and horizontal lines represent relative risk and 95% confidence intervals (CI) for each trial; size of boxes is proportional to the inverse of the variance. *Incidence of cognitive impairment defined as diagnosis of dementia or significant cognitive dysfunction or Mini Mental State Examination ≤23 points.

![Temporal relationship between the critical period for elevated blood pressure and randomized trials of blood pressure-lowering treatment](image)

**Figure 3.** Temporal relationship between the critical period for elevated blood pressure and randomized trials of blood pressure-lowering treatment. Observational studies indicate that the most critical period for elevated blood pressure with regard to cognitive decline is during midlife. The majority of patients included in blood pressure-lowering trials were beyond midlife and the duration of randomized trials was relatively short. *Incidence of cognitive impairment defined as diagnosis of dementia or significant cognitive dysfunction or Mini Mental States Examination ≤23 points. **Standard deviation (SD) for age not specified.
trials according to drug classes, a significantly reduced incidence of dementia was found in trials involving a diuretic or dihydropyridine calcium channel blocker as part of active treatment, whereas this was not the case in trials of renin system inhibitors. However, this finding might be explained by between-group difference in the amount of BP reduction, which was larger for trials involving a diuretic or calcium channel blocker (Figure 2).

In conclusion, there is reasonable evidence from observational studies that in the middle-aged and young elderly, lowering BP can be useful for the prevention of late-life dementia (Table 1). However, considerable uncertainty remains regarding the efficacy of antihypertensive drugs for lowering the risk of dementia in general. This, in part, relates to methodological limitations shared by all BP-lowering trials, including: (1) a short duration of follow-up (Figure 3); (2) a small number of incident cases of cognitive decline or dementia; (3) additional treatments in the placebo and active treatment groups; (4) variable definitions and assessment instruments for cognitive end points; (5) a high number of dropouts with the risk of selective dropout of cognitively impaired patients; and (6) a failure to account for competing risks (Table 2). For example, by reducing mortality, some antihypertensive drugs may have increased the rate of study participants who reached the cognitive end point. In consideration of these limitations, the results of BP-lowering trials should be interpreted with caution. Missing are large sufficiently powered trials with longer follow-up in the appropriate age range and with cognitive end points as the primary outcome. In addition, there is a need for meta-analyses of individual patient data.

**Hyperglycemia and Diabetes**

Chronic hyperglycemia, hyperinsulinemia, the metabolic syndrome, and diabetes are important risk factors for poorer cognitive performance and cognitive decline, although the mechanisms are still debated. Diabetes is associated with an increased risk of VaD and AD. In a meta-analysis of population-based studies, the risk ratio of older diabetic adults compared with nondiabetic individuals was ≈1.5 for all dementia, 1.4 for AD, and 2.4 for VaD, and the diabetes-attributable risk of dementia has been calculated to be between 7% and 13% of all incident cases of dementia. Cognitive changes in type 2 diabetes involve multiple cognitive domains, with slowed processing speed being the most consistently reported abnormality.

The effects of diabetes on cognition could be mediated through a number of mechanisms, including vascular injury, glucose toxicity, hyperinsulinemia, and disturbed amyloid metabolism. Diabetes is associated with microvascular and macrovascular disease, and with functional changes in cerebral blood flow, which may be partly reversed by improved glucose control. Also, diabetic patients are more likely to have silent and symptomatic brain infarcts on neuroimaging, which would fit with the observed association between diabetes and VaD. However, diabetes frequently develops in the context of other risk factors constituting the metabolic syndrome, and it is still debated to what extent the effects on cognition are mediated through diabetes or other risk factors of the metabolic syndrome.

The Memory in Diabetes (MIND) substudy of the ACCORD trial investigated the effects of intensive vs standard glycemic control on brain structure and cognitive function. At 40 months, the total brain volume was significantly greater in the intensive treatment group, reflecting a slower decline in total brain volume compared with baseline. However, there was no significant treatment difference on any of the cognitive tests. Similarly, in the ADVANCE trial, intensive glucose control had no significant effect on the rate of cognitive decline, with a numerically higher proportion of incident dementia in the intensive treatment group.

Taken together, the level of evidence for a protective effect of intensive glucose-lowering with respect to cognitive impairment is very low, as is also reflected by current guidelines (Table 1). However, there is great demand for further trials also involving new antidiabetic drugs and overcoming the methodological limitations outlined in Table 2.

Another potentially important aspect is hypoglycemia. A recent study in elderly patients with type 2 diabetes found an association between severe hypoglycemic episodes and an increased risk of dementia. This finding emphasizes the need for careful glycemic control.

**Lipids and Dyslipidemia**

Cholesterol may be implicated in the pathogenesis of both VaD and AD with partially overlapping mechanisms. Long-term epidemiological studies have found an association between higher midlife serum total cholesterol levels and subsequent cognitive impairment developing many years later. A similar relationship has been reported for both VaD and AD. However, the association between cholesterol and dementia is still debated, especially in late-life cohorts.

Cognitive function was a tertiary outcome in the Heart Protection Study and the PROSPER trial. The average follow-up in these trials was 5 and 3.5 years, respectively. The Heart Protection Study used a validated telephone interview at final follow-up and evaluated both the percentage of patients classified as cognitively impaired and those with incident dementia. The PROSPER trial used 4 different outcome parameters (Mini Mental State Examination, Stroop color-wording, letter digit coding, picture learning) and analyzed the differences between the last on-treatment and the baseline value. There was no treatment effect on any of the cognitive outcomes in the 2 trials. Based on these results, there is no evidence that the use of statins has a favorable effect on cognitive function in the elderly.

**Concomitant Clinical Vascular Disease**

Having a stroke doubles the risk of dementia, even when adjusting for age, sex, education, and exposure to individual stroke risk factors. Moreover, the risk of dementia further increases with recurrent stroke. Coronary artery disease (CAD), peripheral arterial disease (PAD), chronic kidney disease, and low cardiac output all have been associated with cognitive impairment and dementia (Figure 1). An increased risk of VaD has been reported for CAD, AF, chronic kidney disease, and PAD. PAD and low cardiac output
was furthermore found to be associated with AD. Thus, preventing chronic vascular disease may be one of the most efficient strategies to prevent dementia. Given the well-documented efficacy of platelet inhibitors in secondary stroke prevention and the enormous risk reduction achieved with oral anticoagulants in patients with AF, it might be surprising that there is no evidence for a beneficial effect of these agents on the risk of VCI. However, few trials included cognitive end points and in none of them the comparison was against placebo, which, in addition to other factors (Table 2), might explain the missing evidence. Regardless of the paucity of data for cognitive end points, adherence to current guidelines for primary and secondary stroke prevention remains a priority.

Ongoing Trials
Table 3 provides an overview of ongoing trials that are targeted against established risk factors for VaD and in which dementia or cognitive impairment is a major end point. Most single-component interventions such as the SBP intervention trial (SPRINT) and the secondary prevention of small subcortical strokes trial (SPS3) are targeted against cardiovascular end points with cognitive end points as secondary outcome measures. An exception is the efficacy and safety study of nimodipine to prevent mild cognitive impairment after acute ischemic strokes (NICE), which has cognitive function as the primary and VaD as a secondary end point.

Multicomponent interventions target multiple risk factors in parallel, and there are several ongoing trials with cognitive decline or dementia as a primary end point. The Prevention of Dementia by Intensive Vascular Care (PreDIVA) trial examines whether nurse-led intensive vascular care in nondemented elderly subjects decreases the incidence of dementia. Intensive care comprises both medical and lifestyle interventions, including a program for smoking cessation and physical exercise. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and disability (FINGER) and the Austrian Polypol intervention Study to Prevent Cognitive Decline After Ischemic Stroke (ASPIST) recruit younger subjects at increased risk for development of dementia. The first results of these trials are expected in 2013.

Novel Molecular Targets
Genetic approaches and experimental studies in model systems of acute and chronic ischemia have identified a variety of targets linking specific molecules or cellular pathways to VCI. Examples include NOTCH3 and HTRA1 as target genes implicated in cerebral small vessel disease, and the APOE ε4 allele as a risk factor for cerebral amyloid angiopathy. These findings highlight the importance of considering novel disease markers and ethiological subtypes of VCI such as subcortical ischemic vascular disease. Also, there is growing evidence for a key role of radical oxygen species in mediating some of the deleterious effects of aging, hypertension, and amyloid β on small blood vessels, all of which are major risk factors for dementia. These findings provide a starting point for developing targeted preventive treatments.

Challenges and Opportunities
The available data emphasize the need for properly designed trials overcoming the limitations outlined in Table 2. Key aspects include: (1) the inclusion of subjects in the appropriate age range and at increased risk for development of dementia; (2) the use of cognitive test batteries that are sensitive to change and to the typical profile of deficits in patients with VCI; (3) a sufficiently long duration of treatment and follow-up; (4) and specific actions to account for differential dropout and competing risks.

It might be questioned whether preventing VaD as a specific diagnostic category rather than dementia in general represents a meaningful goal. As outlined, VaD and AD have many risk factors in common (Figure 1), which means that most strategies to prevent VaD will likely affect the risk of AD. Also, many patients have mixed vascular and neurodegenerative pathology and disentangling the different components with sufficient diagnostic accuracy requires substantial diagnostic efforts. Apart from imposing a burden on patients, these investigations often are not realistic in the setting of a preventive trial with many thousands of subjects.

Without doubt, however, preventing vascular brain damage remains an important goal. The increasingly recognized association between cognitive impairment and both covert brain infarcts and ischemic white matter lesions illustrates the need to consider neuroimaging in future intervention trials. “Silent” brain infarcts outnumber clinically manifest strokes by a factor of >5 to 1, and including neuroimaging markers as adjunct outcomes may be a way to increase the power of future preventive trials.

In light of the high risk of cognitive decline and dementia after stroke, particularly recurrent stroke, future acute stroke trials and secondary prevention trials should include cognitive end points as standard outcomes. Ideally, this should be combined with longer follow-up than is seen in current trials. The additional costs associated with such an extension are more than justified given the enormous socioeconomic impact of poststroke dementia and VCI in general.

The prevalence of VCI and VaD will likely increase over the next decades both in high-income and low-income countries. Preventing vascular disease remains the most promising strategy to prevent VaD and possibly dementia in general, although the level of evidence remains low for most interventions (Table 1). Thus, there is great demand for large, properly designed trials. In the meantime, multicomponent interventions aimed at reducing the burden of vascular disease should be considered a reasonable approach to prevent cognitive impairment and dementia.

Sources of Funding
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Disclosures
None.
References


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Martin Dichgans and Vera Zietemann

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Prevention of Vascular Cognitive Impairment

Methods
We performed a comprehensive search for articles presenting results regarding the association between individual risk factors (listed in supplement table 1) as well as interventions (listed in supplement table 2) and the following endpoints: cognitive impairment, dementia (unspecified), AD and VaD. We searched MEDLINE and the Cochrane database up to March 2012 and included full-text articles published in English language. Reference lists of all identified reviews, meta-analyses and original studies were manually screened to identify additional potentially relevant citations. We updated eligible reviews with relevant original studies. We included community-based longitudinal studies and randomized controlled trials and considered results from cross-sectional studies and case-control studies for risk factors and therapies where evidence was unavailable or insufficient from prospective studies. Results from relevant older literature are presented if they were excluded in reviews or meta-analyses. Original studies were not cited in supplementary tables 1 and 2 if covered by systematic reviews or meta-analysis, unless they were judged as particularly relevant. Author, publication year, information about study population and effect estimate (if available) were extracted from articles. We present effect estimates stratified for identified relevant effect modifiers (e.g. age, APOE). We furthermore mention if effect measures are derived from specific subgroups (e.g. patients with MCI or stroke).

Nonmodifiable Risk factors
Genetic factors such as the APOE ε4 allele, which is the strongest known risk factor for AD apart from age, are generally considered non-modifiable. Yet, genetic information may aid in tailoring prevention, particularly in monogenic conditions. Mutations in a number of genes implicated in vascular conditions such as CADASIL or sickle cell disease may cause VCI.\textsuperscript{1,2} Up to now, however, there is limited evidence for a contribution of common genetic variants to the risk of VCI.\textsuperscript{3}
S1: Recently published articles stratified for risk factors and type of dementia.

Results derived from meta-analyses (MA) are considered as highest evidence. Results from cross-sectional (CS) or case-control (CC) studies are in italics.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>VaD</th>
<th>AD</th>
<th>Dementia (unspecified)</th>
<th>Cognitive Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Pendlebury 2009&lt;sup&gt;2&lt;/sup&gt; MA: sign. predictor of post-stroke dementia: older age (p&lt;0.0001) Kuller 2005&lt;sup&gt;3&lt;/sup&gt; CHCS: age at MRI (continuous): HR=1.1 [1.1-1.2] Lobo 2000&lt;sup&gt;6&lt;/sup&gt; MA of European population-based studies: prevalence (age-stratified): 65-69y: 0.3%; ≥90y: 5.2%</td>
<td>Reitz 2010&lt;sup&gt;4&lt;/sup&gt; Community-based study: late onset AD: &gt;70-75y: HR=2.2 [0.8-6.6]; &gt;75-80y: HR=3.1 [1.03-9.1]; &gt;80-85y: HR=6.4 [2.1-20.0]; &gt;85y: HR=18.0 [5.9-54.8] Lobo 2000&lt;sup&gt;6&lt;/sup&gt; MA of major European population-based studies: prevalence (age-stratified): 65-69y: 0.8%; ≥90y: 22.2%</td>
<td>Meija-Arango 2011&lt;sup&gt;7&lt;/sup&gt; MHAS: increased incidence rates with age Corrada 2010&lt;sup&gt;5&lt;/sup&gt; 90+Study: rates increased exponentially with age Lobo 2000&lt;sup&gt;6&lt;/sup&gt; MA of major European population-based studies: prevalence (age-stratified): 65-69y: 0.8%; ≥90y: 28.5%</td>
<td>Meija-Arango 2011&lt;sup&gt;7&lt;/sup&gt; (CIND) MHAS: incidence rate/1.000 (age-stratified): 60-69y: 206; 70-79y: 237; ≥80y: 201</td>
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<tr>
<td><strong>Genetic factors</strong> (APOE ε4 carrier vs. non carrier)</td>
<td>Yin 2012&lt;sup&gt;14&lt;/sup&gt; MA (CC studies): OR=1.7 [1.4-2.1] Lui 2012&lt;sup&gt;15&lt;/sup&gt; MA (CC studies): OR=2.1 [1.7-2.5] Kim 2008&lt;sup&gt;16&lt;/sup&gt; CC study: p&gt;0.1</td>
<td>Webster 2010&lt;sup&gt;17&lt;/sup&gt; MA: OR=3.8 [3.4-4.3] Reitz 2010&lt;sup&gt;4&lt;/sup&gt; (late onset probable &amp; possible AD) Community-based study: 1.8 [1.02-3.3] Bertram 2007&lt;sup&gt;18&lt;/sup&gt; MA: rs405509 (Th1/E47cs): OR=0.8 [0.7-0.9] Klages 2005&lt;sup&gt;19&lt;/sup&gt; CS HA: OR=3.5 [1.1-10.5]</td>
<td>Beydoun 2012&lt;sup&gt;19&lt;/sup&gt; BLSA: HR=2.9 [1.9-4.3] Wang 2012&lt;sup&gt;20&lt;/sup&gt; MA from 3 major population-based studies (CS design): OR=3.7 [1.8-7.2]</td>
<td>Boyle 2010&lt;sup&gt;22&lt;/sup&gt; (McD) Religious Orders Study: HR=1.4 [1.04-1.8] Luck 2010&lt;sup&gt;23&lt;/sup&gt; (amyotrophic MCI) AgeCoDe: OR=2.4 [1.5-3.9] Heun 2010&lt;sup&gt;24&lt;/sup&gt; (MCI) LEILA75+: p-value&gt;0.5</td>
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<tr>
<td><strong>Education / Lifestyle</strong></td>
<td>Ott 1995&lt;sup&gt;25&lt;/sup&gt; Rotterdam study (CS-analysis): education (lowest vs. highest quartile): OR=2.1 [1.0-4.5]</td>
<td>Brayne 2010&lt;sup&gt;26&lt;/sup&gt; ECipsE: education (per y): OR=0.89 [0.83-0.94] Ngandu 2007&lt;sup&gt;27&lt;/sup&gt; CAIDE: ≥9y vs. ≤5y education: OR=0.15 [0.05-0.4]</td>
<td>Meija-Arango 2011&lt;sup&gt;7&lt;/sup&gt; MHAS: increased incidence rates associated with lower education Ngandu 2007&lt;sup&gt;27&lt;/sup&gt; CAIDE: ≥9y vs. ≤5y education: OR=0.2 [0.1-0.4]</td>
<td>Marengoni 2011&lt;sup&gt;28&lt;/sup&gt; (CIND) InChianti Study: low vs. high education: OR=1.7 [1.04-2.6] Reuser 2011&lt;sup&gt;29&lt;/sup&gt; (cognitive impairment) HRS: higher education sign. protective</td>
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<td>study</td>
<td>education / lifestyle (continued)</td>
<td>VaD</td>
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<td>Rotterdam study (CS analysis): education (lowest vs. highest quartile): OR=4.0 [2.5-6.2]</td>
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<td>Wang 2012</td>
<td>MA from 3 population-based studies (CS design): ≥8y vs. &lt;8y education OR=0.8 [0.3-0.6]</td>
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<td>Valenzuela 2011</td>
<td>CFAS: high vs. low tertile of cognitive lifestyle score: OR=0.6 [0.4-0.9]</td>
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<td>Karp 2009</td>
<td>Kungsholmen Project: complexity of work: with data: RR=0.85 [0.75-0.95], with people: RR=0.88 [0.80-0.97]</td>
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<td>Mejia-Arango 2011</td>
<td>MHCAS: incidence rate/1.000, duration of education: 0y: 242; 1-6y: 221; &gt;6y: 155</td>
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<td>Luck 2010</td>
<td>MCI: MA (9 studies): evidence for lower education as risk factor</td>
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<td>Peters 2008</td>
<td>MA (2 studies): current smoking: summary ratio=1.8 [1.3-2.5]</td>
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<td>Peters 2008</td>
<td>MA (5 studies): current smoking: summary ratio=1.2 [0.9-1.6]</td>
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<td>Anstey 2007</td>
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**smoking (vs. non or never smoking)**

