Does treating vascular risk factors prevent dementia and Alzheimer’s disease? A systematic review and meta-analysis

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Does Treating Vascular Risk Factors Prevent Dementia and Alzheimer’s Disease? A Systematic Review and Meta-Analysis

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Running title: Treatment of vascular risk factors and dementia

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Abstract

**Background:** Epidemiological evidence has associated Alzheimer’s disease (AD) with vascular risk factors (VRFs), but whether treatment of VRFs reduces the incidence of dementia and AD is uncertain.

**Objective:** To conduct a systematic review and meta-analysis to summarize available data on the impact of treatment of VRFs on dementia and AD incidence.

**Methods:** Pertinent studies published until 1 January 2018 were identified from PubMed. Both randomized controlled trials (RCT) and prospective studies that investigated the impact of treatment of VRFs on dementia or AD incidence were included.

**Results:** Eight RCTs and 52 prospective studies were identified. Antihypertensive treatment was associated with a non-significant reduced risk of dementia in RCTs (n=5; relative risk [RR], 0.84; 95% confidence interval [CI], 0.69–1.02) and prospective studies (n=3; RR, 0.77; 95% CI, 0.58–1.01) and with reduced AD risk in prospective studies (n=5; RR = 0.78; 95% CI, 0.66–0.91). In prospective studies, treatment of hyperlipidemia with statins, but not nonstatin lipid-lowering agents, was associated with reduced risk of dementia (n=17; RR, 0.77; 95% CI, 0.63–0.95) and AD (n=13; RR, 0.86; 95% CI, 0.80–0.92). The single RCT on statins and dementia incidence showed no association. Data from one RCT and six prospective studies did not support a beneficial impact of antidiabetic drugs or insulin therapy on dementia risk.

**Conclusion:** Current evidence indicates that antihypertensives and statins might reduce the incidence of dementia and AD. Further trials to determine the effect of VRF on AD are needed.
INTRODUCTION

Dementia is a growing public health concern because of the globally ageing population and the lack of effective treatments. By 2050, the number of people with dementia worldwide may nearly triple, from 46.8 million to a projected 131.5 million [1]. The major form of dementia is Alzheimer’s disease (AD), accounting for about 60% or more of all cases [2].

Chief pathological hallmarks of the AD brain are neurofibrillary tangles and abnormal accumulation of amyloid-β (Aβ) peptides in amyloid plaques [3]. Recent clinical trials in AD, many based on the amyloid hypothesis, have been disappointing [4] and this has increased interest in other potential therapeutic avenues. Considerable evidence indicates that vascular risk factors (VRFs) [2, 3, 5] are linked to AD. Observational studies have found that modifiable VRFs, including hypertension, hypercholesterolemia, and obesity in midlife, type 2 diabetes mellitus, physical inactivity, and smoking are associated with an increased risk of AD [2, 3, 5-7]. It was recently estimated that a third of all AD cases worldwide might be attributable to potentially modifiable risk factors [6]. This suggests that treatment of VRFs might reduce the incidence of AD, but whether treating VRF does indeed reduce the risk of AD is unclear.

Previous reviews have summarized the evidence from randomized controlled trials (RCTs) or observational studies assessing the effect of hypertension [8-10] or hyperlipidemia [11-14] treatment on dementia risk. However, to the best of our knowledge, there are no systematic reviews summarizing all available evidence from both RCTs and prospective studies on all major VRFs in relation to incidence of AD and all-cause dementia. We therefore performed a contemporary systematic review and meta-analyses to summarize available data from RCTs and prospective observational studies investigating the influence of treatment of established VRFs (hypertension, hyperlipidemia, and type 2 diabetes mellitus) or
smoking cessation, exercise, or weight loss intervention on the incidence of AD and all-cause dementia.

METHODS

Search Strategy

This systematic review and meta-analysis followed the PRISMA guidelines [15]. PubMed was searched, without restrictions, from inception until 1 January 2018. The predefined key words used for the database search are described in Table S1. The reference lists of relevant publications were scrutinized to identify further studies.

Selection criteria

Articles were included if they met the following inclusion criteria: 1) randomized controlled trial (RCT) or prospective study (including register-based cohorts); 2) assessed treatment of an established VRF with available drug treatment (i.e., hypertension, hyperlipidemia, or type 2 diabetes mellitus) or smoking cessation, exercise, or weight loss intervention; 3) the outcome was all-cause dementia or AD; and 4) a relative risk (RR) estimate with corresponding 95% confidence interval (CI) or sufficient data to calculate these were provided. Exclusion criteria were cross-sectional study; case-control study; nonrandomized trial; and animal study. Where duplicate publications were available, the study with the longest follow-up or largest number of participants was included.

Data extraction and quality assessment

The following information was extracted from each study: first author’s last name, year of publication, name of the study or database used, country in which the study was performed, outcome(s) assessed and diagnostic criteria, total number of participants and cases, age of participants, mean follow-up time, type of treatment, variables adjusted for in full model, and
the most fully adjusted RR with corresponding 95% CI. Assessment of study quality (ranging from 0 to 9) was performed using the Newcastle-Ottawa Scale [16]. Details of how the criteria were applied are shown in Figure S1.