- Rusanen 2011
  - MHC: midlife current smoking: HR=2.7 [1.2-6.2]
- Peters 2008
  - MA (4 studies): current smoking: summary ratio=1.3 [0.9-2.0]
- Anstey 2007
  - MA (2 studies): current smoking: RR=1.8 [1.3-2.5]

⇒ strong evidence for increased risk associated with smoking

- Rusanen 2011
  - MHC: midlife current smoking: HR=2.6 [1.6-4.0]
- Rusanen 2010
  - CAIDE: midlife current smoking: OR=2.2 [0.9-5.4]; APOE ε4 carrier: OR=6.6 [1.8-23.9]
- Cataldo 2010
  - MA: without tobacco industry affiliation (14 studies): RR=1.4 [1.2-1.8]; with tobacco industry affiliation (3 studies): RR=0.6 [0.3-1.3]
- Hernan 2008
  - Systematic Review (12 studies): smoking as risk factor in studies with younger participants at baseline, but sometimes protective factor in studies with older participants; discussion of selection bias
- Peters 2008
  - MA (8 studies): current smoking: summary ratio=1.6 [1.1-2.2]
- Anstey 2007
  - MA (4 studies): current smoking: RR=1.8 [1.4-2.2]

⇒ strong evidence for increased risk associated with smoking, maybe modification by APOE

- Rusanen 2011
  - MHC: midlife current smoking: HR=2.1 [1.6-2.8]
- Rusanen 2010
  - CAIDE: midlife current smoking: OR=1.5 [0.7-3.6]; APOE ε4 carrier: OR=4.9 [1.5-16.1]
- Barnes 2010
  - CHCS: secondhand smoke (vs. 0-15y): 16-25y: HR=1.1 [0.4-2.4]; >25y: HR=0.8 [0.3-1.5]; stenosis >25% & SHS >25y: HR=3.0 [1.03-9.7]
- Hernan 2008
  - Systematic Review (6 studies): smoking as risk factor in studies with younger participants at baseline, but sometimes protective factor in studies with older participants; discussion of selection bias
- Peters 2008
  - MA (5 studies): current smoking: summary ratio=1.2 [0.9-1.6]
- Anstey 2007
  - MA (2 studies): current smoking: RR=1.3 [1.02-1.6]

⇒ strong evidence for increased risk associated with smoking, maybe modification by APOE

- Cherbuin 2009
  - MCI: PATH through Life Study: past smoking: OR=3.2 [1.05-9.9]
- Yaffe 2009
  - MA (6 studies): current smoking: summary ratio=1.2 [0.9-1.6]
- Peters 2008
  - MA (5 studies): current smoking: summary ratio=1.2 [0.9-1.6]
- Sabia 2008
  - MA (7 studies): current smoking: memory: OR=1.4 [1.1-1.7]; longitudinal analysis: inconsistent results
- Anstey 2007
  - MA (3 studies): current smoking: β=-0.13 [-0.2 to -0.08] (p<0.001)

⇒ some evidence for increased risk associated with smoking, risk may vary with regard to single cognitive domains
### VaD

<table>
<thead>
<tr>
<th>Diet</th>
<th>Solfrizzi 2011</th>
<th>Review: fatty acids, fish (1 study): no sign. association; dietary dairy products (1 study): almost-daily intake associated with sign. reduced likelihood</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Solfrizzi 2011</td>
<td>Review: MeDi (4 studies): (sign.) reduced risk; fatty acids, fish (6 studies): possible reduced risk; dietary dairy products (1 study): no sign. effect; fruit &amp; vegetable (2 studies): reduced risk</td>
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<td></td>
<td>Morris 2011</td>
<td>Review: dietary antioxidant (9 studies): possible reduced risk; fish &amp; n-3 fatty acids: (sign.) reduced risk</td>
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<td></td>
<td>Fotuhi 2009</td>
<td>Review: (2 cohort studies): MeDi: reduced risk</td>
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</table>

⇒ insufficient evidence

### AD

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<tr>
<th>Dementia (unspecified)</th>
<th>Solfrizzi 2011</th>
<th>Review: fatty acids, fish (4 studies): possible reduced risk; dietary dairy products (1 study): no sign. association; fruit &amp; vegetable (1 study): reduced risk</th>
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<tr>
<td></td>
<td>Morris 2011</td>
<td>Review: dietary antioxidant (4 studies): possible reduced risk; fish &amp; n-3 fatty acids: reduced risk</td>
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<td>Hughes 2010</td>
<td>HARMONY study: fruits &amp; vegetables in diet: associated with decreased risk</td>
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<td>Fotuhi 2009</td>
<td>Systematic Review (7 studies): fish, PUFA: sign. reduced risk (3 studies), sign. only in APOE ε4 non carriers (1 study), no association (3 studies)</td>
</tr>
</tbody>
</table>

⇒ some evidence for decreased risk associated with specific dietary components (fish, antioxidant, fruits, vegetables)

### Cognitive Impairment

<table>
<thead>
<tr>
<th>Dementia (unspecified)</th>
<th>Solfrizzi 2011</th>
<th>Review: fish, monounsaturated fatty acids, PUFA: possible reduced risk</th>
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</thead>
<tbody>
<tr>
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<td>Morris 2011</td>
<td>Review: dietary antioxidant (5 studies): possible reduced risk; fish &amp; n-3 fatty acids: reduced risk</td>
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<tr>
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<td>Tangney 2011</td>
<td>CHAP: MeDi: possible reduced risk</td>
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<td>Cherbuin 2011</td>
<td>Cognitive decline</td>
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<td>Feart 2010</td>
<td>MA: small amounts of alcohol: RR=0.9 [0.7-1.2]</td>
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### Alcohol

<table>
<thead>
<tr>
<th>Alcohol (vs. non-alcohol)</th>
<th>Solfrizzi 2011</th>
<th>Review (4 studies): light-to-moderate alcohol: lower risk</th>
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<tbody>
<tr>
<td></td>
<td>Anstey 2009</td>
<td>MA: light-to-moderate alcohol: RR=0.7 [0.6-0.98]</td>
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<td>Peters 2008</td>
<td>MA: small amounts of alcohol: RR=0.8 [0.5-1.3]</td>
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<td>Weyerer 2011</td>
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<td>Peters 2008</td>
<td>MA: small amounts of alcohol: RR=0.6 [0.4-0.7]</td>
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<td>Panza 2008</td>
<td>MA: small amounts of alcohol: RR=0.7 [0.5-1.0]</td>
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⇒ some evidence for decreased risk associated with specific dietary components (MeDi, fish)

#### MA

<table>
<thead>
<tr>
<th>Alcohol (vs. non-alcohol)</th>
<th>Solfrizzi 2011</th>
<th>Review: light-to-moderate alcohol: lower risk</th>
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<tr>
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<td>Peters 2008</td>
<td>MA: small amounts of alcohol: RR=0.9 [0.7-1.2]</td>
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⇒ inconsistent results
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<tr>
<th>Subheading</th>
<th>Study Details</th>
<th>Results</th>
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<tbody>
<tr>
<td>VaD (vs. non-alcohol) (continued)</td>
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<td>⇒ inconsistent results, some evidence that a light to moderate alcohol consumption is protective</td>
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<td>Alcohol (continued)</td>
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<td>MA (6 CS-studies): SMD=1.30 [0.7-1.8]</td>
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<td>Zylberstein 2011</td>
<td>Prospective population Study of women in Gothenburg: highest vs. lowest Hcy tertile: HR=0.7 [0.3-1.7]</td>
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<td>MA (12 CS-studies): SMD=0.59 [0.4-0.8]</td>
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<td>MA: homocysteine is an independent risk factor for subcortical vascular encephalopathy (OR=5.8)</td>
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<td>Hooshmand 2010</td>
<td>CAIDE: 1µmol/L increase: 1.2 [1.01-1.4]</td>
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<td>Van Dam 2009</td>
<td>MA: highest vs. lowest Hcy tertile: HR=2.4 [1.3-4.7]</td>
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<td>MA (3 studies): RR=2.5 [1.4-4.6]</td>
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<td>Kivipelto 2009</td>
<td>Kungsholmen Project: high vs. low Hcy quartile: OR=2.3 [1.2-4.6]</td>
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<td>Ravaglia 2007</td>
<td>CSBA: HHcy: HR=1.8 [1.02-3.6]</td>
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<td>Ravaglia 2005</td>
<td>CSBA: tHcy&gt;15µmol/L: HR=2.8 [1.3-6.3]</td>
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<td>Seshadri 2002</td>
<td>Framingham Study: each increase of 1SD: RR=1.8 [1.3-2.5]</td>
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<td>Aarsland 2010</td>
<td>MA: highest vs. lowest category: OR=0.6 [0.4-0.9]</td>
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<td>MA: highest vs. lowest category: RR=0.5 [0.4-0.8]</td>
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<td>Physical activity</td>
<td>Aarsland 2010</td>
<td>MA: highest vs. lowest category: OR=0.6 [0.4-0.9]</td>
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<tr>
<td>Physical Activity (continued)</td>
<td>Cognitive Impairment</td>
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<td><strong>VaD</strong></td>
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**VaD**

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<th>Author</th>
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<tbody>
<tr>
<td>Ravaglia 2008*</td>
<td></td>
<td>Total physical activity:</td>
<td>HR=0.2 [0.1-0.6], walking: HR=0.3 [0.1-0.6], moderate activity: HR=0.3 [0.1-0.7]</td>
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<tr>
<td>Scarmeas 2009*</td>
<td></td>
<td>WHICAP: much vs. no physical activity:</td>
<td>HR=0.7 [0.5-0.95]</td>
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<tr>
<td>Ravaglia 2008*</td>
<td></td>
<td>CSBA: no sign. effect on different types of physical activities</td>
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**AD**

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<tr>
<th>Author</th>
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<tbody>
<tr>
<td>Health ABC Study</td>
<td>2009</td>
<td>Weekly moderate to vigorous exercise:</td>
<td>OR=1.3 [1.0-1.6]</td>
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<tr>
<td>Sturman 2005*</td>
<td></td>
<td>Cognitive decline</td>
<td>CHAP:</td>
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**Dementia (unspecified)**

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<th>Author</th>
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<tbody>
<tr>
<td>Yaffe 2009*</td>
<td></td>
<td>(maintaining cognitive function)</td>
<td></td>
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**BMI (vs. normal)**

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<tbody>
<tr>
<td>Anstey 2011*</td>
<td></td>
<td>MA (2 studies):</td>
<td>midlife overweight BMI: RR=1.3 [1.02-1.7]</td>
</tr>
<tr>
<td>Xu 2011*</td>
<td></td>
<td>Swedish Twin Registry:</td>
<td>overweight: OR=1.2 [0.7-2.0]; obesity: OR=3.5 [1.4-9.0]; continuous: OR=1.11 [1.04-1.2]</td>
</tr>
<tr>
<td>Beydoun 2008*</td>
<td></td>
<td>MA (3 studies):</td>
<td>obesity: OR=1.7 [0.5-6.3]; baseline age &lt;60y: RR=5.0 [3.0-8.4]; baseline age 60+: RR=0.9 [0.5-1.6]</td>
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**BMI**

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<tr>
<td>Anstey 2011*</td>
<td></td>
<td>MA (3 studies):</td>
<td>midlife overweight BMI: RR=1.3 [1.2-1.5]; midlife obese BMI: RR=2.0 [1.6-2.6]; midlife low BMI: RR=2.0 [1.3-2.9]</td>
</tr>
<tr>
<td>Xu 2011*</td>
<td></td>
<td>Swedish Twin Registry:</td>
<td>overweight: OR=1.9 [1.3-2.8]; obesity: OR=3.4 [1.5-7.9]; continuous: OR=1.06 [1.01-1.1]</td>
</tr>
<tr>
<td>Profenno 2010*</td>
<td></td>
<td>MA (8 studies):</td>
<td>obesity: OR=1.6 [1.02-2.5]</td>
</tr>
<tr>
<td>Beydoun 2008*</td>
<td></td>
<td>MA (4 studies):</td>
<td>obesity: OR=1.8 [1.00-3.3]; baseline age &lt;60y: RR=3.1 [2.2-4.4]; baseline age 60+: RR=1.4 [0.9-1.7]</td>
</tr>
<tr>
<td>Kivipelto 2005*</td>
<td></td>
<td>CAIDE: BMI&gt;30:</td>
<td>1.8 [0.9-3.5]</td>
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<td>midlife overweight BMI: RR=1.3 [1.1-1.4]; midlife obese BMI: RR=1.6 [1.3-2.0]</td>
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<td>Kerwin 2011*</td>
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<td>WHIMS: waist-hip ratio &amp; BMI:</td>
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<td>Beydoun 2008*</td>
<td></td>
<td>MA (4 studies):</td>
<td>obesity: OR=1.7 [1.07-1.7]; overweight (5 studies): OR=0.9 [0.6-1.3]; obesity (3 studies): OR=1.4 [0.9-2.2]; sign. U-shaped association; obesity: baseline age &lt;60y: RR=1.7 [1.3-2.3]; baseline age 60+: RR=1.3 [0.7-2.4]</td>
</tr>
<tr>
<td>Whitmer 2008*</td>
<td></td>
<td>MHC: highest vs. lowest sagittal abdominal diameter (SAD):</td>
<td>HR=2.7 [2.3-3.3]; BMI&gt;30 &amp; high SAD: HR=3.6 [2.8-4.5]</td>
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<td>OR=2.1 [1.2-3.8]</td>
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<td>Stewart 2005*</td>
<td></td>
<td>HAAS: men with incident dementia had an additional yearly weight loss:</td>
<td>0.4kg [-0.5 to -0.2]</td>
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<td>(MMSE) Whitehall II Study:</td>
<td>obese at 2 or 3 occasions: difference in mean T scores: MMSE: -1.5 [-2.8 to -0.2], memory score: -1.3 [-2.5 to -0.07], executive function: -1.3 [-2.4 to -0.2]; underweight at ≥2 occasions: executive function: -4.6 [-4.9 to -2.2]</td>
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<td>MA (4 studies):</td>
<td>obesity: OR=1.7 [1.07-1.7]; overweight (5 studies): OR=0.9 [0.6-1.3]; obesity (3 studies): OR=1.4 [0.9-2.2]; sign. U-shaped association; obesity: baseline age &lt;60y: RR=1.7 [1.3-2.3]; baseline age 60+: RR=1.3 [0.7-2.4]</td>
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<td>Dementia (unspecified)</td>
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<td>---------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Blood pressure, (hypertension vs. no hypertension)</td>
<td>Sharp 2011(^{17})&lt;br&gt;MA (6 studies): OR=1.6 [1.3-1.9]</td>
<td>Guan 2011(^{17})&lt;br&gt;MA (9 studies; 2 studies with baseline age &lt;60): RR=1.02 [0.9-1.1]</td>
<td>Kimm 2011(^{18})&lt;br&gt;cohort study: unspecified dementia: stage 2 hypertension: men: HR=1.5 [1.1-2.0], women: HR=1.4 [1.1-1.7]</td>
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<td></td>
<td>Kimm 2011(^{18})&lt;br&gt;cohort study: stage 2 hypertension: men: HR=2.6 [1.7-3.8], women: HR=2.3 [1.6-3.3]</td>
<td>Power 2011(^{19})&lt;br&gt;MA (18 studies, mainly late life measures of BP): hypertension: RR=0.97 [0.8-1.2], 10-mm SBP increase: RR=0.95 [0.9-1.0], 10-mm DBP increase: RR=0.94 [0.8-1.04]</td>
<td>Ninomiya 2011(^{19})&lt;br&gt;Hisayama Study: stage 2 hypertension: HR=1.2 [0.7-2.0]</td>
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<td></td>
<td>Ninomiya 2011(^{19})&lt;br&gt;Hisayama Study: stage 2 hypertension: HR=7.3 [1.5-34.2]</td>
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<td>Stewart 2009(^{22})&lt;br&gt;HAAS: men who develop dementia: in midlife additional increase in SBP, in late-life additional decline in SBP</td>
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<td>Duron 2008(^{21})&lt;br&gt;Review (4 studies): sign. positive association (2 studies), positive association (2 studies)</td>
<td>Bermejo-Pareja 2010(^{23})&lt;br&gt;NEDICES: drug-untreated: HR=2.1 [0.98-4.4], drug-treated: HR=1.4 [0.89-2.2]</td>
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<td>Feldstein 2010(^{24})&lt;br&gt;Review: midlife hypertension (3 studies): 2 studies sign. increased; &gt;65y (5 studies): 4 studies no sign. association, controversial effects</td>
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<tr>
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<td>Nagai 2010(^{20})&lt;br&gt;Review (4 studies): sign. increased (1 study), no sign. association (3 studies)</td>
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<td>Kennelly 2009(^{25})&lt;br&gt;Review: hypotension in late life: increased risk</td>
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<td></td>
<td>Duron 2008(^{21})&lt;br&gt;Review (8 studies): sign. positive association (5 studies), positive association (1 study), no association (1 study), negative association (1 study)</td>
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<td>Ohara 2011(^{27})&lt;br&gt;Hisayama Study: HR=1.8 [0.9-3.7]</td>
<td>Ohara 2011(^{27})&lt;br&gt;Hisayama Study: HR=2.0 [1.2-3.6]</td>
<td>Ohara 2011(^{27})&lt;br&gt;Hisayama Study: HR=1.7 [1.2-2.5]</td>
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\(^{11}\)Strong evidence for increased risk associated with higher blood pressure

\(^{12}\)Inconsistent results, age-dependent association

\(^{13}\)Hyper-glycemia, diabetes
| hyper-glycemia, diabetes (vs. no diabetes) (continued) | Kimm 2011\textsuperscript{114} cohort study: men: HR=2.0 [1.5-2.8], women: HR=2.8 [2.0-3.9] | Huang 2016\textsuperscript{115} cohort study: high cholesterol: men: HR=1.2 [1.0-1.5], women: HR=1.3 [1.0-1.5] | Hsu 2011\textsuperscript{116} Taiwan’s National Health Insurance database: DM without oral agents: HR=2.4 [2.2-2.7], DM with oral agents: HR=1.6 [1.5-1.8] | Raffaitin 2011\textsuperscript{117} (cognitive decline) 3-City Study: Isaccs Set Test: HR=1.2 [1.03-1.4], Benton Visual Retention Test: HR=1.2 [1.02-1.4] |
| | Ahniluoto 2010\textsuperscript{111} cohort of Medicare recipients (Manhattan): higher HDL-C: HR=0.4 [0.2-0.9] | Reitz 2010\textsuperscript{112} cohort study: unspecified dementia: high cholesterol: men: HR=1.0 [0.8-1.3], women: HR=1.1 [0.9-1.4] | Solomon 2009\textsuperscript{116} CAIDE: high midlife cholesterol associated with poorer late-life episodic memory & category fluency | Anstey 2008\textsuperscript{112} MA: midlife cholesterol associated with cognitive impairment, but only weak evidence for association with cognitive decline |
| | Verdelho 2010\textsuperscript{110} LADIS Study: HR=2.4 [1.3-2.0] | Haas: cholesterol levels declined at least 15 years before diagnosis | Reitz 2008\textsuperscript{111} 3-City Study: high triglyceride level: HR=1.4 [1.05-2.00] | Reitz 2008\textsuperscript{111} (MCI) Longitudinal cohort of Medicare recipients (Manhattan): no association between lipids and risk of amnestic or nonamnestic MCI |
| | Luchsinger 2010\textsuperscript{113} MA (8 studies): RR=1.4 [1.2-1.7] | | | ⇒ inconsistent results, most studies no association |
| | Review: association seems to be stronger for VaD compared to AD | | | ⇒ inconsistent results, may be age-dependent association |
| | Lu 2009\textsuperscript{114} MA (6 studies): RR=1.5 [1.2-1.7] | | | => some evidence for increased risk associated with diabetes |
| | Biessels 2006\textsuperscript{115} Systematic Review (13 studies): higher risk with diabetes (8 studies) | | | => inconsistent results, most studies no association |
| | Biessels 2006\textsuperscript{115} Systematic Review (9 studies): higher risk with diabetes (6 studies) | | | => inconsistent results, most studies no association |
| lipids | Kimm 2011\textsuperscript{114} cohort study: high cholesterol: men: HR=1.1 [0.8-1.6], women: HR=0.9 [0.7-1.3] | Kimm 2011\textsuperscript{114} cohort study: high cholesterol: men: HR=1.2 [1.0-1.5], women: HR=1.1 [0.9-1.3] | Kimm 2011\textsuperscript{114} cohort study: unspecified dementia: high cholesterol: men: HR=1.0 [0.8-1.3], women: HR=1.1 [0.9-1.4] | Beydoun 2011\textsuperscript{115} BLSA: highest vs. lowest cholesterol quartile: HR=1.3 [0.8-2.1] |
| | Solomon 2009\textsuperscript{110} MHC: midlife high cholesterol: HR=1.3 [0.8-2.0] | Reitz 2010\textsuperscript{112} cohort of Medicare recipients (Manhattan): higher HDL-C: HR=0.4 [0.2-0.9] | Solomon 2009\textsuperscript{110} MHC: midlife high cholesterol: HR=1.6 [1.2-2.0] | Solomon 2009\textsuperscript{116} CAIDE: high midlife cholesterol associated with poorer late-life episodic memory & category fluency |
| | Raffaitin 2009\textsuperscript{111} 3-City Study: high triglyceride level: HR=2.3 [1.2-4.4] | Reitz 2010\textsuperscript{112} cohort of Medicare recipients (Manhattan): higher HDL-C: HR=0.4 [0.2-0.9] | Anstey 2008\textsuperscript{112} MA: high midlife but not late-life cholesterol associated with AD | Anstey 2008\textsuperscript{112} MA: midlife cholesterol associated with cognitive impairment, but only weak evidence for association with cognitive decline |
| | Anstey 2008\textsuperscript{112} MA: cholesterol (midlife or late-life) in no study associated with VaD | | | Reitz 2008\textsuperscript{111} (MCI) Longitudinal cohort of Medicare recipients (Manhattan): no association between lipids and risk of amnestic or nonamnestic MCI |
| | ⇒ inconsistent results, most studies no association | ⇒ inconsistent results, most studies no association | ⇒ inconsistent results, maybe age-dependent association | ⇒ inconsistent results, most studies no association |
### Inflammation

**VaD**

- Ravaglia 2007<br> CSBA: CRP: HR=2.9 [1.4-6.2], IL6: no association, combination of CRP & IL6: HR=2.6 [1.2-5.5]
- Schmidt 2002<br> HAAS: highest vs. lowest midlife CRP quartile: OR=5.1 [1.8-14.8] (p for trend: <0.006)
- Engelhart 2004<br> Rotterdam Study; CRP: RR=1.3 [1.06-1.6], IL6: RR=1.3 [0.97-1.6]

⇒ some evidence for increased risk associated with inflammation

**AD**

- Eriksson 2011<br> STR (nested CC (incident) sample): CRP: OR=1.3 [0.7-2.5], IL6: OR=1.3 [0.6-2.9]
- Sundeløf 2009<br> ULSAM: CRP, IL6, SAA, PGF₂α: no association
- Tan 2007<br> CSBA: CRP, IL6, combination of CRP & IL6: HR=1.6 [1.03-2.4]
- Schmidt 2002<br> HAAS: highest vs. lowest midlife CRP quartile: OR=2.8 [1.6-5.1] (p for trend: <0.002)
- Engelhart 2004<br> Rotterdam Study; CRP: RR=1.1 [0.96-1.3], IL6: RR=1.3 [1.06-1.5]

⇒ inconsistent results, most studies no association

### Stroke

**MA:** post-stroke dementia: previous stroke: OR=1.9 [1.5-2.3], multiple strokes: OR=2.5 [1.9-3.1], recurrent stroke: OR=2.3 [1.5-3.5]

- Kuller 2005<br> CHCS: incident stroke: HR=4.5 [3.1-6.5]

⇒ strong evidence for increased risk associated with stroke

**Cognitive Impairment**

- Gorelick 2010<br> Review (including HAAS, MSSA, WHICAP II, Framingham Offspring Study): consistent relationship between systemic inflammatory marker & dementia
- Sundeløf 2009<br> HAAS: highest vs. lowest midlife CRP quartile: OR=2.2 [0.9-5.1] (p for trend: <0.05, sign. for 2nd & 3rd quartile)
- Engelhart 2004<br> Rotterdam Study; CRP: RR=1.1 [0.99-1.2], IL6: RR=1.3 [1.05-1.6]

⇒ some evidence for increased risk associated with inflammation

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**Dementia (unspecified)**

- Gorelick 2010<br> Review (including HAAS, MSSA, WHICAP II, Framingham Offspring Study): consistent relationship between systemic inflammatory marker & dementia
- Sundeløf 2009<br> HAAS: highest vs. lowest midlife CRP quartile: OR=5.1 [1.8-14.8] (p for trend: <0.006)
- Engelhart 2004<br> Rotterdam Study; CRP: RR=1.1 [0.96-1.3], IL6: RR=1.3 [1.06-1.5]

⇒⇒⇒ some evidence for increased risk associated with inflammation

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**MoVIES**

- stroke/TIA history: HR=1.7 [0.9-1.8], CRP22: HR=1.3 [0.5-3.5], IL6: HR=2.6 [0.9-6.1], TNF-alpha: HR=2.6 [1.1-6.1]
- Schmidt 2002<br> Framingham study: highest tertile: CRP16: HR=0.4 [0.1-1.8], CRP22: HR=1.7 [0.7-3.7], IL6: HR=1.3 [0.5-3.5], IL1: HR=2.6 [0.9-6.1], TNF-alpha: HR=2.6 [1.1-6.1]
- Engelhart 2004<br> Rotterdam Study; CRP: RR=1.1 [0.96-1.3], IL6: RR=1.3 [1.06-1.5]

⇒⇒⇒ some evidence for increased risk associated with inflammation

**Post-stroke dementia**

- previous stroke: OR=1.9 [1.5-2.3], multiple strokes: OR=2.5 [1.9-3.1], recurrent stroke: OR=2.3 [1.5-3.5]
- Liman 2011<br> MA: post-stroke dementia: previous stroke: OR=1.9 [1.5-2.3], multiple strokes: OR=2.5 [1.9-3.1], recurrent stroke: OR=2.3 [1.5-3.5]

⇒⇒⇒ some evidence for increased risk associated with stroke

**Post-stroke dementia**

- previous stroke: OR=1.9 [1.5-2.3], multiple strokes: OR=2.5 [1.9-3.1], recurrent stroke: OR=2.3 [1.5-3.5]
- Liman 2011<br> MA: post-stroke dementia: previous stroke: OR=1.9 [1.5-2.3], multiple strokes: OR=2.5 [1.9-3.1], recurrent stroke: OR=2.3 [1.5-3.5]

⇒⇒⇒ some evidence for increased risk associated with stroke
<table>
<thead>
<tr>
<th>coronary artery disease (CAD)</th>
<th>VaD</th>
<th>AD</th>
<th>Dementia (unspecified)</th>
<th>Cognitive Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuller 2005&lt;sup&gt;5&lt;/sup&gt; CHCS: history of CAD: HR=1.4 [1.1-1.9] history of bypass surgery: HR=2.6 [1.7-4.1]</td>
<td>Vidal 2010&lt;sup&gt;175&lt;/sup&gt; CHS: history of coronary bypass surgery identified as risk factor</td>
<td>( \Rightarrow ) some evidence for increased risk associated with CAD</td>
<td>( \Rightarrow ) some evidence for increased risk associated with CAD</td>
<td></td>
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<tr>
<td>Beeri 2006&lt;sup&gt;174&lt;/sup&gt; Autopsy sample: CAD associated with the density of cardinal neuropathologic lesions of AD, more pronounced for APOE e4 carrier</td>
<td>Barnes 2009&lt;sup&gt;176&lt;/sup&gt; CHCS: history of coronary bypass surgery identified as risk factor</td>
<td>( \Rightarrow ) insufficient evidence</td>
<td>( \Rightarrow ) insufficient evidence</td>
<td></td>
</tr>
<tr>
<td>CHS: history of CAD: HR=1.4 [1.1-1.9], history of bypass surgery: HR=2.6 [1.7-4.1]</td>
<td>( \Rightarrow ) some evidence for increased risk associated with CAD</td>
<td>( \Rightarrow ) some evidence for increased risk associated with CAD</td>
<td>( \Rightarrow ) some evidence for increased risk associated with CAD, from cross-sectional analyses</td>
<td></td>
</tr>
</tbody>
</table>

| atherosclerosis | Rabkin 2011<sup>178</sup> Review (6 studies): pulse wave velocity significantly higher in VaD compared with controls: mean difference: 0.7 [0.4 to 0.9] | Rabkin 2011<sup>178</sup> Review (6 studies): pulse wave velocity higher in VaD compared with AD: mean difference: 0.4 [0.1 to 0.7] | Dolan 2010<sup>40</sup> BLSA: atherosclerosis of the intracranial arteries (but not coronary or aortic atherosclerosis) is an independent risk factor | Pase 2011<sup>41</sup> (cognitive decline) MA (6 studies): arterial stiffness predictive of cognitive decline in 5 studies: \( \beta \approx 0.03 \) [-0.06 to 0.01] |
| Rabkin 2011<sup>178</sup> Review (6 studies): pulse wave velocity higher in VaD compared with AD: mean difference: 0.7 [0.4 to 0.9] | Dolan 2010<sup>40</sup> BLSA: atherosclerosis of the intracranial arteries (but not coronary or aortic atherosclerosis) is an independent risk factor | \( \Rightarrow \) insufficient evidence | \( \Rightarrow \) insufficient evidence |
| \( \Rightarrow \) some evidence for increased risk associated with atherosclerosis, from case-control studies | \( \Rightarrow \) some evidence for increased risk associated with atherosclerosis, from case-control studies | \( \Rightarrow \) some evidence for increased risk associated with atherosclerosis, from case-control studies | \( \Rightarrow \) some evidence for increased risk associated with atherosclerosis, from case-control studies |

| atrial fibrillation (AF) | Bunch 2010<sup>146</sup> Intermountain Heart Collaborative Study database: OR=1.7 (p=0.001); \( \leq 69y: OR=2.2 \) (p=0.004), 70-79y: OR=1.7 (p=0.02), 80-89y: OR=1.3; p>0.4 | Dublin 2011<sup>147</sup> ACT: HR=1.5 [1.2-1.9] | Kwok 2011<sup>149</sup> MA (14 studies): OR=2.0 [1.4-2.7], stroke patients (7 studies): OR=2.4 [1.7-3.5], patients without stroke (7 studies): OR=1.6 [1.0-2.7] | Mead 2001<sup>150</sup> Systematic Review (1 prospective study, 4 CS-studies, 5 CC-studies): 7 studies found association with at least 1 measure of cognition |
| Marengoni 2011<sup>148</sup> Kingston Project: HR=0.8 [0.4-1.5] | Marengoni 2011<sup>148</sup> Kingston Project: HR=0.8 [0.4-1.5] | Dublin 2011<sup>147</sup> ACT: HR=1.4 [1.1-1.7] | Mead 2001<sup>150</sup> Systematic Review (1 prospective study, 4 CS-studies, 5 CC-studies): 7 studies found association with at least 1 measure of cognition |

| \( \Rightarrow \) some evidence for increased risk associated with atherosclerosis | \( \Rightarrow \) some evidence for increased risk associated with atherosclerosis | \( \Rightarrow \) some evidence for increased risk associated with atherosclerosis | \( \Rightarrow \) some evidence for increased risk associated with atherosclerosis |

| \( \Rightarrow \) some evidence for increased risk associated with cardiovascular disease | \( \Rightarrow \) some evidence for increased risk associated with cardiovascular disease | \( \Rightarrow \) some evidence for increased risk associated with cardiovascular disease | \( \Rightarrow \) some evidence for increased risk associated with cardiovascular disease |