Statistical analysis

Where results for a treatment-outcome association were reported by two or more studies, results were combined in a meta-analysis, using a random-effects model [17]. Between-study heterogeneity was assessed with the $I^2$ statistic [18]. The following interpretation for the $I^2$ values were used: $<30\% =$ no or low heterogeneity; $30\%–75\% =$ moderate heterogeneity; and $>75\% =$ notable heterogeneity. Meta-regression and subgroup analyses were carried out if feasible ($\geq 2$ studies per stratum) to assess potential sources of heterogeneity by study quality (quality score 0–7 [low quality] vs 8–9 [high quality]), duration of follow-up ($<5$ vs $\geq 5$ years), and number of cases ($<200$ vs $\geq 200$). Publication bias was evaluated with Egger’s test [19]. All statistical analyses were carried out using Stata, version 14.2 (StataCorp, College Station, TX). We considered $p$-values $<0.05$ to be statistically significant.

RESULTS

Literature search

A total of 7136 articles of which 60 met the inclusion criteria were identified (Figure S2). The eligible studies comprised 8 RCTs and 52 articles based on prospective studies (Table 1).

Randomized controlled trials

A striking feature was the paucity of data from RCTs with only 8 studies in total, including five on antihypertensive treatment, one each on hyperlipidemia and type 2 diabetes
mellitus treatment, and one that assessed the effectiveness of a multifactorial VRF intervention.

_Hypertension treatment_

Four of the five RCTs [20-24] found a reduction in dementia incidence in patients randomized to antihypertensive treatment [20, 21, 23, 24] but results reached statistical significance in only one trial [21] (Table S2). In a meta-analysis of these RCTs (total of 22 016 patients and 936 cases) the combined RR of dementia for active treatment vs placebo was 0.84 (95% CI, 0.69–1.02), with moderate heterogeneity between trials (Figure 1). In a sensitivity analysis in which one trial at the time was omitted and the rest analyzed to assess the influence of single trials on the overall results, the RRs ranged from 0.79 (95% CI, 0.64–0.98) when the Study on Cognition and Prognosis in the Elderly trial [22] was excluded to 0.90 (95% CI, 0.78–1.03) when the Systolic Hypertension in Europe Study [21] was excluded. There was no evidence of significant publication bias.

_Hyperlipidemia treatment_

The single RCT assessing the influence of hyperlipidemia treatment on dementia incidence was the Heart Protection Study [25]. In this trial, 20 536 UK adults, 40–80 years of age, with non-fasting total cholesterol concentrations of at least 3.5 mmol/L (135 mg/dL) and a history of coronary heart disease, other occlusive arterial disease, or diabetes mellitus were randomly allocated to receive simvastatin or matching placebo. The average difference in low-density lipoprotein cholesterol concentration during a mean follow-up of 5 years was 1.2 mmol/L. Patients assigned to simvastatin had statistically significantly reduced all-cause and coronary mortality but the number of incident dementia cases during follow-up was similar in both groups (0.3%; n = 31 cases).
**Type 2 diabetes mellitus treatment**

One RCT evaluated the efficacy of intensive glucose control on vascular outcomes in 11,140 type 2 diabetes mellitus patients [26]. The mean glycated hemoglobin concentration was lower in the intensive-control group (6.5%) than in the standard-control group (7.3%) after a median 5 years of follow-up. Intensive glucose control reduced the incidence of combined major macrovascular and microvascular events but not dementia (n = 109 cases) [26].

**Multifactorial VRF intervention**

One RCT has examined whether more intensive treatment of VRFs in patients with first ever stroke or transient ischemic attack influences poststroke cognitive functioning or risk of dementia (secondary outcome) [27]. Pharmacological intervention included antiplatelet agents or warfarin, antihypertensives, statins, antidiabetic drugs, and vitamin B complex including folic acid. Patients were also offered smoking cessation courses and were encouraged to perform regular moderate physical activity, to consume a diet rich in fruit, vegetables, fish, and low-fat dairy products, and less sugar, and not to use alcohol excessively. Patients were randomized either to the intervention group (n = 98) or the control group (n = 97) that received care as usual. One-year poststroke, 11 (13%) patients in the intervention group and 17 (19%) in the control group had developed dementia (p = 0.30) [27].

**Prospective observational studies**

Among the prospective studies, results on hypertension, hyperlipidemia, and type 2 diabetes mellitus treatment were reported in respectively 20, 27, and seven studies (two studies reported results on two treatments).
Hypertension treatment

Thirteen prospective studies [28-40] were included in the meta-analysis of hypertension treatment and dementia or AD risk (Table S3). The combined RRs for any antihypertensive medication use vs nonuse were 0.77 (95% CI, 0.58–1.02) for dementia, with moderate heterogeneity among studies, and 0.78 (95% CI, 0.66–0.91) for AD, with low heterogeneity (Figure 2). In two studies that reported results on duration of use of antihypertensive drugs in relation to risk of dementia or AD, the inverse association was more pronounced with longer use [32, 36]. Of the different classes of antihypertensive drugs, angiotensin receptor blockers, calcium channel blockers, and diuretics were statistically significantly inversely associated with risk of dementia and AD (Figure 2). There was no evidence of publication bias.

Seven studies compared different classes of antihypertensive drugs and risk of dementia or AD [41-47] (Table S4). Among three studies that compared angiotensin-converting enzyme inhibitors with other antihypertensive drugs, one study observed a stronger inverse association with angiotensin-converting enzyme inhibitors [44], whereas the other two studies found no clear difference [41, 42]. Angiotensin receptor blockers seemed to be more strongly inversely related to risk of dementia or AD than angiotensin-converting enzyme inhibitors or other antihypertensive drugs in three [43, 44, 46] out of four studies [43-46]. One study found that use of calcium-channel blockers was associated with reduced risk of dementia and AD [47].