**Not applicable**
<table>
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<tr>
<th>atrial fibrillation (AF) (continued)</th>
<th>VaD</th>
<th>AD</th>
<th>Dementia (unspecified)</th>
<th>Cognitive Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>⇒ some evidence for increased risk associated with AF</td>
<td>Bunch 2010\textsuperscript{176} Intermountain Heart Collaborative Study database: OR=1.1 (p=0.6); 70y: OR=2.3 (p=0.001), &gt;70y: p&gt;0.3</td>
<td></td>
<td>Marengoni 2011\textsuperscript{175} Kungsholmen Project: HR=0.9 [0.5-1.7]</td>
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<tr>
<td>⇒ some evidence for increased risk associated with AF</td>
<td>Bunch 2010\textsuperscript{176} (nonspecific dementia) Intermountain Heart Collaborative Study database: OR=1.4 (p=0.0001), 70y: OR=2.9 (p&lt;0.0001), &gt;80y: p&gt;0.4</td>
<td></td>
<td>⇒ inconsistent results for broader population, maybe modification by stroke and age</td>
<td></td>
</tr>
</tbody>
</table>

| peripheral arterial disease (PAD) | Guerchet 2011\textsuperscript{151} Systematic Review (2 prospective studies, 1 CS study): low ABI: sign. association (2 studies), not sign. decreased (1 study) | Guerchet 2011\textsuperscript{151} Systematic Review (3 prospective studies, 1 CS study): low ABI: sign. association (2 studies), not sign. increased (2 studies) | Guerchet 2011\textsuperscript{151} Systematic Review (4 prospective studies, 2 CS studies): low ABI: sign. association (5 studies) | |
| ⇒ some evidence for increased risk associated with PAD | Newman 2005\textsuperscript{152} CHS: PAD: HR=2.2 [1.1-4.5] | ⇒ some evidence for increased risk associated with PAD | ⇒ strong evidence for increased risk associated with PAD | |

| chronic kidney disease | Helmer 2011\textsuperscript{155} 3-City Study: low eGFR level: RR=0.3 [0.04-2.3]; eGFR decline >4mL/min/1.73m\textsuperscript{2}/y: RR=5.3 [1.8-16.3] Seliger 2004\textsuperscript{154} CHCS: elevated serum creatinine: HR=1.6 [1.1-2.3] | Helmer 2011\textsuperscript{155} 3-City Study: low eGFR level: RR=0.7 [0.4-1.4]; eGFR decline >4mL/min/1.73m\textsuperscript{2}/y: RR=1.3 [0.7-2.4] Seliger 2004\textsuperscript{154} CHCS: elevated serum creatinine: HR=1.1 [0.7-1.6] | Helmer 2011\textsuperscript{155} (MMSE) 3-City Study: low eGFR level: β=0.01 (p=0.5); eGFR decline >4mL/min/1.73m\textsuperscript{2}/y: β=0.123 (p=0.01) | |
| ⇒ some evidence for increased risk associated with chronic kidney disease | ⇒ insufficient evidence | ⇒ strong evidence for increased risk associated with chronic kidney disease | ⇒ strong evidence for increased risk associated with chronic kidney disease | |

| low cardiac output | ⇒ no study identified | Quu 2006\textsuperscript{178} Kungsholmen Project: heart failure: HR=1.8 [1.2-2.6] | ⇒ some evidence for increased risk associated with low cardiac output | |

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Bunch 2010\textsuperscript{176} (MMSE) (cognitive impairment) INVADE: moderate-to-severe kidney disease: OR=2.1 [1.2-3.9] Buchman 2009\textsuperscript{157} (cognitive decline) Rush Memory and Aging Project: impaired kidney function: estimate: -0.03, p=0.003

⇒ some evidence for increased risk associated with chronic kidney disease

⇒ strong evidence for increased risk associated with chronic kidney disease

Quo 2006\textsuperscript{178} (test battery) cohort study: cardiac output predicted decline in attention-executive-psychomotor function

Hoth 2010\textsuperscript{160} (follow-up: 3 month): left ventricular ejection fraction associated with executive functioning (p=0.007), visuospatial function (p=0.01), global cognition (p=0.02)
<table>
<thead>
<tr>
<th></th>
<th>VaD</th>
<th>AD</th>
<th>Dementia (unspecified)</th>
<th>Cognitive Impairment</th>
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<tbody>
<tr>
<td>low cardiac output</td>
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<td></td>
<td>Festa 2011&lt;sup&gt;1&lt;/sup&gt; Retrospective study: left ventricular ejection fraction associated with memory performance but only in persons ≥63y</td>
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<td>(continued)</td>
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<td>Jefferson 2011&lt;sup&gt;2&lt;/sup&gt; (tests) Framingham Heart Study Offspring Cohort: left ventricular ejection fraction associated with mean cognitive performance</td>
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<td></td>
<td>Jefferson 2007&lt;sup&gt;3&lt;/sup&gt; (tests) Geriatric outpatients: low cardiac output sign. associated with DKEFS Tower Test &amp; TMT, no association with other cognitive indices</td>
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<td>⇒⇒⇒⇒ some evidence for increased risk associated with low cardiac output</td>
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<tr>
<td>depression</td>
<td>Lenoir 2011&lt;sup&gt;4&lt;/sup&gt; 3-City Study: depressive symptoms: HR=4.8 [2.2-10.7]</td>
<td>Lenoir 2011&lt;sup&gt;4&lt;/sup&gt; 3-City Study: depressive symptoms: HR=1.0 [0.7-1.6]</td>
<td></td>
<td>Goveas 2011&lt;sup&gt;5&lt;/sup&gt; (MCI) WHI: depressive disorder: HR=2.0 [1.3-2.9]</td>
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<td></td>
<td>Dotson 2010&lt;sup&gt;6&lt;/sup&gt; BLSA: elevated depressive symptoms &gt;1x: HR=1.5 [0.7-3.0], having exactly 1x: HR=1.8 [1.1-3.0]</td>
<td>Spira 2011&lt;sup&gt;7&lt;/sup&gt; SOF: GDS score ≥6: OR=3.1 [1.03-9.6]</td>
<td></td>
<td>Spira 2011&lt;sup&gt;8&lt;/sup&gt; (MCI) SOF: GDS score ≥6: OR=3.7 [1.3-10.6]</td>
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<td>Blasko 2010&lt;sup&gt;9&lt;/sup&gt; VITA: sGDS: OR=1.2 [1.0-1.5]</td>
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<td></td>
<td>Panza 2010&lt;sup&gt;10&lt;/sup&gt; (MCI) Review (4 studies): sign. association (2 studies)</td>
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<td></td>
<td>Becker 2009&lt;sup&gt;11&lt;/sup&gt; CHCS: no sign. association</td>
<td></td>
<td></td>
<td>Dotson 2010&lt;sup&gt;12&lt;/sup&gt; BLSA: elevated depressive symptoms &gt;1x: HR=0.7 [0.3-1.8]</td>
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<td>Irie 2008&lt;sup&gt;13&lt;/sup&gt; HAAS: depressed men: HR=1.3 [0.3-5.8]; without APOE ε4: HR=0.6 [0.1-4.8], with APOE ε4: HR=4.1 [0.5-33.7]</td>
<td></td>
<td></td>
<td>Panza 2008&lt;sup&gt;14&lt;/sup&gt; (MCI) ILSA: depressive symptoms: RR=1.2 [0.8-1.8]</td>
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<td>⇒⇒⇒⇒ inconsistent results</td>
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<td>Goveas 2011&lt;sup&gt;5&lt;/sup&gt; (MCI) ILSA: depressive symptoms: RR=3.7 [1.3-10.6]</td>
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<td>⇒⇒⇒⇒ inconsistent results</td>
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<td>Pathways Epidemiologic Follow-up Study (patients with diabetes): major depression: HR=2.7 [1.8-4.1]</td>
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<td>⇒⇒⇒⇒ strong evidence for increased risk associated with depressive disorder</td>
</tr>
</tbody>
</table>

⇒⇒⇒⇒ inconsistent results
Abbreviations
CIND: cognitive impairment no dementia; MeDi: Mediterranean diet; sign.: significant; y: years

Abbreviations longitudinal studies
ABC study: Health Aging and Body Composition study
ACT: Adult Changes in Thought study
AgeCoDe: German Study on Ageing, Cognition and Dementia in Primary Care Patients
AGES-Reykjavik: Age, Gene/Environment Susceptibility–Reykjavik Study
BLSA: Baltimore Longitudinal Study of Aging
CAIDE: Cardiovascular Risk Factors, Aging and Dementia study
CFAS: Medical Research Council Cognitive Function and Ageing Study
CHAP: Chicago Health and Aging Project
CHCS: Cardiovascular Health Cognition Study
CHS: Cardiovascular Health Study
CIVIC: The consortium to investigate vascular impairment of cognition
CODAS: Cognitive Disorders After Stroke
CSBA: Conselice Study of Brain Aging
CSHA: Canadian Study of Health and Aging
DISTANCE: Diabetes Study of Northern California
EClipSE: Epidemiological Clinico-pathological Studies in Europe
HAAS: Honolulu-Asia Aging Study
HARMONY study: Swedish Twin Registry
HRS: Health and Retirement Study
ILSA: Italian Longitudinal Study on Aging
INVADE: Intervention project on cerebrovascular diseases and dementia in the district of Ebersberg, Bavaria
KPNC: Kaiser Permanente of Northern California
LADIS: Leukoaraiosis and Disability prospective multinational European study
MHAS: Mexican Health and Aging Study
MIC: Kaiser Permanente Medical Care Program of Northern California (Multiphasic Health Checkup)
MoVIES: Monongahela Valley Independent Elders Survey project
MRC CFAS: Medical Research Council Cognitive Function and Ageing Study
MSSA: MacArthur Studies of Successful Aging
MEDICES: Neurological Disorders in Central Spain, a longitudinal cohort study
SCOPE: Study on Cognition and Prognosis in the Elderly
SOF: Study of Osteoporotic Fractures
STR: Swedish Twin Registry
ULSAM: Uppsala Longitudinal Study of Adult Men
VITA: Vienna Transdanube Aging study
WHI: Women’s Health Initiative
WHICAP: Washington Heights-Inwood Columbia Aging Project
WHICAP II: Washington/Hamilton Heights-Inwood Columbia Aging Project II
WHIMS: Women’s Health Initiative Memory Study

Recently published reviews discussing several risk factors
Cognitive decline
Plassman 2010
Method: search of MEDLINE and the Cochrane Database of Systematic Reviews from 1984 through October 2009.
Table 1: Evidence of association with cognitive decline for factors with observational data only
Investigated factors: saturated fat, trace metals, Mediterranean diet, fruits and vegetables, diabetes, metabolic syndrome, hyperlipidemia, homocysteine, obesity, depression, anxiety, traumatic brain injury, resiliency, sleep apnea, childhood exposure, education, occupation, social engagement, other leisure activities, alcohol, tobacco, pesticides, APOE;
Table 2: Evidence of association with cognitive decline for factors with both observational and RCT data
Investigated factors: B vitamins and folate, vitamins C and E and beta-carotene, Ginkgo biloba, omega-3 fatty acids, statins, antihypertensives, NSAIDs, gonadal steroids, cholinesterase inhibitors, physical activity, cognitive engagement
Table 3: Summary of findings on potential risk factors and interventions for cognitive decline

AD
Qiu 2011
Method: comprehensive search of PubMed database & web of Science for articles published in English up to February 2011 (Box 1)
Table 1: Summary of systematic reviews and meta-analyses of prospective studies on cardiovascular risk factors and related disorders for AD and dementia
Investigated factors: cigarette smoking, alcohol intake, physical activity, blood pressure, obesity, total cholesterol, high homocysteine, diabetes mellitus, stroke;
Risk factors discussed in the main text: cigarette smoking, alcohol consumption, physical activity, blood pressure, obesity / overweight, total cholesterol, dietary patterns & nutrients, diabetes mellitus, inflammatory markers, metabolic syndrome, stroke

VCI
Gorelick 2011
Method: use of systematic literature reviews (primarily covering publications from 1990 to May 2010), Table 1
Main text: chapter 5: impact of cardiovascular risk factors at different ages on the risk of cognitive decline: age, sex, genetic factors, education, diet, physical activity, alcohol intake, obesity, smoking, social support / networks, depression, blood pressure, hyperglycemia / insulin resistance / metabolic syndrome / diabetes, lipids, inflammation, coronary artery disease, stroke, chronic kidney disease, atrial fibrillation, peripheral arterial disease, low cardiac output
S2: Recently published articles stratified for type of therapy and type of dementia.
Results derived from randomized clinical trials (RCTs) and from meta-analyses (MA) on RCTs are considered as highest evidence.

<table>
<thead>
<tr>
<th></th>
<th>VaD</th>
<th>AD</th>
<th>Dementia (unspecified)</th>
<th>Cognitive Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>cognitive training</td>
<td>⇒ no study identified</td>
<td>⇒ no study identified</td>
<td>⇒ no study identified</td>
<td>Martin 2011[174]</td>
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<td>Cochrane Review (MCI patients &amp; healthy elderly, 36 RCTs):</td>
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<td>Healthy elderly: treatment vs. no contact: mean differences: immediate recall: 0.43 [0.06 to 0.81], delayed recall: 0.39 [0.16 to 0.62]; improvements did not exceed the improvement in the active control condition; MCI patients: treatment vs. no contact: mean differences: immediate recall: 0.50 [0.02 to 0.98], delayed recall: 0.69 [0.00 to 1.39]; improvements did not exceed the improvement in the active control condition</td>
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<tr>
<td>Li 2011[179]</td>
<td>MA (MCI patients, 3 RCTs, 3 uncontrolled trials): cognitive training can significantly improve overall cognition, but improvements may be domain-specific</td>
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<tr>
<td>Gates 2011[180]</td>
<td>Systematic Review (MCI patients, 5 RCTs, 3 non-randomized controlled trials, 2 uncontrolled trials): cognitive exercises can produce moderate-to-large beneficial effect on memory-related outcomes &amp; may lead to greater benefits than memory strategies</td>
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<tr>
<td>Zehnder 2009[181]</td>
<td>MA (MCI patients &amp; healthy elderly, 24 RCTs): Healthy elderly: significant training effects for paired associated learning &amp; immediate and delayed recall, but trainings effects no larger than those for active control conditions; MCI patients: significant training effect for immediate recall, but trainings effects no larger than those for active control conditions</td>
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<tr>
<td>Papp 2009[182]</td>
<td>MA (healthy elderly, 10 RCTs): weighted mean effect size: 0.16 [0.14 to 0.19]</td>
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<tr>
<td>Acevedo 2007[183]</td>
<td>Review (normal elderly, 4 RCTs, 1 uncontrolled trial): some evidence of improvement</td>
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<tr>
<td>SimA study (Oswald 2006)[184]</td>
<td>non-randomized controlled trial, 5 years FU: cognitive, physical, psychoeducational training: improvement by training</td>
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<tr>
<td>RCT (selection of relevant publications)</td>
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<tr>
<td>MCI patients</td>
<td>Kinsella 2009[185]</td>
<td>4 months FU: memory training: significant improvement in everyday memory</td>
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<tr>
<td>Barnes 2009[186]</td>
<td>6 week training, no FU after training: cognitive exercise: most group differences not statistically significant</td>
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<tr>
<td>Troyer 2008[187]</td>
<td>3 months FU: memory strategies: no group differences in memory beliefs</td>
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<tr>
<td>VaD</td>
<td>AD</td>
<td>Dementia (unspecified)</td>
<td>Cognitive Impairment</td>
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<tr>
<td>cognitive training (continued)</td>
<td>Rozzini 2007\textsuperscript{158}</td>
<td>1y FU: neuropsychological training: significant improvements in different cognitive areas (such as memory, abstract reasoning)</td>
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<td>Olazaran 2004\textsuperscript{159}</td>
<td>1y structured program, no FU after training: cognitive-motor intervention: significant cognitive decline only in the control group</td>
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<td>Rapp 2002\textsuperscript{160}</td>
<td>6 months FU: memory strategies training: significant better memory appraisals, trend towards better word list recall</td>
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<tr>
<td>Normal elderly</td>
<td>SHARP-P study (Legault 2011\textsuperscript{155})</td>
<td>4 months FU: cognitive training: composite outcome: p=0.9, executive function: p=0.5, episodic memory: p=0.4</td>
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<td></td>
<td>Khoumag 2010\textsuperscript{152}</td>
<td>women, 6 months FU: computer course: immediate recall: β=1.2 [0.4 to 2.0], delayed recall: β=1.02 [0.2 to 1.8], TMT: β=0.2 [-0.5 to -0.02]</td>
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<td>DL.S (Buiza 2008\textsuperscript{157})</td>
<td>2y FU: cognitive rehabilitation: significant improvement in working memory, immediate memory, logic memory</td>
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<td></td>
<td>Stuss 2007\textsuperscript{154}</td>
<td>6 months FU: memory skills, goal management &amp; psychosocial training: no improvement on most outcome measures</td>
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<td>Craik 2007\textsuperscript{155}</td>
<td>3 months FU: cognitive rehabilitation training: no improvement in working memory, primary memory, recognition memory; some evidence for improvement in secondary memory &amp; strategic processing</td>
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<td>ACTIVE (Wills 2006\textsuperscript{156})</td>
<td>5y FU: memory, reasoning, speed processing &amp; booster training: improvement on cognitive abilities specific to the abilities trained</td>
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<td>Mahncke 2006\textsuperscript{157}</td>
<td>3 months FU: processing speed &amp; working memory training: improvement on the trained tasks</td>
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<tr>
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<td>Edwards 2005\textsuperscript{156}</td>
<td>no FU after training: processing speed training: improvement on the trained tasks</td>
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<tr>
<td></td>
<td>⇒ ⇒ ⇒ ⇒ ⇒ some evidence for protective effect of cognitive training, but high quality RCTs with sufficient follow-up times are limited</td>
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<thead>
<tr>
<th>smoking cessation</th>
<th>⇒ no study identified</th>
<th>⇒ no study identified</th>
<th>⇒ no study identified</th>
<th>Observational study</th>
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<tbody>
<tr>
<td></td>
<td>Almeida 2011\textsuperscript{157}</td>
<td>Effect of smoking cessation on (ADAS-cog) score: scores became worse in unsuccessful quitters compared to successful quitters (p=0.006)</td>
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<tr>
<td></td>
<td>⇒ limited evidence for protective effect of smoking cessation</td>
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</tbody>
</table>
**Cognitive Impairment**

| dietary supplementation | VaD | AD | Dementia (unspecified) | RCT

### Vitamin E

- **Isaac 2008**[^200]: Cochrane Review, vitamin E: only Petersen 2005 identified.  
  - RCT: Isaac 2008[^200]: no study identified.  
  - Grima 2012[^203]: (cognitive performance)  
  - MA (10 RCTs): antioxidant vitamins: immediate free recall memory: SMD=0.24 [0.06 to 0.42], delayed free recall memory: SMD=0.10 [-0.23 to 0.43], verbal fluency: SMD=0.06 [-0.05 to 0.18]  
  - Isaac 2008[^200]: Cochrane Review: vitamin E: only Petersen 2005 identified.  
  - Petersen 2005[^201]: MCI patients, 3y FU: Vitamin E vs. placebo: HR=1.02 [0.7-1.4].  
  - HPS (2002): Adults with coronary disease, other occlusive arterial disease or diabetes, mean 5y FU: antioxidant vitamin (vitamin E, C, beta-carotene) vs. placebo: subgroup analysis of participants developed dementia.  
  - RCT: HPS (2002): no evidence for protective effect of vitamin E supplements, but high quality RCTs with sufficient follow-up times are limited.  

### Antioxidant Vitamin Supplements

- **WACS (Kang 2009)**[^209]: Women with cardiovascular disease or ≥3 coronary risk factors, 5.4y FU: cognitive change (mean difference, vs. placebo): vitamin E: -0.01 [-0.05 to 0.04], beta carotene: 0.03 [-0.02 to 0.07], vitamin C: 0.02 [-0.03 to 0.07].  
  - Elderly women, 9.6y FU: Vitamin E vs. placebo: Global score: mean difference: 0.00 [-0.04 to 0.04], mean cognitive change: mean difference: 0.02 [-0.01 to 0.05]; substantial decline in global score: RR=0.9 [0.8-1.1].  
  - WACS (Kang 2009): Elderly women, 9.6y FU: Vitamin E vs. placebo: Global score: mean difference: 0.00 [-0.04 to 0.04], mean cognitive change: mean difference: 0.02 [-0.01 to 0.05].  
  - PHS (Grodstein 2007): Healthy men, mean treatment duration 18y: beta carotene vs. placebo (mean difference): mean global score: 0.05 (p=0.03), verbal memory: 0.06 (p=0.007).  
  - McNeil 2007[^210]: Healthy elderly, 1y FU: multivitamin & multimineral vs. placebo: whole group: digit span forward & verbal fluency: no association; group with deficiency: mean difference: 2.5 [-1.0 to 6.1]; ≥75 years: mean difference: 2.8 [-0.6 to 6.2].  
  - HPS (2002): Adults with coronary disease, other occlusive arterial disease or diabetes, mean 5y FU: antioxidant vitamin (vitamin E, C, beta-carotene) vs. placebo: no significant difference in percentages classified as cognitively impaired or in mean TICS-m score.  
  - MIDAS (Yurko-Mauro 2010): Healthy elderly, 24 weeks FU: DHA vs. placebo: improvement in immediate & delayed verbal recognition memory scores (p=0.02), but not in working memory or executive function.  
  - Vakhapova 2010[^211]: Elderly with memory complaints, 15 weeks FU: phosphatidylserine-DHA vs. placebo: significant improvement in verbal immediate recall.  
  - Van de Rest 2008[^212]: Healthy elderly, 26 weeks FU: EPA-DHA vs. placebo: no significant differential changes in any cognitive domains.  

[^200]: Isaac 2008[^200]: no study identified.  
[^201]: Petersen 2005[^201]: MCI patients, 3y FU: Vitamin E vs. placebo: HR=1.02 [0.7-1.4].  
[^202]: HPS (2002): no evidence for protective effect of vitamin E supplements, but high quality RCTs with sufficient follow-up times are limited.  
[^203]: Grima 2012[^203]: (cognitive performance)  
[^204]: Jia 2008[^204]: (cognitive decline)  
[^205]: PHS (Grodstein 2007): Healthy men, mean treatment duration 18y: beta carotene vs. placebo (mean difference): mean global score: 0.05 (p=0.03), verbal memory: 0.06 (p=0.007).  
[^206]: McNeil 2007[^210]: Healthy elderly, 1y FU: multivitamin & multimineral vs. placebo: whole group: digit span forward & verbal fluency: no association; group with deficiency: mean difference: 2.5 [-1.0 to 6.1]; ≥75 years: mean difference: 2.8 [-0.6 to 6.2].  
[^208]: MIDAS (Yurko-Mauro 2010): Healthy elderly, 24 weeks FU: DHA vs. placebo: improvement in immediate & delayed verbal recognition memory scores (p=0.02), but not in working memory or executive function.  
[^210]: Vakhapova 2010[^211]: Elderly with memory complaints, 15 weeks FU: phosphatidylserine-DHA vs. placebo: significant improvement in verbal immediate recall.  
[^211]: Van de Rest 2008[^212]: Healthy elderly, 26 weeks FU: EPA-DHA vs. placebo: no significant differential changes in any cognitive domains.
**B-vitamin, folic acid supplementation**

<table>
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<tr>
<th>VaD</th>
<th>AD</th>
<th>Dementia (unspecified)</th>
<th>Cognitive Impairment</th>
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<tbody>
<tr>
<td>⇒⇒ ⇒⇒ no study identified</td>
<td>⇒⇒ ⇒⇒ no study identified</td>
<td>RCT Health in Men Study (Ford 2010)²¹³ hypertensive men, 8y FU: B₆, B₁₂, folic acid vs. placebo: HR=0.72 [0.3-1.8]</td>
<td>Ford 2012²¹⁴ (cognitive function) MA (19 RCTs): B-vitamins: patients without cognitive impairment (13 RCT): SMD=-0.03 [-0.1 to 0.04]; patients with cognitive impairment (6 RCT): SMD=0.10 [-0.08 to 0.28]</td>
</tr>
<tr>
<td>⇒⇒ ⇒⇒ no evidence for protective effect of B₆, B₁₂ and folic acid supplements but high quality RCTs are limited</td>
<td></td>
<td>Morris 2011²¹⁵ (cognitive decline) Review: B₁₂ / folic acid (several RCTs): no association, but most participants have no low folate status</td>
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<td>Malouf 2008²¹⁶ Cochrane Review (healthy older people &amp; cognitive impaired patients): folic acid (with or without B₁₂): no adequate evidence of benefit; sign. benefit for people with high Hcy (global functioning, memory storage, information-processing speed)</td>
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<td></td>
<td>Malouf 2008²¹⁷ Cochrane Review (healthy elderly): vitamin B₁₂: no statistically sign. benefits on cognition</td>
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</table>

**RCT (selection of relevant publications)**

d'e Jaeger 2012²¹⁷ (MCI)
MCI patients, 2y FU: B₆, B₁₂, folic acid vs. placebo: sign. benefit among participants with Hcy above the median: global cognition: p<0.001, episodic memory: p=0.001, semantic memory: p=0.04
Health in Men Study (Ford 2010²¹⁴, cognitive impairment)
Hypertensive men, 8y FU: B₆, B₁₂, folic acid vs. placebo: OR=0.72 [0.2-2.1]
VISP (Viswanathan 2009²¹⁸, cognitive change)
Patients with ischemic stroke, 2y FU: pyridoxine, B₁₂, folic acid high-dose vs. low-dose: no effect on MMSE VA HOST (Brady 2009²¹⁹, neuropsychological tests)
Patients with advanced chronic kidney disease & end stage renal disease, median 3y FU: B₆, B₁₂, folic acid vs. placebo: no effect on TICS, neuropsychological test battery WAFACS (Kang 2008²²⁰, cognitive decline)
Women with CVD or CVD risk factors, 5.4y FU: B₆, B₁₂, folic acid vs. placebo: no delayed cognitive decline; difference in change in global score: 0.03 [-0.03 to 0.08]; low overall dietary vitamin B intake: global score: 0.09 [-0.01 to 0.2], verbal score: 0.12 [0.00 to 0.2], TICS score: 0.74 [0.2 to 1.2]
van Uffelen 2008²²¹ MCI patients, 1y FU: B₆, B₁₂, folic acid vs. placebo: no association FACTT (Durga 2007²²²)
Healthy people with raised Hcy, 3y FU: folic acid vs. placebo (difference in Z scores): memory: 0.13 [0.03 to 0.23], processing speed: 0.09 [0.02 to 0.16], sensorimotor speed: 0.06 [-0.001 to 0.13]
McMahon 2006²²³ (test scores)
Healthy people, Hcy ≥13µmol/l, 2y FU: B₆, B₁₂, folic acid vs. placebo: no sign. differences in scores on cognition tests Stott 2005²²⁴ (cognitive function)
Eldey patients with vascular disease, 1y FU: B₆, B₁₂, folic acid vs. placebo: no sign. effect on letter digit coding test & TICS

⇒⇒ ⇒⇒ no evidence for effect of B₆, B₁₂ and folic acid supplements, but high quality RCTs with patients with vitamin deficits are limited & effect may be specific for certain cognitive domains

---

²¹³ Ford 2012
²¹⁴ Morris 2011
²¹⁵ Malouf 2008
²¹⁶ Malouf 2008
²¹⁷ d'e Jaeger 2012
²¹⁸ Viswanathan 2009
²¹⁹ Brady 2009
²²⁰ Kang 2008
²²¹ van Uffelen 2008
²²² Durga 2007
²²³ McMahon 2006
²²⁴ Stott 2005
Cognitive Impairment

<table>
<thead>
<tr>
<th>VaD</th>
<th>AD</th>
<th>Dementia (unspecified)</th>
<th>Cognitive Impairment</th>
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<tbody>
<tr>
<td>physical activity</td>
<td></td>
<td>RCT Lam 2011</td>
<td>some evidence for</td>
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<tr>
<td>study identified</td>
<td></td>
<td>(interim analysis)</td>
<td>protective effect of</td>
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<td>physical activity for</td>
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<td>MCI patients, but</td>
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<td>available evidence is</td>
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<td>based on one study</td>
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<td>with very short</td>
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<td>follow-up</td>
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Lam 2011: exercise interventions heterogeneous: SMD=0.20 [0.04 to 0.36]; effect smaller for studies that met all 4 quality criteria.

Smith 2010: aerobic exercise (between group difference): attention & processing speed: 0.16 [0.05 to 0.26], executive function: 0.12 [0.02 to 0.22], memory: 0.13 [0.01 to 0.24], working memory: 0.03 [-0.10 to 0.17]; rigorous RCTs with larger samples, appropriate controls & longer follow-up periods are needed.

Angevaren 2008: Cochrane Review (older people without cognitive impairment, 11 RCTs): the majority of comparisons yielded no sign. results; evidence for beneficial effect for motor function, cognitive speed, auditory attention, visual attention.

RCTs (selection of relevant publications)

SHARP-P study (Legault 2011): Elderly at risk for cognitive decline, 4 months FU: physical activity training vs. health education control: composite outcome: p=0.7, executive function: p=0.5, episodic memory: p=0.2.

Erickson 2011: Normal elderly, 1y FU: aerobic vs. stretching: no improvement in spatial memory above that achieved by the stretching group, but size of hippocampal volume increased.

Lam 2011: (interim analysis)

MCI patients, 5 months FU: Tai Chi vs. stretching: improvement in visual spans: p<0.001, stable CDR: OR=0.1 [0.03-0.7].

Klussmann 2010: Healthy women, 6 months FU: exercise vs. control: immediate recall: β=1.02 [0.2 to 1.8], delayed recall: β=1.1 [0.3 to 1.9], TMT: β=-0.3 [-0.5 to -0.04].

Muscari 2010: Healthy elderly, 1y FU: exercise training vs. control group with educational material: improvement in MMSE (p=0.02), stable cognitive status: OR=2.7 [1.2-6.5].

Liu-Ambrose 2010: Women, 1y FU: resistance training vs. tone training: improvement in Stroop test (p<0.03).

Baker 2010: MCI patients, 6 months FU: aerobic vs. stretching: some improvement especially for women.

Baker 2010: Adults with glucose intolerance, 6 months FU: aerobic vs. stretching: improved executive function (p=0.04).

LIFE-trial Pilot Study (Williamson 2009): Sedentary persons, 1y FU: moderate-intensity physical activity vs. health education: no sign. group differences in cognitive scores; ongoing study.

FABs (Lautenschlager 2008): Patients with subjective memory complaints or MCI, 1.5y FU: physical activity vs. usual care: ADAS-Cog score difference: -1.3 [-2.4 to -0.2], several tests no sign. change.

van Uffelen 2008: MCI patients, 1y FU: walking vs. low-intensity placebo: no association, improvement only in people with better adherence.

⇒⇒ ⇒⇒ some evidence for protective effect of physical activity, but available evidence is limited & effect may be restricted to specific domains.
### Longitudinal studies

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<th>MA</th>
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**Chang-Quan 2011**

- 30y FU: 0-5y treatment: HR=0.6 [0.3-1.3], 5-12y treatment: HR=0.5 [0.1-2.3], >12y treatment: HR=0.3 [0.1-2.6], thiazide-diuretic: HR=0.7 [0.3-1.4] - 30y FU: hypertension & untreated: <50y: HR=2.3 [1.4-3.6], ≥50y: HR=1.05 [0.9-1.3]; hypertension & treated: <50y: HR=1.2 [0.8-1.7], ≥50y: HR=0.8 [0.6-0.9]

**Peila 2006**

- 30y FU: hypertension & untreated: <50y: HR=2.3 [1.4-3.6], ≥50y: HR=1.05 [0.9-1.3]; hypertension & treated: <50y: HR=1.2 [0.8-1.7], ≥50y: HR=0.8 [0.6-0.9]

**Cache County Study (community based)**

- Khachatariyan 2005
  - 3.2y FU: any drugs: HR=0.64 [0.4-0.98], ACE-I: HR=1.13 [0.6-2.0], BB: HR=0.5 [0.2-1.1], CCB: HR=0.9 [0.4-1.5], DHP-CCB: HR=0.5 [0.2-1.3], non DHP-CCB: HR=1.2 [0.5-2.2], diuretic: HR=0.6 [0.4-0.98], potassium-sparing diuretic: HR=0.3 [0.1-0.6], loop-diuretic: HR=1.4 [0.8-2.6], thiazide-diuretic: HR=0.7 [0.3-1.4]

**HYVET-COG (Peters 2008)**

- Patients without prior cerebrovascular disease: HR=0.87 [0.6-1.3]

### RCTs

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<th>MA</th>
<th>MA (3 RCTs, including PROGRESS): RR=0.76 [0.57-1.00]</th>
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**Chang-Quan 2011**

- 30y FU: 0-5y treatment: HR=0.6 [0.3-1.3], 5-12y treatment: HR=0.5 [0.1-2.3], >12y treatment: HR=0.3 [0.1-2.6], thiazide-diuretic: HR=0.7 [0.3-1.4]

**BILSA (community based)**

- Yasar 2005
  - Mean 11y FU: CCB: RR=0.6 [0.3-1.3], DHP-CCB: RR=0.3 [0.1-1.2], non DHP-CCB: RR=0.8 [0.4-1.8]

**CSHA (population based)**

- Lindsay 2002
  - 5y FU: any drug: OR=0.91 [0.6-1.3]

### Cognitive Impairment

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<th>MA</th>
<th>MA (only Rotterdam study identified)</th>
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**Duron 2010**

- Review (including Kungsholmen project, Rotterdam Study, BLSA, EPESE, CSHA, Cache County Study, HAAS): studies suggest an association, but lack of precision concerning the duration of treatment

**Fournier 2009**

- Review (including Kungsholmen project, Rotterdam study, BLSA, Cache County study, OSCAR study, EVA study): inconsistent evidence

**McGuinness 2009**

- MMSE (4 RCTs, patients without prior cerebrovascular disease): WMD=0.42 [0.30 to 0.53]

**Birns 2006**

- Mean 8y FU: any drug: HR=0.95 [0.90-0.99], <75y: HR=0.92 [0.86-0.98], ≥75y: HR=0.97 [0.90-1.04], thiazide diuretics: HR=0.97 [0.90-1.05], high ceiling diuretics: HR=0.89 [0.78-1.01], BB: HR=0.93 [0.87-1.00], CCB: HR=1.00 [0.91-1.09], ACE-I: HR=1.07 [0.99-1.09], ARB: HR=0.85 [0.44-1.66], other: HR=1.04 [0.88-1.24]