Hyperlipidemia treatment

A total of 27 studies were included in the meta-analysis of hyperlipidemia treatment and risk of dementia or AD (Table S5). Among these, 25 studies reported results on statin therapy [46, 48-71], eight on nonstatin lipid-lowering agents [48, 50-52, 61, 62, 65, 66], and three on any lipid-lowering agent (statins or nonstatins) [58, 72, 73]. The combined RRs for statin use vs nonuse were 0.77 (95% CI, 0.63–0.95) for dementia, with notable heterogeneity among
studies, and 0.86 (95% CI, 0.80–0.92) for AD, with moderate heterogeneity (Figure 3). The associations of statin therapy with dementia and AD risk did not differ significantly by study quality, follow-up time, or number of cases (all \( p > 0.10 \); Table S6). High potency statins (i.e., atorvastatin, rosuvastatin, and simvastatin) appeared to be more strongly associated with reduced risk of dementia and AD than low potency statins (i.e., fluvastatin, lovastatin, and pravastatin) [55, 63, 68, 71] (Table S6). In seven studies that reported results on duration of statin use [49, 50, 66-69, 74], the combined RRs of dementia or AD were 0.83 (95% CI, 0.68–1.01) for short-term use and 0.57 (95% CI, 0.40–0.82) for long-term use.

Nonstatin lipid-lowering agents were not associated with dementia or AD risk in the overall analysis (Figure 4) or in stratified analysis by study quality, follow-up time, and number of cases (data not shown). Use of any lipid-lowering agent (statins or nonstatins) was associated with a lower risk of dementia/AD (RR, 0.47; 95% CI, 0.35–0.62; \( I^2 = 48\% \)). No evidence of publication bias was noted.

Type 2 diabetes mellitus treatment

Seven prospective studies of antidiabetic treatment in relation to risk of dementia or AD [56, 75-80] were identified (Table S7). In two cohorts of type 2 diabetes mellitus patients [77, 79], the combined RRs of dementia or AD were 0.94 (95% CI, 0.91–0.97; \( I^2 = 0\% \)) for oral antidiabetic drug use and 1.17 (95% CI, 0.80–1.71; \( I^2 = 68.2\% \)) for insulin therapy. In four studies that included both diabetics and nondiabetics, the combined RRs of dementia or AD were 1.51 (95% CI, 0.83–2.77; \( I^2 = 86.7\% \)) for oral antidiabetic drug use [75-77] and 2.10 (95% CI, 1.14–3.85; \( I^2 = 55.0\% \)) for insulin therapy [56, 75, 77], relative to nondiabetics.

One study investigated whether metformin is associated with a lower incidence of dementia compared with sulfonylureas [80]. After accounting for confounding by indication, metformin vs sulfonylurea use was associated with a lower risk of dementia in those <75 years of age but not in those \( \geq 75 \) years of age [80] (Table S7).
DISCUSSION

This systematic review found evidence that antihypertensive use may lower the incidence of dementia and AD. Statin use was related to a lower risk of dementia in prospective studies but not in the single RCT. There was no support for a beneficial effect of treatment with nonstatin lipid-lowering agents or antidiabetic drugs. Studies on smoking cessation, exercise, and weight loss interventions in relation to dementia or AD incidence were lacking, except for a small (<200 participants) multifactorial VRF intervention study showing no beneficial effect. This finding is consistent with a small lifestyle-based intervention showing no benefit of 24-month multidomain intervention with focus on improvement in lifestyle and vascular risk factors on the incidence of poststroke cognitive decline in comparison with standard stroke care [81].

Four of the five RCTs of antihypertensive therapy observed a 12% to 55% reduction in dementia incidence in the active treatment group. However, the number of dementia cases in each RCT was limited and the results were statistically significant only in the Systolic Hypertension in Europe Study [21]. The inconsistent results may partly be related to different antihypertensive therapies, and to differences in the reduction in blood pressure in the active treatment and placebo groups. In the Study on Cognition and Prognosis in the Elderly trial, which did not show a lower dementia risk with treatment, patients were allocated to receive an angiotensin receptor blocker or placebo, with open-label active antihypertensive therapy added as needed [22]. This resulted in 84% of the placebo group taking additional antihypertensive medication. As a consequence, systolic and diastolic blood pressure at the end of follow-up was only marginally lower in the treatment group than in the placebo group. Other trials showed larger differences in the reduction in blood pressure between treatment arms. Different participant characteristics and diagnostic criteria for dementia may also have contributed to the inconsistent findings. The RCTs did not have dementia as the primary
endpoint [20-23] or the main trial was stopped early [24] and therefore was not powered to
detect a statistically significant effect of blood pressure-lowering on dementia incidence. The
prospective studies of any antihypertensive therapy and risk of dementia or AD were also
generally based on a limited number of cases, ranging from 65 to 333 AD cases and 108 to
440 dementia cases, but an overall statistically significant inverse association between any
antihypertensive medication use and risk of AD was observed in the meta-analysis.

AD begins many years before dementia symptoms emerge and VRF in midlife appear to
be better related to dementia than VRF in old age [82]. The RCTs and most prospective
studies of antihypertensive treatment and dementia risk were short term (2.2-5 years in the
RCTs), or had short follow-up, and generally included older participants (≥60 years of age).
The short-term antihypertensive treatment in old age may explain negative findings in RCTs
and some of the prospective studies.