**In’t Veld 2001**

- Mean 2.2y FU: any drugs: RR=0.7 [0.4-1.0], CCB: RR=0.7 [0.3-1.5], diuretics: RR=0.8 [0.3-1.3]
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<th>VaD</th>
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<tbody>
<tr>
<td>antihypertensive therapy (continued)</td>
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<tr>
<td>Rotterdam study (community based)</td>
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<td>Kungsholmen project (community based)</td>
<td>HYVET-Cog (Peters 2008)(^{239}) Patients without prior cerebrovascular disease: HR=0.9 [0.8-1.05]</td>
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<tr>
<td>Haag 2009(^{257}) Mean 8y FU: HR per year of treatment: any drugs: HR=0.94 [0.90-0.99]; &lt;75y: HR=0.92 [0.85-0.99], &gt;75y: HR=0.96 [0.89-1.04]</td>
<td></td>
<td>PRoFESS (Diener 2008)(^{265}) Patients with recent stroke (&lt;90 days): MMSE score ≤ 24 points: RR=1.01 [0.9-1.1]; 3 points or more in MMSE: RR=0.95 [0.9-1.05]</td>
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<td>≥75y: HR=0.92 [0.85-1.04]</td>
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<td>ADVANCE (Patel 2007)(^{267}) Patients with type 2 diabetes mellitus: OR=0.98 [0.9-1.1]</td>
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<td>In’t Veld 2001(^{256}) Mean 2.2y FU: any drugs: RR=0.8 [0.5-1.2]</td>
<td></td>
<td>TRANSCEND (Anderson 2011)(^{267}) Patients at high risk of cardiometabolic disease, but not patients with type 2 diabetes mellitus: OR=0.98 [0.9-1.1]</td>
<td></td>
</tr>
<tr>
<td>EPSE (community based)</td>
<td>Administrative database of the US Veteran Affairs (predominantly men)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morris 2001(^{256}) 4y FU: any drug: OR=0.66 (not sign.); thiazide diuretic: OR=1.13 [0.7-2.6], potassium-sparing diuretic: OR=0.63 [0.3-1.5], loop diuretic: OR=1.06 [0.4-3.1], BB: OR=0.9 [0.3-3.2]</td>
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<tr>
<td>Kungsholmen project</td>
<td>RCT</td>
<td></td>
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</tr>
<tr>
<td>Quu 2003(^{257}) Median 5.7y FU: RR=0.6 [0.5-0.9]; APOE ε4 carrier: 1.0 [0.6-1.6], no APOE ε4 carrier: 0.7 [0.5-1.0]</td>
<td></td>
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<tr>
<td>Quu 2003(^{257}) Median 5y FU: any drugs: RR=0.7 [0.5-0.9]</td>
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<tr>
<td>Administrative database of the US Veteran Affairs (predominantly men)</td>
<td>RCT</td>
<td></td>
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<tr>
<td>Li 2010(^{257}) 4y FU: ARB vs. ACE-I: HR=0.81 [0.73-0.90], ARB vs. cardiovascular drugs (BB, CCB): HR=0.76 [0.69-0.84], ACE-I vs. cardiovascular drugs (BB, CCB): HR=0.94 [0.91-0.97], ARB+ACE-I vs. ACE-I: HR=0.54 [0.51-0.57]</td>
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<tr>
<td>RCT</td>
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<tr>
<td>Chang-Quan 2011(^{256}) 2 RCTs: RR=0.79 [0.53-1.18]</td>
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<tr>
<td>II) Original RCTs</td>
<td>RCT</td>
<td></td>
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<tr>
<td>(for further detail see figure 2 &amp; 3 and supplement table 3)</td>
<td>RCT</td>
<td></td>
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</tr>
<tr>
<td>HYVET-COG (Peters 2008)(^{257}) Patients without prior cerebrovascular disease: HR=0.85 [0.6-1.1]</td>
<td>II) Original RCTs (for further detail see figure 2 &amp; 3 and supplement table 3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syst-Eur (Forette 2002)(^{256}) evidence from extended FU: OR=0.4 [0.3-0.6] (calculated by the authors)</td>
<td>SHEP(^{266}) Patients without prior cerebrovascular disease: RR=0.84 [0.5-1.3]</td>
<td></td>
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</tr>
<tr>
<td>⇒⇒⇒ inconsistent results</td>
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</tbody>
</table>

⇒⇒⇒ inconsistent results
<table>
<thead>
<tr>
<th>antihypertensive therapy (continued)</th>
<th>SCOPE (Lithell 2003)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients without prior cerebrovascular disease: OR=1.08 [0.7-1.5]</td>
<td></td>
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<tr>
<td>HYVET-COG (Peters 2008)</td>
<td></td>
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<tr>
<td>Patients without prior cerebrovascular disease: HR=0.86 [0.7-1.1]</td>
<td></td>
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<tr>
<td>PRoFESS (Diener 2008)</td>
<td></td>
</tr>
<tr>
<td>Patients with recent stroke (&lt;90 days): OR=1.0 [0.9-1.1], dementia with recurrent stroke: OR=1.3 (p=0.14)</td>
<td></td>
</tr>
<tr>
<td>ADVANCE (Patel 2007)</td>
<td></td>
</tr>
<tr>
<td>Patients with type 2 diabetes mellitus: OR=1.04 [0.7-1.6]</td>
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</tbody>
</table>

⇒⇒⇒ some evidence for an protective effect of antihypertensive drugs (mainly from observational studies with long follow-up), but effect may depend on type of drug, duration of use, age of use

<table>
<thead>
<tr>
<th>antidiabetic medication</th>
<th>no study identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longitudinal studies</td>
<td></td>
</tr>
</tbody>
</table>
| Hsu 2011
Taiwan’s National Health Insurance database, patients with type 2 DM, ~7y FU: sulfonylureas vs. no medication: HR=0.85 [0.7-1.01]; metformin vs. no medication: HR=0.76 [0.6-0.98]; sulfonylureas + metformin vs. no medication: HR=0.65 [0.6-0.74] |

⇒⇒⇒ inconsistent results, evidence for protective effect only in one observational study

<table>
<thead>
<tr>
<th>RCT</th>
<th>ADVANCE (Patel 2008)</th>
</tr>
</thead>
<tbody>
<tr>
<td>patients with diabetes, median 5y FU: intensive vs. standard control: HR=1.3 [0.9-1.9]</td>
<td></td>
</tr>
</tbody>
</table>

⇒⇒⇒ inconsistent results, evidence for protective effect only in 2 observational studies

<table>
<thead>
<tr>
<th>Cognitive Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longitudinal studies</td>
</tr>
<tr>
<td>Abbatecola 2010 (cognitive test)</td>
</tr>
<tr>
<td>Patients with diabetes &amp; MCI, 36 weeks FU: rosiglitazone+ metformin vs. metformin: difference in Ray Verbal Auditory Learning Test: p=0.01</td>
</tr>
<tr>
<td>Wu 2003 (cognitive tests)</td>
</tr>
<tr>
<td>SALSA project (population based, ~2y FU): patients with diagnosed diabetes ≤5 years: MMSE: mean=2.3 [0.05 to 4.5], Word-list test: mean=-0.05 [-0.6 to 0.5]; patients with diagnosed diabetes &gt;5 years: MMSE: mean=6.3 [3.2 to 9.5], Word-list test: mean=-0.7 [-1.6 to 0.1]; combination therapy appeared to be more effective than monotherapy</td>
</tr>
<tr>
<td>RCT</td>
</tr>
<tr>
<td>Cochrane Review: no studies were found to be appropriate for inclusion</td>
</tr>
<tr>
<td>ACCORD-MIND (Launer 2011, cognitive function)</td>
</tr>
<tr>
<td>Patients with diabetes, 2.2y FU: intensive vs. standard glycaemic control: DSST: mean difference: 0.3 [-0.3 to 0.9]</td>
</tr>
<tr>
<td>ADVANCE (Patel 2008, cognitive decline)</td>
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<tr>
<td>Patients with diabetes, median 5y FU: intensive vs. standard control: HR=0.98 [0.9-1.1]</td>
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</tbody>
</table>

⇒⇒⇒ inconsistent results, evidence for protective effect only in 2 observational studies
<table>
<thead>
<tr>
<th>Statin Use</th>
<th>Longitudinal Studies</th>
<th>AD</th>
<th>Dementia (unspecified)</th>
<th>Cognitive Impairment</th>
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<tbody>
<tr>
<td>VaD</td>
<td>Mcguinnes 2010</td>
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<td></td>
<td>Maungpaisan 2010</td>
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<td></td>
<td>Systematic Review (2</td>
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<td>Solomon 2004</td>
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<tr>
<td></td>
<td>studies): no associa-</td>
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<td>Review (7 cohort</td>
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<td>tion</td>
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<td>studies, 2 case-</td>
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<td></td>
<td>Bettermann 2011</td>
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<td></td>
<td>control studies):</td>
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<tr>
<td></td>
<td>(vascular component)</td>
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<td></td>
<td>statin use:</td>
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<tr>
<td>GEMS, mean 6</td>
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<td>Protective effect</td>
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<tr>
<td>FU: without</td>
<td>(cognitive decline)</td>
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<td></td>
<td>(8 studies), no assoc</td>
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<tr>
<td>MCI at baseline:</td>
<td></td>
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<td>iation (1 study)</td>
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<td>current statin use:</td>
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<tr>
<td>HR&lt;1 (not sign.):</td>
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<td>other lipid-lowering medication ever use:</td>
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<tr>
<td>HR=0.7 [0.5-1.1]:</td>
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<tr>
<td>Li 2010</td>
<td></td>
<td></td>
<td>RR=0 [0.4-1.1]</td>
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<tr>
<td>ACT, mean 6.1y FU:</td>
<td></td>
<td></td>
<td>RR=0.8 [0.4-0.97]:</td>
<td></td>
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<tr>
<td>Arvanitakis 2006</td>
<td></td>
<td></td>
<td>RR=0.8 [0.2-0.3]:</td>
<td></td>
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<tr>
<td>Religious Orders Study, up to 12y FU:</td>
<td></td>
<td></td>
<td>RR=0.8 [0.6-0.98]:</td>
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<tr>
<td>baseline statin use:</td>
<td></td>
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<td>RR=0.8 [0.6-0.9]:</td>
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<tr>
<td>cumulative statin use:</td>
<td></td>
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<td>RR=0.6 [0.4-1.1]:</td>
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<tr>
<td>Tendolkar 2012</td>
<td></td>
<td></td>
<td>RR=0.8 [0.37-0.49]:</td>
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<tr>
<td>PROSPER (Trompet 2010)</td>
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<tr>
<td>Elderly with a history of, or risk factors for, vascular disease, mean 3.5y FU:</td>
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<tr>
<td>HPS (2002):</td>
<td>Adults with coronary disease, other occlusive arterial disease or diabetes, mean 5y FU:</td>
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<tr>
<td>PROSPER (Trompet 2010)</td>
<td></td>
<td></td>
<td>simvastatin vs. placebo: similar number developed dementia</td>
<td></td>
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<tr>
<td>Tenderk [279]</td>
<td>(patients with atrial fibrillation)</td>
<td></td>
<td></td>
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<tr>
<td>RCT (n=34), 1y FU:</td>
<td>atorvastatin vs. placebo: improvement in cognitive speed &amp; memory</td>
<td></td>
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<tr>
<td>HPS (2002):</td>
<td>Adults with coronary disease, other occlusive arterial disease or diabetes, mean 5y FU:</td>
<td></td>
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<td>Tenderk [279]</td>
<td>(patients with atrial fibrillation)</td>
<td></td>
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</tr>
</tbody>
</table>
### VaD

**NSAIDs use**
- **Longitudinal studies**
  - Szekely 2008\(^{281}\)
    - CHS, up to 10y FU: NSAIDs use: HR=0.92 [0.6-1.3]; acetaminophen: HR=1.1 [0.8-1.5]
  - In’t Veld 2001\(^{282}\)
    - Rotterdam Study, mean 7y FU: long-term NSAIDs use: RR=0.99 [0.7-0.6]

- **no RCT identified.**
  - no evidence of protective effect, but lack of sufficient data

### AD

**Longitudinal studies**
- Szekely 2008\(^{283}\)
  - MA (6 studies): NSAIDs use: HR=0.8 [0.6-0.9]; SALA only: HR=0.8 [0.7-0.99], non-SALA only: HR=0.6 [0.4-0.9]; acetaminophen: HR=0.9 [0.8-1.1]
  - Ettman 2003\(^{284}\)
  - Breitner 2009\(^{285}\)
    - ACT, up to 12y FU: NSAIDs heavy use: HR=1.5 [1.1-2.2; 2.2-2.7]

- **MA (6 studies):** NSAIDs use: HR=0.8 [0.6-0.9]; SALA only: HR=0.8 [0.7-0.99], non-SALA only: HR=0.6 [0.4-0.9]; acetaminophen: HR=0.9 [0.8-1.1]

### Dementia (unspecified)

**Longitudinal studies**
- De Craen 2005\(^{285}\)
  - MA (4 studies): NSAIDs use: HR=0.92 [0.6-1.3]; acetaminophen: HR=1.1 [0.8-1.5]

- **CHS, up to 10y FU:**
  - NSAIDs use: HR=0.92 [0.6-1.3]; acetaminophen: HR=1.1 [0.8-1.5]

- **no RCT identified.**
  - no evidence of protective effect, but lack of sufficient data

### Cognitive Impairment

**Longitudinal studies**
- Waldstein 2010\(^{286}\)
  - CHS, up to 45y FU: NSAIDs use: less decline on 2 cognitive measures

- **Arvanitakis 2008\(^{287}\)**
  - Religious Orders Study, up to 12y FU: NSAIDs use: increased risk in the first 2.5 years

- **⇒ conflicting results,**
  - maybe dependent on duration, APOE alleles & kind of medication

- **no RCT identified,**
  - consistent results in observational studies

### RCTs

- **ADAPT (Lyketsos 2007\(^{287}\), Breitner 2011\(^{288}\))**
  - Elderly with family history of AD, ~4y FU: NSAIDs use: increased risk in the first 2.5 years

### aspirin use

**Longitudinal studies**
- Szekely 2008\(^{281}\)
  - CHS, up to 10y FU: aspirin use: HR=1.4 [1.05-1.9]

- **In’t Veld 2001\(^{282}\)**
  - Rotterdam Study, mean 7y FU: salicylates use: >1 to 23 months: RR=3.0 [1.6-5.7]; ≥24 months: RR=4.9 [2.4-10.0]

- **⇒ no RCT identified.**
  - some evidence for harmful effect of aspirin in observational studies

**Longitudinal studies**
- Szekely 2008\(^{283}\)
  - MA (6 studies): aspirin use (no other NSAIDs): HR=0.78 [0.7-0.92]

- Arvanitakis 2008\(^{286}\)
  - Religious Orders Study, up to 12y FU: aspirin use: HR=0.8 [0.6-1.1]

- **⇒ no RCT identified.**
  - some evidence for protective effect of aspirin in observational studies

### RCTs

- **ADAPT (Lyketsos 2007\(^{287}\), Breitner 2011\(^{288}\))**
  - Elderly with family history of AD, ~2y FU: NSAIDs vs. placebo: no improvement in 7 tests of cognitive function and summary score

- **⇒ no evidence for effect.**
  - inconsistent results in observational studies

### RCTs

- **ADAPT (Martin 2008\(^{289}\))**
  - Elderly with family history of AD, ~2y FU: NSAIDs vs. placebo: no improvement in 7 tests of cognitive function and summary score

### Cognitive Impairment

**Longitudinal studies**
- Waldstein 2010\(^{286}\)
  - CHS, up to 45y FU: aspirin use: greater decline on selected measures

- **Almeida 2010\(^{289}\)**
  - Health in Men Study: past aspirin use: OR=1.2 [0.9-1.5], past & current aspirin use: OR=1.2 [1.0-1.4]

- **Grandstein 2008\(^{290}\)**
  - Religious Orders Study, up to 12y FU: NSAIDs use: increased risk in the first 2.5 years

- **⇒ conflicting results,**
  - maybe dependent on duration, APOE alleles & kind of medication

- **no RCT identified,**
  - consistent results in observational studies

### RCTs

- **ADAPT (Lyketsos 2007\(^{287}\), Breitner 2011\(^{288}\))**
  - Elderly with family history of AD, ~2y FU: NSAIDs vs. placebo: no improvement in 7 tests of cognitive function and summary score

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### Cognitive Impairment

**Longitudinal studies**
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### Cognitive Impairment

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- **Grandstein 2008\(^{290}\)**
  - Religious Orders Study, up to 12y FU: NSAIDs use: increased risk in the first 2.5 years

- **⇒ conflicting results,**
  - maybe dependent on duration, APOE alleles & kind of medication