Antihypertensive treatment might reduce the risk of dementia and AD by decreasing
blood pressure or by specific neuroprotective effects. Hypertension is the major risk factor for
cerebral white matter hyperintensities visible on T2-weighted MRI, which are associated with
an increased risk of dementia [83]. In the Perindopril Protection Against Recurrent Stroke
Study trial, antihypertensive therapy delayed the progression of white matter hyperintensities
[84] and reduced the incidence of dementia by 34% in patients with recurrent stroke but had
no effect on dementia incidence in the absence of recurrent stroke [23]. Antihypertensive
drugs that cross the blood-brain barrier may have specific neuroprotective actions. For
example, an experimental study in mice showed that the calcium channel blocker nifedipine,
which can cross the blood-brain barrier, attenuated peroxide anion production in the brain and
this reduction in oxidative stress was related to better cognitive performance [85]. Two other
experimental studies showed that certain calcium channel blockers, including nifedipine and
nitrendipine (the antihypertensive drug used in the Systolic Hypertension in Europe Study
decreased brain Aβ peptide concentrations [86, 87] and improved Aβ clearance across the blood-brain barrier [86]. A prospective study found that angiotensin-converting enzyme inhibitors that cross the blood-brain barrier were more strongly inversely associated with AD risk than angiotensin converting enzyme-inhibitors that cannot cross the blood-brain barrier [41].

Results from the present meta-analysis of prospective studies showed that statin therapy was associated with a reduced risk of dementia and AD. However, a large RCT did not support a reduction in dementia incidence with simvastatin therapy [25]. Whether hypercholesterolemia is a risk factor for dementia and AD remains elusive. Observational studies have found that hypercholesterolemia in midlife is associated with AD risk [7], but Mendelian randomization studies, which are less prone to bias, do not support a causal association between cholesterol levels and AD [88, 89]. Statins may have neuroprotective actions through their ability to improve blood-flow, modulate the immune system and lower oxidative damage [90].

A meta-analysis of published studies inherits the limitations of the original studies. Observational studies are susceptible to confounding and reverse causality and we cannot rule out the possibility that these biases may have affected the results. Another potential limitation is the accuracy of dementia diagnosis and differentiation of AD from other causes of dementia. An AD diagnosis based on standard criteria has good sensitivity and specificity for differentiating between AD patients and individuals without dementia but the ability to discern between AD and other causes of dementia is less accurate [3]. Another shortcoming is that the literature search and data extraction were performed by a single investigator, and that only one database was searched. We therefore cannot preclude the possibility that we may have missed relevant studies for inclusion. Finally, as a meta-analysis of published studies, the possibility that publication bias may have affected the results cannot be excluded. We
found no evidence of such bias but tests for publication bias have low power, in particular when the number of studies is limited.

In conclusion, available evidence from RCTs and prospective studies indicates that antihypertensive therapy might have a role in preventing dementia and AD. Further studies are required, particularly on whether more intensive lowering of blood pressure to 120 mm Hg systolic or below, which has been shown to reduce cardiovascular outcomes [91], is also associated with a lowering of the incidence of dementia and AD. Prospective studies have indicated an inverse association between statin use and risk of dementia and AD, but there is yet no support from RCTs that statins are beneficial.

A striking feature was the paucity of RCTs investigating the effect of treatment of vascular risks factors on AD. A cost-efficient method of obtaining such data would be to include long-term follow-up for cognitive endpoints in trials of cardiovascular prevention. This is important considering both the huge population burden of dementia, and the lack of other effective treatment approaches.

ACKNOWLEDGMENTS

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SUPPLEMENTARY MATERIAL

Supplementary material is available for this paper.
REFERENCES


### Table 1

Number of randomized controlled trials and prospective studies included in the review

<table>
<thead>
<tr>
<th>Vascular risk factor and drug treatment or intervention</th>
<th>No. of randomized controlled trials</th>
<th>No. of prospective studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensive drug use vs. nonuse/placebo</td>
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<td>13</td>
</tr>
<tr>
<td>Comparison of antihypertensive drug classes</td>
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<td>7</td>
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<td><strong>Hyperlipidemia</strong></td>
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</tr>
<tr>
<td>Statin</td>
<td>1</td>
<td>25*</td>
</tr>
<tr>
<td>Nonstatin lipid-lowering drug</td>
<td>0</td>
<td>8*</td>
</tr>
<tr>
<td>Any lipid-lowering drug (statin or nonstatin)</td>
<td>0</td>
<td>3*</td>
</tr>
<tr>
<td><strong>Type 2 diabetes mellitus</strong></td>
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<td></td>
</tr>
<tr>
<td>Oral antidiabetic drug</td>
<td>1</td>
<td>6†</td>
</tr>
<tr>
<td>Insulin therapy</td>
<td>0</td>
<td>5†</td>
</tr>
<tr>
<td><strong>Vascular risk factor intervention</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking cessation</td>
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<td>0</td>
</tr>
<tr>
<td>Exercise</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Weight loss</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Multifactorial intervention</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

*Some studies provided results on both statins and nonstatins or a combination of these.

†Most studies provided results on both oral antidiabetic drugs and insulin therapy.
Fig. 1. Relative risks of dementia for antihypertensive treatment vs placebo in individual randomized controlled trials and all trials combined. Trials are ordered by year of publication. Squares represent trial-specific relative risk (RR) (size of the square reflects the trial-specific statistical weight); the horizontal lines represent 95% confidence intervals (CIs); diamond represents combined RR with its 95% CI. HYVET-COG, Hypertension in the Very Elderly Trial-Cognition; PROGRESS, Perindopril Protection Against Recurrent Stroke Study; SCOPE, Study on Cognition and Prognosis in the Elderly; SHEP, Systolic Hypertension in the Elderly Program; SYST-EUR, Systolic Hypertension in Europe Study.
**Fig. 2.** Combined relative risks of dementia and Alzheimer’s disease for use of any antihypertensive drug and classes of antihypertensive drugs vs nonuse in prospective studies. Results for antihypertensive drug classes are for dementia or Alzheimer’s disease. *Number of studies in each subgroup. ACE-I, angiotensin-converter enzyme inhibitor; AH, antihypertensive; CI, confidence interval; RR, relative risk.
**Fig. 3.** Relative risks of dementia and Alzheimer’s disease for statin use vs nonuse in individual prospective studies and all studies combined. *First author’s last name and year of publication. Studies are ordered by year of publication. NS, not specified; M, men; W, women. Squares represent study-specific relative risks (RR) (size of the square reflects the study-specific statistical weight); the horizontal lines represent 95% confidence intervals (CIs); diamonds represent the combined RR with its 95% CI.
**Fig. 4.** Forest plot of prospective studies of nonstatin lipid-lowering agent use vs nonuse in relation to incidence of dementia and Alzheimer’s disease. *First author’s last name and year of publication. LLA, lipid-lowering agent; M, men; W, women. Squares represent study-specific relative risks (RR) (size of the square reflects the study-specific statistical weight); the horizontal lines represent 95% confidence intervals (CIs); diamonds represent the combined RR with its 95% CI.
Supplementary Material

Does Treating Vascular Risk Factors Prevent Dementia and Alzheimer’s Disease? A Systematic Review and Meta-Analysis

Supplemental tables, figures, and references

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Table S1: Search terms used for the electronic database search

(Alzheimer's Disease OR Alzheimer OR dementia) AND (vascular risk factor OR hypertension OR blood pressure OR antihypertensive agents OR angiotensin converting enzyme inhibitors OR angiotensin receptor blockers OR beta blockers OR calcium channel blockers OR diuretics OR hyperlipidemia OR hypercholesterolemia OR cholesterol OR lipid lowering agents OR statins OR diabetes OR antidiabetic agents OR hypoglycemic agents OR glucose control OR insulin therapy OR overweight OR obesity OR weight loss OR exercise OR physical activity OR smoking) AND (randomized controlled trial OR clinical trial OR intervention study OR prospective study OR cohort study OR follow-up study OR longitudinal study OR nested case-control study)
<table>
<thead>
<tr>
<th>Reference</th>
<th>Trial name, country</th>
<th>Participant characteristics</th>
<th>Mean Follow-up, years</th>
<th>No. of dementia cases; diagnostic criteria</th>
<th>Antihypertensive medication</th>
<th>∆SBP/DBP (active–placebo)</th>
<th>RR (95% CI) of dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHEP Research Group, 1991 [1]</td>
<td>SHEP, United States</td>
<td>4736 adults (43% men) ≥60 years of age; SBP 160–219 mmHg, DBP &lt;90 mmHg; no history of major CVDs</td>
<td>5</td>
<td>81; expert diagnosis evaluation (Short-Care Test)</td>
<td>Diuretic (chlorthalidone) ± β-blocker (atenolol) vs placebo</td>
<td>−11.1/3.4 mmHg</td>
<td>0.84 (0.55–1.30)*</td>
</tr>
<tr>
<td>Forette et al, 2002 [2]</td>
<td>SYST-EUR, 19 countries</td>
<td>2902 adults (34% men) ≥60 years of age; SBP 160–219 mmHg, DBP &lt;95 mmHg</td>
<td>3.9</td>
<td>64; DSM-III-R and results of CT scan</td>
<td>CCB (nitrendipine) ± diuretic (hydrochlorothiazide), ACE-I (enalapril) or both drugs vs placebo</td>
<td>−7.0/3.2 mmHg</td>
<td>0.45 (0.27–0.76)</td>
</tr>
<tr>
<td>Lithell et al, 2003 [3]</td>
<td>SCOPE, 15 countries</td>
<td>4937 adults (36% men) 70–89 years of age; SBP 160–179 mmHg, DBP 90–99 mmHg; MMSE score ≥24</td>
<td>3.7</td>
<td>119; modified ICD-10 research criteria</td>
<td>ARB (candercetan) ± diuretic (hydrochlorothiazide) vs placebo</td>
<td>−3.2/1.6 mmHg</td>
<td>1.08 (0.76–1.54)*</td>
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<td>Tzourio et al, 2003 [4]</td>
<td>PROGRESS, 10 countries</td>
<td>6105 adults (70% men), mean age 64 years; prior stroke or transient ischemic attack</td>
<td>3.9</td>
<td>410; DSM-IV</td>
<td>ACE-I (perindopril) ± diuretic (indapamide) vs placebo</td>
<td>−9/4 mmHg</td>
<td>0.88 (0.72–1.08)</td>
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<tr>
<td>Peters et al, 2008 [5]</td>
<td>HYVET-COG, 13 countries</td>
<td>3336 adults (40% men) ≥80 years of age; SBP 160–200 mmHg, DBP &lt;110 mmHg</td>
<td>2.2</td>
<td>263; DSM-IV and results of CT scan</td>
<td>Diuretic (indapamide) ± ACE-I (perindopril) vs placebo</td>
<td>−15/5.9 mmHg</td>
<td>0.86 (0.67–1.09) [0.85 (0.63–1.15) for Alzheimer’s disease and 0.87 (0.57–1.34) for vascular dementia]</td>
</tr>
</tbody>
</table>

Abbreviations: ACE-I, angiotensin converting enzyme-inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; CT, computerized tomography; CVD, cardiovascular disease; CI, confidence interval; CT, computed tomography; DBP, diastolic blood pressure; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases; HYVET-COG, Hypertension in the Very Elderly Trial-Cognition; MMSE, Mini-Mental State Examination; PROGRESS, Perindopril Protection Against Recurrent Stroke Study; RR, relative risk; SBP, systolic blood pressure; SCOPE, Study on Cognition and Prognosis in the Elderly; SHEP, Systolic Hypertension in the Elderly Program; SYST-EUR, Systolic Hypertension in Europe Study.