- **no RCT identified,**
  - consistent results in observational studies
<table>
<thead>
<tr>
<th>Treatment</th>
<th>VaD</th>
<th>AD</th>
<th>Dementia (unspecified)</th>
<th>Cognitive Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>aspirin use (continued)</td>
<td>RCT PERFORM (Bousser 2011&lt;sup&gt;296&lt;/sup&gt;) Patients with ischemic stroke or TIA, mean 2.3y FU: terutroban vs. aspirin: OR=1.05 [0.8-1.3] PRoFESS (Diener 2008&lt;sup&gt;295&lt;/sup&gt;) Patients with ischemic stroke, median 2.4y FU: aspirin vs. clopidogrel: 5% in each group (p=0.2); subgroup with recurrent stroke: 12% in aspirin group, 11% in clopidogrel group (p=0.5) ⇒ no evidence for effect</td>
<td>RCT PERFORM (Bousser 2011&lt;sup&gt;296&lt;/sup&gt;, cognitive decline) Patients with ischemic stroke or TIA, mean 2.3y FU: terutroban vs. aspirin: OR=0.96 [0.9-1.02] PROfESS (Diener 2008&lt;sup&gt;295&lt;/sup&gt;) Patients with ischemic stroke, median 2.4y FU: aspirin vs. clopidogrel: MMSE≤34 points: RR=1.0 [0.9-1.1]; decrease of ≥3 points in MMSE: RR=0.9 [0.8-1.0] AAA trial (Price 2008&lt;sup&gt;297&lt;/sup&gt;) Middle aged to elderly with moderately increased cardiovascular risk, at average 5y in trial: aspirin vs. placebo: proportion achieving over the median general factor cognitive score: OR=0.9 [0.8-1.05], no sign. difference in mean scores on individual cognitive tests WHS (Kang 2007&lt;sup&gt;298&lt;/sup&gt;) Healthy women, mean 5.6y FU: aspirin vs. placebo: mean difference in global score: -0.01 [-0.04 to 0.02], risk of substantial decline: RR=0.9 [0.8-1.1], category fluency: RR=0.8 [0.7-0.97] ⇒⇒⇒⇒ no evidence for effect</td>
<td></td>
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<tr>
<td>citicoline use</td>
<td>⇒ no study identified</td>
<td>⇒ no study identified</td>
<td>⇒ no study identified</td>
<td>Alvarez-Sabin 2011&lt;sup&gt;299&lt;/sup&gt; Patients after stroke: randomly half of the patients continued citicoline until 6 months, all received citicoline until week 6: sign. reduction in cognitive impairment (attention, temporal orientation, executive function)</td>
</tr>
<tr>
<td>coronary artery bypass grafting (CABG)</td>
<td>⇒ no study identified</td>
<td>Palotas 2010&lt;sup&gt;300&lt;/sup&gt; Observational study (patients with CAD &amp; CABG): gradual cognitive decline, changes in biomarkers similar to that seen in AD</td>
<td>Mutch 2011&lt;sup&gt;301&lt;/sup&gt; Population-based longitudinal study (patients with ischemic heart disease): CABG vs. medical management: HR=0.9 [0.7-1.1]; percutaneous coronary intervention vs. medical management: HR=0.6 [0.5-0.8]; percutaneous coronary intervention vs. CABG: HR=0.7 [0.5-1.1]</td>
<td>Rosengart 2006&lt;sup&gt;302&lt;/sup&gt; Nonrandomized study (3 groups): percutaneous coronary intervention patients, CABG patients, matched controls without clinical evidence of coronary artery disease: impairment was statistically associated with type of treatment for only 1 of 13 measures McKhann 2005&lt;sup&gt;318&lt;/sup&gt; Nonrandomized study (4 groups): CABG patients, off-pump coronary surgery patients, nonsurgical cardiac controls, heart healthy controls: no evidence that CABG patients differed from that of control groups in cognitive test performance</td>
</tr>
<tr>
<td>antidepressant</td>
<td>⇒ no study identified</td>
<td>⇒ no study identified</td>
<td>⇒ no study identified</td>
<td>Price 2011&lt;sup&gt;303&lt;/sup&gt; Systematic Review (3 studies): patients with multiple sclerosis: significant improvement (1 study); patients with cerebrovascular accident: no sign. improvement (1 study), no sign. worse outcome (1 study)</td>
</tr>
</tbody>
</table>
Abbreviations

FU: follow-up, y: year(s)

Abbreviations RCTs

AAA trial: aspirin for asymptomatic atherosclerosis trial
ACTIVE: Advanced Cognitive Training for Independent and Vital Elderly study
ADAPT: AD Anti-inflammatory Prevention Trial
DLS: Donostia Longitudinal Study
FABS: Fitness for the Aging Brain Study
FACTIT: Folic Acid and Carotid Intima media Thickness trial
HPS: Heart Protection Study
MIDAS: Memory Improvement with DHA Study
PERFORM: Prevention of Cerebrovascular and Cardiovascular Events of Ischemic Origin with Terutroban in Patients with a History of Ischemic Stroke or Transient Ischemic Attack Study
PHS: Physicians’ Health Study
PROFESS: Prevention Regimen for Effectively Avoiding Second Strokes
PROSPER: Prospective Study of Pravastatin in the Elderly at Risk
VA HOST: Department of Veterans Affairs Cooperative Studies Program Homocysteine Study
VISP: Vitamin Intervention in Stroke Prevention study.
WACS: Women’s Antioxidant and Cardiovascular Study
WAFACS: Women’s Antioxidant and Folic Acid Cardiovascular Study
WHS: Women’s Health Study

Abbreviations not-randomized controlled trials

SimA study: selbständig im Alter

Abbreviations longitudinal studies

ACT: Adult Changes in Thought study
BLSA: Baltimore Longitudinal Study of Aging
CHAP: Chicago Health and Ageing Project
CHS: Cardiovascular Health Study
CSHA: Canadian Study of Health and Aging
EPESE: Established Populations for Epidemiologic Studies of the Elderly
FINRISK: Finnish population study
GEMS: Ginkgo Evaluation of Memory Study
SALSA: Sacramento Area Latino Study on Aging project
NEDICES: population based study of older people in central Spain

Recently published reviews encompassing several risk factors and therapies

Cognitive decline

Plassman 2010††
Method: search of MEDLINE and the Cochrane Database of Systematic Reviews from 1984 through October 2009.
Table 2: Evidence of association with cognitive decline for factors with both observational and RCT data
Investigated factors: B vitamins and folate, vitamins C and E and beta-carotene, Ginkgo biloba, omega-3 fatty acids, statins, antihypertensives, NSAIDs, gonadal steroids, cholinesterase inhibitors, physical activity, cognitive engagement
Table 3: Summary of findings on potential risk factors and interventions for cognitive decline

AD

Qiu 2011††
Method: comprehensive search of PubMed database and web of Science for articles published in English up to February 2011 (Box 1)
Table 2: Summary of clinical trials and meta-analyses of the trials that target vascular risk factors or related disorders against AD and dementia
Investigated therapies: antihypertensive therapy, anti-inflammatory therapy, hormone replacement therapy, cholesterol-lowering therapy (statins), ginkgo biloba

VCI

Gorelick 2011††
Method: use of systematic literature reviews (primarily covering publications from 1990 to May 2010), Table 1
Main text: chapter 11: prospects for prevention of VCI and Alzheimer disease by risk factor control: hypertension, diabetes, lipids, antaggregants, lifestyle, vitamin supplements
### S3: Study characteristics of randomized placebo controlled trials of antihypertensive drugs

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnosis of dementia</th>
<th>Type of dementia (number of cases)</th>
<th>Active treatment</th>
<th>Number of patients with dementia / total</th>
<th>Information on treatment during study / at study termination</th>
<th>Definition of cognitive decline / cognitive function</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHEP²⁸¹</td>
<td>Expert-based; DSM-III-R</td>
<td>Not defined (81)</td>
<td>Chlorthalidone; If the SBP goal was not achieved: addition of atenolol or reserpine (when atenolol was contraindicated)</td>
<td>37 / 2365</td>
<td>Active: chlorthalidone only: 46%; combination with atenolol or reserpine: 23%, other medication: 21%, no medication: 9%; unknown: 1%</td>
<td>At the 5-year visit: no medication: 54%; active antihypertensive drug: 44%, unknown: 2%</td>
</tr>
<tr>
<td>Syst-Eur²⁸²</td>
<td>Expert-based; DSM-III-R</td>
<td>AD (23); VaD (2); Mixed dementia (7)</td>
<td>Nitrendipine; If necessary combination with or replaced by enalapril and/or hydrochlorothiazide; In the placebo-group matching placebos were used</td>
<td>11 / 1238</td>
<td>Active: nitrendipine: 69%; enalapril: 25%, hydrochlorothiazide: 12%</td>
<td>At the final visit: nitrendipine-placebo: 68%; enalapril-placebo: 39%, hydrochlorothiazide-placebo: 23%, other drugs: 1%</td>
</tr>
<tr>
<td>PROGRESS²⁸²</td>
<td>Expert-based; DSM-IV</td>
<td>Not defined (410); Dementia with recurrent stroke (108)</td>
<td>Perindopril and whenever possible indapamide; Randomization was stratified for the intention to begin combination therapy or single drug therapy</td>
<td>193 / 3051</td>
<td>The use of active drugs permanently discontinued: 23%; no detailed information about drug use</td>
<td>The use of placebo permanently discontinued: 21%; no detailed information about drug use</td>
</tr>
<tr>
<td>SCOPE²⁷⁵</td>
<td>ICD-10 criteria; Independent clinical event committee</td>
<td>Not defined (119)</td>
<td>Candesartan; If needed: addition of open hydrochlorothiazide and/or other drugs</td>
<td>62 / 2477</td>
<td>During study: candesartan only: 25%; use of add on: 49%, diuretics: 33%, BB: 17%, CCB: 18%, ACE-I: 8%, ARB: 3%</td>
<td>During study: placebo only: 16%; use of add on: 66%, diuretics: 44%, BB: 26%, CCB: 28%, ACE-I: 11%, ARB: 4%</td>
</tr>
<tr>
<td>HYVET²⁷⁹</td>
<td>Expert-based; DSM-IV</td>
<td>AD (164); VaD (84)</td>
<td>Indapamide; With the option: addition of perindopril</td>
<td>126 / 1687</td>
<td>At 2 years: indapamide only: 26%; add on perindopril: 73%</td>
<td>At 2 years: corresponding placebo: 99%</td>
</tr>
<tr>
<td>PROFESS²⁸³</td>
<td>Clinical impression of dementia</td>
<td>Not defined (817)</td>
<td>Telmisartan; All patients also received BP-lowering therapy at the discretion of the investigators</td>
<td>408 / 8624</td>
<td>At the end of the study: telmisartan: 68%; diuretics: 23%, ACE-I: 28%, CCB: 26%, BB: 22%</td>
<td>At the end of the study: non-study ARB: 2.5%, diuretics: 28%, ACE-I: 34%, CCB: 31%, BB: 25%</td>
</tr>
</tbody>
</table>
(Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnosis of dementia</th>
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<th>Definition of cognitive decline / cognitive function</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADVANCE</td>
<td>ICD-10 criteria; Independent data and safety monitoring committee</td>
<td>Not defined (not reported)</td>
<td>Perindopril and indapamide; All patients also received BP-lowering therapy at the discretion of the physician with 2 exceptions: no use of thiazide diuretics and open-label perindopril was the only ACE-inhibitor allowed</td>
<td>n.s. / 5569 n.s. / 5571</td>
<td>At the end of follow-up: perindopril: 45%; other ACE-I: 5%; ARB: 10%, BB: 31%, CCA: 32%, thiazides: 3%, other diuretics: 14%; other: 10%; Any BP lowering drug: 74%</td>
<td>At the end of follow-up: perindopril: 55%, other ACE-I: 5%, ARB: 13%, BB: 35%, CCA: 43%, thiazides: 5%, other diuretics: 16%; other: 14%; Any BP lowering drug: 83%</td>
</tr>
<tr>
<td>TRANSCEND</td>
<td>-</td>
<td>-</td>
<td>Telmisartan; (given on top of varying background treatments)</td>
<td>239 / 2694 245 / 2689</td>
<td>At the end of the study: telmisartan: 81%; non-study ARB: 6%, diuretics: 34%, CCB: 38%, BB: 57%, AB: 5%</td>
<td>Cognitive impairment: diagnosis of dementia OR significant cognitive dysfunction OR MMSE ≤ 23 points; Cognitive decline: decrease of ≥ 3 points on MMSE from baseline during follow-up</td>
</tr>
</tbody>
</table>

n.s. = not specified
### Classification of recommendations and level of evidence using standard AHA criteria

<table>
<thead>
<tr>
<th>LEVEL A</th>
<th>LEVEL B</th>
<th>LEVEL C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multiple populations evaluated</strong>&lt;sup&gt;*&lt;/sup&gt;</td>
<td><strong>Limited populations evaluated</strong>&lt;sup&gt;*&lt;/sup&gt;</td>
<td><strong>Very limited populations evaluated</strong>&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Data derived from multiple randomized clinical trials or meta-analyses</td>
<td>Data derived from a single randomized trial or nonrandomized studies</td>
<td>Only consensus opinion of experts, case studies, or standard of case</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT</th>
<th>SIZE OF TREATMENT EFFECT</th>
<th>CLASS III or CLASS III Harm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLASS I</strong></td>
<td>Benefit &gt;&gt; Risk</td>
<td>Procedure/Treatment SHOULD be performed/administered</td>
</tr>
<tr>
<td>CLASS Ia</td>
<td>Benefit &gt;&gt; Risk</td>
<td>Additional studies with focused objects needed&lt;sup&gt;177&lt;/sup&gt;</td>
</tr>
<tr>
<td>CLASS Iib</td>
<td>Benefit &gt; Risk</td>
<td>Additional studies with broad objectives needed; additional registry data would be helpful</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level</th>
<th>Recommendation</th>
<th>Level of Evidence</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LEVEL A</strong></td>
<td>Recommendation that procedure or treatment is useful/effective</td>
<td>A</td>
<td>Treatment/strategy A is recommended/indicated in preference to treatment B</td>
</tr>
<tr>
<td></td>
<td>Sufficient evidence from multiple randomized trials or meta-analyses</td>
<td>A</td>
<td>It is reasonable to choose treatment A over treatment B</td>
</tr>
<tr>
<td></td>
<td>Recommendation that procedure or treatment is useful/effective</td>
<td>A</td>
<td>May/might be considered</td>
</tr>
<tr>
<td></td>
<td>Evidence from single randomized trial or nonrandomized studies</td>
<td>A</td>
<td>Potential harms, excess morbidity/mortality</td>
</tr>
<tr>
<td></td>
<td>Recommendation that procedure or treatment is useful/effective</td>
<td>A</td>
<td>Should not be performed/other</td>
</tr>
<tr>
<td></td>
<td>Only expert opinion, case studies, or standard of case</td>
<td>A</td>
<td>Not useful, beneficial, effective</td>
</tr>
</tbody>
</table>

**Suggested phrases for writing recommendations**

- Should is recommended
- Is indicated
- Is useful/effective/beneficial
- Treatment/strategy A is recommended/indicated in preference to treatment B
- Treatment A should be chosen over treatment B
- Is reasonably can be useful/effective/beneficial
- Treatment A is probably recommended/indicated in preference to treatment B
- It is reasonable to choose treatment A over treatment B
- May/might be considered
- May/might be reasonable
- Usefulness/effectiveness is unknown/unclear/uncertain or not well established
- Is probably recommended or indicated

**Comparative effectiveness phrases**

- Treatment/strategy A is recommended/indicated in preference to treatment B
- Treatment A should be chosen over treatment B

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*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and Ia; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

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Data are from reference 177; a recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.
Prevention of Vascular Cognitive Impairment

Background

Dementia has become a pressing health issue, with numbers steadily increasing. Vascular injury is the second most common cause of dementia following Alzheimer’s disease (AD) and a defining feature of vascular cognitive impairment (VCI), which encompasses the full range from vascular dementia (VaD) to mild cognitive impairment (MCI) of vascular origin.

There are various manifestations of vascular brain injury including silent or covert brain infarcts, white matter lesions, and clinically overt strokes, all of which may contribute to cognitive decline. Cerebral small vessel disease has been recognized as the most common etiology of VCI but there are multiple vascular causes and mechanisms, which share major risk factors and may run in parallel. Adding to this complexity vascular pathology frequently coincides with neurodegenerative pathology and disentangling the contribution of individual pathologies to cognitive decline is notoriously difficult even with advanced diagnostic tools. This is reflected by current classification schemes, which distinguish between probable and possible VaD as well as probable and possible vascular MCI. However, there have been various sets of diagnostic criteria in the past, which must be kept in mind when interpreting the results from epidemiological studies and randomized controlled trials (RCTs).

Regardless of these methodological challenges vascular brain injury represents an increasingly recognized target for prevention of cognitive decline and dementia. There are various modifiable factors that have been associated with VCI or VaD in clinical and epidemiological studies (Figure 1) although in many cases the causal relationships are not fully established and evidence for a preventive effect of strategies to control these factors is mostly weak.

In the following, we i) review potential targets for prevention with a focus on longitudinal observational studies and RCTs, ii) provide an overview on current recommendations by health care professionals from the American Heart Association (AHA) / American Stroke Association (ASA), iii) summarize some of the ongoing trials, and iv) discuss future challenges and opportunities.

Potential targets for prevention

Lifestyle factors

Education

Low educational level is associated with an increased risk of cognitive impairment and dementia but the factors underlying this relationship are still discussed. Up to now, there is no convincing evidence that education protects individuals from developing vascular or neurodegenerative brain pathology. Instead, education seems to attenuate the impact of pathology on the clinical expression of dementia. The impact of cognitive lifestyle during mid- and late-life and of structured cognitive intervention programs on the manifestation of dementia remains insufficiently explored.
Smoking
Smoking is associated with cognitive decline\cite{34,35} and a significantly increased risk of VaD,\cite{33,34,35} AD,\cite{33,34,35} and unspecified dementia (Figure 1).\cite{33,34,35} Current smoking has been found to be associated with deficits in specific cognitive domains including psychomotor speed, flexibility, and memory,\cite{306} but the mechanisms connecting smoking and cognitive decline are still debated. Cigarette smoking is associated with reduced microstructural integrity of the cerebral white matter\cite{307} and there is some evidence that smoking cessation protects against these changes. However, there is insufficient data from interventional studies to conclude on the effects of smoking cessation on cognition.\cite{199} Based on currently available evidence the latest AHA/ASA guidelines issue a class IIa/A evidence for smoking cessation in people at risk for VCI (Table 1).

Diet
Observational studies show promise for protection against cognitive decline\cite{43,45} and dementia\cite{43,45} through a number of dietary components. The most consistent evidence exists for dietary intakes of the antioxidant vitamin E, fish, n-3 fatty acids, a high ratio of polyunsaturated to saturated fats, and B-vitamins, in particular B12 and folate.\cite{45} These components are prominent in the Mediterranean diet that is high in fruits, vegetables, fish, whole grains, nuts, and mono-unsaturated oils, and low in high-fat dairy and meat. Several prospective studies found that adherence to a Mediterranean diet is associated with a lower risk of cognitive decline\cite{49,50,51} and AD\cite{43,49,50} although there are few data for VCI and VaD.\cite{43} Studies on E- and B-vitamins suggest that low basal vitamin status is critical, whereas persons with adequate status probably don’t benefit from supplementary intake of vitamins.\cite{308} In general RCTs have failed to demonstrate a benefit from dietary supplementation.\cite{45} However, this may relate to methodological limitations such as the inclusion of subjects with normal vitamin status,\cite{308} supplementation through other sources and short follow-up (Table 2).\cite{205} Against this background a Mediterranean-type diet may be reasonable (Table 1).\cite{177}

Homocysteine and Hyperhomocysteinemia
Elevated concentrations of plasma total homocysteine (tHcy) may cause vascular damage.\cite{309,310} They are associated with lower cognitive performance\cite{70,71} and an increased risk of AD\cite{61,63} and dementia\cite{64,67} although it is still debated whether this link is causal.\cite{57,68} The levels of tHcy can be lowered by about 20% with oral supplementation of specific B-vitamins marking it a potentially modifiable risk factor. However, several RCTs have failed to show any obvious benefits of Hcy-lowering therapy on cognitive performance.\cite{213,214,215} This might relate to limitations in study design such as the inclusion of subjects with normal Hcy levels\cite{308} and too short follow-up (Table 2). Also, there are no trials with AD or VaD as an endpoint. However it is currently not recommended to give B-vitamins for the prevention of VCI (Table 1).

Physical activity
Physical activity has multiple biological effects including beneficial actions on synaptogenesis and neurogenesis\cite{311} and in fact, observational studies demonstrate a beneficial role of physical activity on the risk of VaD,\cite{72} AD,\cite{73} dementia,\cite{73} and cognitive decline.\cite{74} However, there are few data from RCTs.\cite{227,228} The so far largest trial compared a 24-week home-based program of physical activity with education and usual care in 170 non-demented volunteers with subjective memory impairment. Physical activity provided a modest improvement in cognition over an 18-month follow-up period as assessed by the ADAS-Cog.\cite{235}
Cognitive function is a secondary outcome in the ongoing Lifestyle Interventions and Independence for Elders (LIFE) Study, which compares supervised moderate-intensity physical activity with an aging health education program in sedentary older persons. In a pilot study of that trial group differences in cognitive scores were not significant but improvements in cognitive scores were associated with improvements in physical function. The LIFE study aims to recruit 1,600 subjects and is expected to be completed in 2014. The AHA/ASA guidelines issue a class IIb/B evidence for physical activity for the prevention of cognitive impairment (Table 1). However, a number of questions remain including the optimal type and frequency of physical activity, and the period in life when individuals benefit most.

Obesity and BMI
Overweight and obesity measured by the body mass index (BMI) are established risk factors for dementia although disentangling the impact of obesity from other components of the metabolic syndrome such as hypertension and insulin resistance is challenging. BMI has a U-shaped relationship with dementia in that both underweight and overweight in mid-life are associated with an increased risk of dementia, AD and VaD. A study from Northern California found that central obesity increased the risk of dementia independent of BMI and of diabetes and cardiovascular comorbidities.

Up to now, there are no interventional studies examining the effect of targeted weight loss on cognitive trajectories. Nevertheless, weight control may be reasonable to prevent VCI (Table 1). There is some evidence that BMI measured in late-life has an inverse association with risk of dementia but a number of factors including methodological aspects might explain this “obesity paradox”.

Physiological risk factors

Hypertension
There is strong evidence that long-standing hypertension in midlife increases the risk of cognitive impairment and dementia in late-life, whereas the association between hypertension in late-life and dementia is less consistent. Blood pressure (BP) values frequently drop in late-life and this drop has been reported to be stronger in subjects with dementia than in non-demented subjects. A J- or U-shaped relation with late-life cognitive decline has been found for systolic BP (SBP) and to a lesser degree for diastolic BP. However, the mechanisms underlying these relationships are still debated. As demonstrated by a recent meta-analysis hypertension is associated with an increased risk of incident VaD (OR=1.59; 1.29-1.95) whereas the relationship is less clear for AD. Among subjects not taking antihypertensive medication in the Honolulu Asia Aging Study (HAAS) 27% of late-life dementia cases were attributable to midlife SBP levels ≥120 mmHg.

Despite conclusive evidence for the role of hypertension there is considerable uncertainty regarding the efficacy of antihypertensive treatment for lowering the risk of dementia: Published data suggest some preventive effect of antihypertensive treatment when given to younger people. Specifically, several studies found an association between the use of BP lowering drugs and risk of AD, which was more pronounced when patients were followed for extended time periods. The Rotterdam study and the HAAS presented data on VaD. Antihypertensive treatment was associated with a reduced risk of VaD in both studies. However, hazard ratios varied between studies and there was no clear effect of the duration of follow-up.
The preventive effects of antihypertensive drugs on the risk of stroke differ depending on drug classes independently of effects on mean BP. Data on dementia are much less consistent. Most observational studies found no differences between individual classes of antihypertensive drugs with regard to risk of dementia. Two studies reported on a stronger effect of diuretics, especially potassium-sparing diuretics. Other studies found a stronger protective effect for angiotensin receptor blockers (ARB) and angiotensin-converting enzyme inhibitors (ACE-I). However, these observations may in part relate to limitations in study design. Two studies reported data for VaD but again there was no consistent finding regarding the effects of specific drug classes.

**RCTs:** Eight large RCTs investigated the effect of antihypertensive treatment on incident dementia (7 studies) or cognitive decline (6 studies) (Suppl. Table 3). All trials included patients at increased risk for cardiovascular events but with variable inclusion criteria. The mean age at baseline ranged from 64 to 84 years, the duration of follow-up (mean or median) ranged from 2.0 to 4.7 years, and the mean difference in SBP achieved by active treatment vs. placebo ranged from 3 to 15mmHg (Figure 2 and 3). In all but one trial (PRoFESS) antihypertensive treatment reduced the incidence of stroke or a combined vascular endpoint. A beneficial effect on the risk of incident dementia was reported in the Syst-Eur trial (p=0.05). However, there was no clear cut effect on dementia in any of the other trials (Figure 2). Furthermore, there was no clear effect on cognitive performance except in one trial (PROGRESS).

The Syst-Eur trial included patients with a BP of 160-219mmHg systolic and below 95mmHg diastolic. Active treatment was initiated with nitrendipine and if necessary combined with or replaced by enalapril, hydrochlorothiazide or both titrated to reduce SBP by predefined margins. The mean decrease in SBP between the active and placebo group was 8.3mmHg (diastolic: 3.8mmHg). The trial was stopped prematurely because of a significant benefit from treatment for lowering stroke risk. The rate of incident dementia was reduced by 50% (Figure 2) with most cases classified as AD. In an open-label extension study the principal result was confirmed with a similar effect on mixed or VaD. In the PROGRESS trial treatment with perindopril with or without the addition of indapamide was associated with a reduced incidence of dementia in the subgroup of patients with recurrent stroke (risk reduction 23%; 3 – 55%) and in patients receiving combination therapy (risk reduction 23%; 0 – 41%). However, in meta-analyses on all trials antihypertensive treatment had no significant effect on the risk of dementia, cognitive impairment or cognitive decline. When stratifying trials according to drug classes a significantly reduced incidence of dementia was found in trials involving a diuretic or dihydropyridine calcium channel blocker (CCB) as part of active treatment whereas this was not the case in trials of renin system inhibitors. However, this finding might be explained by between-group difference in the amount of BP reduction which was larger for trials involving a diuretic or CCB (Figure 2).

In conclusion, there is reasonable evidence from observational studies that in the middle aged and young-elderly, lowering BP can be useful for the prevention of late-life dementia (Table 1). However, considerable uncertainty remains regarding the efficacy of antihypertensive drugs for lowering the risk of dementia in general. This in part relates to methodological limitations shared by all BP-lowering trials including 1) a short duration of follow-up (Figure 3), 2) a small number of incident cases of cognitive decline or dementia, 3) additional treatments in the placebo and active treatment groups, 4) variable definitions and assessment instruments for cognitive endpoints, 5) a high number of dropouts with the risk of selective dropout of cognitively impaired patients, and 6) a failure to account for competing risks (Table 2). For example, by reducing mortality some antihypertensive drugs may have
increased the rate of study participants who reached the cognitive endpoint. In consideration of these limitations the results of BP-lowering trials should be interpreted with caution. What is missing are large sufficiently powered trials with longer follow-up in the appropriate age range and with cognitive endpoints as the primary outcome. In addition, there is a need for meta-analyses on individual patient data.

Hyperglycemia and Diabetes
Chronic hyperglycemia, hyperinsulinemia, the metabolic syndrome and diabetes are important risk factors for poorer cognitive performance and cognitive decline although the mechanisms are still debated. Diabetes is associated with an increased risk of VaD and AD. In a meta-analysis of population-based studies the risk ratio of older diabetic adults compared with non-diabetics was around 1.5 for all dementia, 1.4 for AD, and 2.4 for VaD and the diabetes attributable risk of dementia has been calculated to be between 7 and 13% of all incident cases of dementia. Cognitive changes in type 2 diabetes (T2D) involve multiple cognitive domains with slowed processing speed being the most consistently reported abnormality.

The effects of diabetes on cognition could be mediated through a number of mechanisms including vascular injury, glucose toxicity, hyperinsulinemia, and disturbed amyloid metabolism. Diabetes is associated with micro- and macrovascular disease, and with functional changes in CBF, which may in part be reversed by improved glucose control. Also, diabetic patients are more likely to have silent and symptomatic brain infarcts on neuroimaging which would fit with the observed association between diabetes and VaD. However, diabetes frequently develops in the context of other risk factors constituting the metabolic syndrome and it is still debated to what extent the effects on cognition are mediated through diabetes or other risk factors of the metabolic syndrome.

The Memory in Diabetes (MIND) substudy of the ACCORD trial investigated the effects of intensive versus standard glycaemic control on brain structure and cognitive function. At 40 months the total brain volume (TBV) was significantly greater in the intensive-treatment group, reflecting a slower decline in TBV compared to baseline. However, there was no significant treatment difference on any of the cognitive tests. Similarly, in the ADVANCE trial intensive glucose control had no significant effect on the rate of cognitive decline with a numerically higher proportion of incident dementia in the intensive treatment group. Taken together the level of evidence for a protective effect of intensive glucose lowering with respect to cognitive impairment is very low as is also reflected by current guidelines (Table 1). However, there is great demand for further trials also involving new antidiabetic drugs and overcoming the methodological limitations outlined in Table 2.

Another potentially important aspect is hypoglycemia. A recent study in elderly patients with T2D found an association between severe hypoglycemic episodes and an increased risk of dementia. This finding emphasizes the need for careful glycemic control.

Lipids and Dyslipidemia
Cholesterol may be implicated in the pathogenesis of both VaD and AD with partially overlapping mechanisms. Long-term epidemiological studies have found an association between higher midlife serum total cholesterol levels and subsequent cognitive impairment developing many years later. A similar relationship has been reported for both VaD and AD. However, the association between cholesterol and dementia is still debated especially in late-life cohorts.
Cognitive function was a tertiary outcome in the Heart Protection Study (HPS)\textsuperscript{202} and the PROSPER trial.\textsuperscript{331} The average follow-up in these trials was 5 and 3.5 years, respectively. The HPS used a validated telephone interview at final follow-up and evaluated both the percentage of patients classified as cognitively impaired and those with incident dementia. The PROSPER trial used four different outcome parameters (MMSE, Stroop color-wording, letter digit coding, picture learning) and analyzed the differences between the last on-treatment and the baseline value. There was no treatment effect on any of the cognitive outcomes in the two trials. Based on these results there is no evidence that the use of statins has a favorable effect on cognitive function in the elderly.

\underline{Concomitant clinical vascular disease}

Having a stroke doubles the risk of dementia even when adjusting for age, sex, education, and exposure to individual stroke risk factors\textsuperscript{332}. Moreover, the risk of dementia further increases with recurrent stroke.\textsuperscript{4} Coronary artery disease (CAD), peripheral arterial disease (PAD), chronic kidney disease, and low cardiac output have all been associated with cognitive impairment and dementia (figure 1). An increased risk of VaD has been reported for CAD,\textsuperscript{5} AF,\textsuperscript{146} chronic kidney disease,\textsuperscript{153} and PAD.\textsuperscript{151} PAD and low cardiac output was furthermore found to be associated with AD. Thus, preventing chronic vascular disease may be one of the most efficient strategies to prevent dementia. Given the well-documented efficacy of platelet inhibitors in secondary stroke prevention and the enormous risk reduction achieved with oral anticoagulants in patients suffering from AF it might surprise that there is no evidence for a beneficial effect of these agents on the risk of VCI. However, few trials included cognitive endpoints\textsuperscript{263} and in none of them the comparison was against placebo, which in addition to other factors (table 2) might explain the missing evidence. Regardless of the paucity of data for cognitive endpoints, adherence to current guidelines for primary and secondary stroke prevention remains a priority.

\underline{Ongoing Trials}

Table 3 provides an overview on ongoing trials that are targeted against established risk factors for VaD and in which dementia or cognitive impairment is a major endpoint. Most single-component interventions such as the SBP intervention trial (SPRINT) and the secondary prevention of small subcortical strokes trial (SPS3) are targeted against cardiovascular endpoints with cognitive endpoints as secondary outcome measures. An exception is the efficacy and safety study of nimodipine to prevent mild cognitive impairment after acute ischemic strokes (NICE), which has cognitive function as the primary and VaD as a secondary endpoint.

Multi-component interventions target multiple risk factors in parallel and there are several ongoing trials with cognitive decline or dementia as a primary endpoint. The Prevention of Dementia by Intensive Vascular Care (PreDIVA) trial examines whether a nurse-led intensive vascular care in non-demented elderly subjects decreases the incidence of dementia. Intensive care comprises both medical and lifestyle interventions including a program for smoking cessation and physical exercise. The Finnish Geriatric Intervention Study to Prevent cognitive Impairment and disability (FINGER) and the Austrian Polyintervention Study to Prevent Cognitive Decline After Ischemic Stroke (ASPIS) recruit younger subjects at increased risk of developing dementia. The first results of these trials are expected in 2013.
Novel molecular targets
Genetic approaches and experimental studies in model systems of acute and chronic ischemia have identified a variety of targets linking specific molecules or cellular pathways to VCI. Examples include NOTCH3 and HTRA1 as target genes implicated in cerebral small vessel disease, and the APOE ε4 allele as a risk factor for cerebral amyloid angiopathy. These findings highlight the importance of considering novel disease markers and ethiological subtypes of VCI such as subcortical ischemic vascular disease. Also, there is growing evidence for a key role of radical oxygen species in mediating some of the deleterious effects of aging, hypertension, and Amyloid β on small blood vessels, all of which are major risk factors for dementia. These findings provide a starting point for developing targeted preventive treatments.

Challenges and Opportunities
The available data emphasize the need for properly designed trials overcoming the limitations outlined in table 2. Key aspects include i) the inclusion of subjects in the appropriate age range and at increased risk of developing dementia, ii) the use of cognitive test batteries that are sensitive to change and to the typical profile of deficits in patients with VCI, iii) a sufficiently long duration of treatment and follow-up, iv) and specific actions to account for differential dropout and competing risks.

It might be questioned whether preventing VaD as a specific diagnostic category rather than dementia in general represents a meaningful goal. As outlined VaD and AD have many risk factors in common (figure 1), which means that most strategies to prevent VaD will likely affect the risk of AD. Also, many patients have mixed vascular and neurodegenerative pathology and disentangling the different components with sufficient diagnostic accuracy requires substantial diagnostic efforts. Apart from imposing a burden on patients these investigations are often not realistic in the setting of a preventive trial with many thousand subjects.

Without doubt, however, preventing vascular brain damage remains an important goal. The increasingly recognized association between cognitive impairment and both covert brain infarcts and ischemic white matter lesions illustrates the need to consider neuroimaging in future interventional trials. “Silent” brain infarcts outnumber clinically manifest strokes by a factor of greater than 5 to 1 and including neuroimaging markers as adjunct outcomes may be one way to increase the power of future preventive trials.

In light of the high risk of cognitive decline and dementia after stroke, in particular recurrent stroke, future acute stroke trials and secondary prevention trials should include cognitive endpoints as standard outcomes. Ideally, this should be combined with longer follow-up than is seen in current trials. The additional costs associated with such an extension are more than justified given the enormous socioeconomic impact of post-stroke dementia and VCI in general.

The prevalence of VCI and VaD will likely increase over the next decades both in high- and low-income countries. Preventing vascular disease remains the most promising strategy to prevent VaD and possibly dementia in general although the level of evidence remains low for most interventions (Table 1). Thus, there is great demand for large, properly designed trials. In the meantime, multi-component interventions aimed at reducing the burden of vascular disease should be considered a reasonable approach to prevent cognitive impairment and dementia.
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