*The risk estimate was not reported in the article but was estimated based on the number of cases and non-cases in the two treatment arms.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study name, country</th>
<th>Participants; baseline age</th>
<th>Mean follow-up, years</th>
<th>Outcome (No. of cases); diagnostic criteria</th>
<th>NOS score</th>
<th>Adjustments</th>
<th>Adjusted RR (95% CI) of dementia or AD for AH drug use vs nonuse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morris et al, 2001 [6]</td>
<td>East Boston Study, United States</td>
<td>634 adults; ≥65 years</td>
<td>4</td>
<td>AD (n=99); NINCDS-ADRA</td>
<td>7</td>
<td>Age, sex, education</td>
<td>BB, 0.91 (0.26–3.17) Diuretics, 1.03 (0.63–1.65) for any, 1.06 (0.37–3.06) for loop, 1.33 (0.68–2.61) for thiazide, and 0.63 (0.26–1.54) for potassium-sparing</td>
</tr>
<tr>
<td>in’t Veld et al, 2001 [7]</td>
<td>Rotterdam Study, The Netherlands</td>
<td>7046 adults; ≥55 years</td>
<td>2.2</td>
<td>Dementia (n=118), AD (n=82); DSM-III-R, NINCDS-ADRA</td>
<td>8</td>
<td>Age, sex, education, living situation, BMI, smoking, diabetes, stroke, PAD, DBP, SBP, baseline MMSE</td>
<td>Any AH, dementia: 0.67 (0.45–1.00); AD: 0.77 (0.49–1.24)</td>
</tr>
<tr>
<td>Lindsay et al, 2002 [8]</td>
<td>Canadian Study of Health and Aging, Canada</td>
<td>4088 adults; ≥65 years</td>
<td>5</td>
<td>AD (n=194); NINCDS-ADRA</td>
<td>7</td>
<td>Age, sex, education</td>
<td>Any AH, 0.91 (0.64–1.30)</td>
</tr>
<tr>
<td>Yasar et al, 2005 [9]</td>
<td>Baltimore Longitudinal Study of Aging, United States</td>
<td>1092 adults; ≥60 years</td>
<td>11</td>
<td>AD (n=115); DSM-III-R, NINCDS-ADRA</td>
<td>7</td>
<td>Age, sex, education, smoking, blood pressure, heart disease</td>
<td>CCB, 0.63 (0.31–1.28) [0.30 (0.07–1.25) for dihydropyridine and 0.82 (0.37–1.83) for nondihydropyridine]</td>
</tr>
<tr>
<td>Peila et al, 2006 [10]</td>
<td>Honolulu Asia Aging Study, United States</td>
<td>1294 men; ≥72 years</td>
<td>5</td>
<td>Dementia (n=108), AD (n=65); DSM-III-R, NINCDS-ADRA</td>
<td>8</td>
<td>Age, sex (all men), education, APOE-ε4 status, blood pressure, BMI, smoking status, coronary heart disease</td>
<td>Any AH, dementia: 0.59 (0.35–1.00)<em>; AD: 0.48 (0.29–0.78)</em></td>
</tr>
<tr>
<td>Qiu et al, 2006 [11]</td>
<td>Kungsholmen Project, Sweden</td>
<td>1301 adults; 75–101 years</td>
<td>5</td>
<td>Dementia (n=440), AD (n=333); DSM-III-R, NINCDS-ADRA</td>
<td>9</td>
<td>Age, sex, education, follow-up survival status, BMI, diabetes, heart failure, stroke, pulse rate, SBP, DBP, baseline MMSE</td>
<td>Any AH, dementia: 0.92 (0.75–1.13); AD: 0.84 (0.67–1.07)</td>
</tr>
<tr>
<td>Johnson et al, 2012 [12]</td>
<td>Cohort from Veterans Administration, United States</td>
<td>377 838 adults; ≥65 years</td>
<td>2</td>
<td>Dementia (n=14 580); ICD-9-CM codes</td>
<td>6</td>
<td>Age, sex, ethnicity, comorbidities, co-medications</td>
<td>ACE-I, 0.89 (0.85–0.93) ARB, 0.76 (0.70–0.83) BB, 0.96 (0.92–0.995) CCB, 0.93 (0.89–0.97) Diuretic, 0.86 (0.83–0.90)</td>
</tr>
<tr>
<td>Qui et al, 2013 [13]</td>
<td>National Alzheimer’s Disease Coordinating Center, United States</td>
<td>4830 adults; mean age 76 years</td>
<td>3.4</td>
<td>AD (n=1331); DSM-IV, NINCDS-ADRA</td>
<td>6</td>
<td>Age, sex, ethnicity, education, drinking, follow-up time, diabetes, hypertension, stroke, heart failure, mild cognitive impairment</td>
<td>ACE-I, 0.77 (0.67–0.89)† [0.79 (0.67–0.93) for central ACE-I and 0.73 (0.57–0.94) for peripheral ACE-I]</td>
</tr>
<tr>
<td>Yasar et al, 2013 [14]</td>
<td>Ginkgo Evaluation of Memory Study, United States</td>
<td>1928 adults; ≥75 years</td>
<td>5.6</td>
<td>AD (n=290); DSM-IV, NINCDS-ADRA</td>
<td>9</td>
<td>Age, sex, education, income, BMI, SBP, DBP, vascular diseases, mild cognitive impairment</td>
<td>ACE-I, 0.56 (0.37–0.85) ARB, 0.35 (0.19–0.65) BB, 0.64 (0.44–0.72) Diuretic, 0.46 (0.32–0.68)</td>
</tr>
<tr>
<td>Chiu et al, 2014 [15]</td>
<td>National Health Insurance Research</td>
<td>140 140 adults; ≥50</td>
<td>10.3</td>
<td>Dementia (n=11 075); ICD-9 codes 290.0–</td>
<td>8</td>
<td>Age, sex, income, urbanization, hypertension, coronary heart disease, diabetes,</td>
<td>ACE-I, dementia: 1.14 (1.08–1.19); AD: 1.11 (0.98–1.26)</td>
</tr>
</tbody>
</table>

Table S3: Prospective studies of antihypertensive medication use vs nonuse and incidence of dementia and Alzheimer’s disease
<table>
<thead>
<tr>
<th>Study</th>
<th>Database, Location</th>
<th>Sample Size</th>
<th>Age</th>
<th>Analysis</th>
<th>Risk Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chuang et al., 2014 [16]</td>
<td>Cache County Study, United States</td>
<td>3227 adults; ≥65 years</td>
<td>7.1</td>
<td>Dementia (n=325); DSM-III-R, NINCDS-ADRDA</td>
<td>AD: 0.59 (0.56–0.62); BB: 0.61 (0.54–0.68); CCB: 0.81 (0.77–0.84); Diuretic: 0.87 (0.83–0.91); AD: 0.78 (0.68–0.90)</td>
</tr>
<tr>
<td>Chitnis et al., 2015 [17]</td>
<td>Medicare Advantage Prescription Drug, United States</td>
<td>8062 adults; mean age 75 years</td>
<td>3</td>
<td>Dementia (n=1135); ICD-9-CM codes 046.1, 046.0, 290.0–290.4, 291.2, 292.82, 294.10, 294.11, 294.8, 294.9, 331.0, 331.11, 331.19, 331.2, 331.7, 331.82, 331.89, 331.9</td>
<td>ACE-I/ARB, 0.90 (0.70–1.16) for current use and 0.89 (0.71–1.10) for former use</td>
</tr>
<tr>
<td>Tully et al., 2016 [18]</td>
<td>3C Study, France</td>
<td>6537 adults; ≥65 years</td>
<td>8.4</td>
<td>Dementia (n=446); NINCDS-ADRDA</td>
<td>ACE-I, 0.87 (0.64–1.18); ARB, 0.87 (0.58–1.31); BB, 1.13 (0.85–1.51); CCB, 0.56 (0.31–1.00); Diuretics, 0.45 (0.22–0.93) for loop, 0.91 (0.40–2.05) for thiazide, and 0.83 (0.55–1.25) for potassium-sparing</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer’s disease; ACE-I, angiotensin converting enzyme-inhibitor; AH, antihypertensive; ARB, angiotensin receptor blocker; APOE, apolipoprotein E; BB, β-blockers; BMI, body mass index; CCB, calcium channel blockers; CI, confidence interval; DBP, diastolic blood pressure; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association; NOS, New-Castle Ottawa Scale (quality assessment of prospective studies); MMSE, Mini-Mental State Examination; PAD peripheral atherosclerotic disease; RR, relative risk; SBP, systolic blood pressure.

*The risk estimate was obtained by combining the reported risk estimates for 0–5, 5–12, and >12 years of use.
†The risk estimate was obtained by combining the reported risk estimates for central and peripheral ACE-I.
‡For both dementia and AD, the inverse association was stronger with higher cumulative dose and longer duration of ARB use.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study name, country</th>
<th>Participants; baseline age</th>
<th>Mean follow-up, years</th>
<th>Outcome (No. of cases); diagnostic criteria</th>
<th>NOS score</th>
<th>Adjustments</th>
<th>Adjusted RR (95% CI) of dementia or AD comparing different AH drug classes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ohrui et al, 2004 [19]</td>
<td>No name, Japan</td>
<td>4124 adults; ≥65 years</td>
<td>8</td>
<td>AD (n=90); NS</td>
<td>1 NS</td>
<td>No difference in AD risk for ACE-I, BB, CCB, or diuretics; however, among ACE-I users, the use of ACE-I s that inhibit brain ACE, compared with other ACE-I s, was associated with a lower risk of AD (0.25; 0.08–0.75)</td>
<td>ACE-I vs other AH medications, 1.05 (0.91–1.21)</td>
</tr>
<tr>
<td>Sink et al, 2009 [20]</td>
<td>Cardiovascular Health Study, United States</td>
<td>1054 adults; ≥65 years</td>
<td>6</td>
<td>Dementia (n=158); DSM-IV, NINCDS-ADRDA</td>
<td>8</td>
<td>Age, sex, race, education, income, smoking, alcohol, diabetes, coronary artery disease, serum creatinine, serum low-density lipoprotein, MMSE, depression</td>
<td>ARB vs ACE-I, dementia: 0.81 (0.73–0.90); AD: 0.81 (0.68–0.96)</td>
</tr>
<tr>
<td>Li et al, 2010 [21]</td>
<td>US Veterans Affairs Health System, United States</td>
<td>799069 (dementia); 819 491 (AD); ≥65 years</td>
<td>4</td>
<td>Dementia (NS), AD (NS); ICD-9 codes (NS)</td>
<td>6</td>
<td>Age, sex, (98% men), diabetes, stroke, cardiovascular disease</td>
<td>ARB vs ACE-I, dementia: 0.55 (0.49–0.62); AD: 0.47 (0.37–0.58)</td>
</tr>
<tr>
<td>Davies et al, 2011 [22]</td>
<td>General Practice Research Database, United Kingdom</td>
<td>9197 cases and 39 166 controls; ≥60 years</td>
<td>NS</td>
<td>Dementia (n=9197), AD (n=5797); NS</td>
<td>6</td>
<td>Age, sex, region, diabetes, stroke, coronary artery disease, blood pressure, number of consultations</td>
<td>ARB vs other AH medications, dementia: 0.80 (0.76–0.84); AD: 0.84 (0.71–1.00)</td>
</tr>
<tr>
<td>Hsu et al, 2013 [23]</td>
<td>National Health Insurance Research Database, Taiwan</td>
<td>32 911 adults; mean age 58 years</td>
<td>5.2</td>
<td>Dementia (n=1031); ICD-9 codes 290.0, 290.20, 290.21, 290.3, 331.0</td>
<td>9</td>
<td>Age, sex, diabetes, coronary artery disease, arrhythmia, hypertension, hyperlipidemia</td>
<td>ARB vs other AH medications, dementia: 1.00 (0.88–1.13)</td>
</tr>
<tr>
<td>Goh et al., 2015 [24]</td>
<td>Clinical Practice Research Datalink, United Kingdom</td>
<td>426 089 adults; ≥18 years</td>
<td>4.3</td>
<td>Dementia (n=6517); Read codes</td>
<td>6</td>
<td>Age, sex, calendar year, SES, number of consultations, BMI, smoking, diabetes, hypertension, heart failure, statin use, alcohol use</td>
<td>ARB vs ACE-I, 0.92 (0.85–1.00)</td>
</tr>
<tr>
<td>Hwang et al, 2017 [25]</td>
<td>National Health Insurance Service Senior Cohort, Korea</td>
<td>18 423 adults; ≥60 years</td>
<td>9.6</td>
<td>Dementia (4005); AD (1987); ICD-10 codes F00-F07, G20-G26, G30-G32</td>
<td>9</td>
<td>Age, sex, BMI, income, urbanization, smoking, alcohol, blood pressure, hypertensive drugs, CAD, diabetes, hypercholesterolemia,</td>
<td>CCB vs non-CCB, dementia: 0.81 (0.75–0.87); AD: 0.80 (0.72–0.88)</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer’s disease; ACE-I, angiotensin converting enzyme-inhibitor; AH, antihypertensive; ARB, angiotensin receptor blocker; BB, ß-blockers; BMI, body mass index; CCB, calcium channel blockers; CI, confidence interval; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases; MMSE, Mini-Mental State Examination; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease Related Disorders Association; NOS, Newcastle Ottawa Scale (quality assessment of prospective studies); NS, not specified; SES, socioeconomic status; RR, relative risk.
**Table S5: Prospective studies of hyperlipidemia medication use vs nonuse and incidence of dementia and Alzheimer’s disease**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study name, country</th>
<th>Participants; baseline age</th>
<th>Mean Follow-up, years</th>
<th>Outcome (No. of cases); diagnostic criteria</th>
<th>NOS score</th>
<th>Adjustments</th>
<th>Adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jick et al, 2000</td>
<td>General Practice Research Database, United Kingdom</td>
<td>284 cases and 1080 controls; ≥50 years</td>
<td>NS</td>
<td>Dementia (n=284); NS</td>
<td>5</td>
<td>Age, sex, calendar time, practice, BMI, smoking, diabetes, years of recorded history in database, hypertension, CAD, coronary artery bypass surgery, TIA</td>
<td>0.29 (0.13–0.63)</td>
</tr>
<tr>
<td>Reitz et al, 2004</td>
<td>Washington Heights, United States</td>
<td>1168 adults; ≥65 years</td>
<td>4.4</td>
<td>AD (n=119); DSM-III-R, NINCDS-ADRDA</td>
<td>8</td>
<td>Age, sex, education, race, BMI, diabetes, hypertension, heart disease, APOE-e4</td>
<td>NA</td>
</tr>
<tr>
<td>Zamrini et al, 2004</td>
<td>US Veterans Affairs Medical Center, United States</td>
<td>309 male cases, 3088 male controls; ≥50 years</td>
<td>NS</td>
<td>AD (n=309); ICD-9-CM codes 290.0, 290.10, 290.13, 290.20, 290.21, 290.3, 331.0</td>
<td>6</td>
<td>Age, sex (all men), diabetes, lipid metabolism disorders, hypertension, CAD, cerebrovascular disease, arterial disease</td>
<td>0.61 (0.42–0.87)</td>
</tr>
<tr>
<td>Li et al, 2004</td>
<td>Adult Changes in Thought Study, United States</td>
<td>2356 adults; ≥65 years</td>
<td>5.6</td>
<td>Dementia (n=312); DSM-IV, NINCDS-ADRSA</td>
<td>9</td>
<td>Age, education, APOE-e4, use of other LLAs or statins; no adjustments for sex, BMI, and comorbidities because of lack of association with dementia/AD</td>
<td>1.19 (0.82–1.75)</td>
</tr>
<tr>
<td>Zandi et al, 2005</td>
<td>Cache County Study, United States</td>
<td>3308 adults; ≥65 years</td>
<td>3</td>
<td>Dementia (n=182), AD (n=102); DSM-III-R, NINCDS-ADRSA</td>
<td>8</td>
<td>Age, sex, education, diabetes, hypertension, APOE-e4, age*ε4 interaction</td>
<td>Dementia: 1.19 (0.53–2.34); AD: 1.19 (0.35–2.96)</td>
</tr>
<tr>
<td>Rea et al, 2005</td>
<td>Cardiovascular Health Study, United States</td>
<td>2798 adults; ≥65 years</td>
<td>5.4</td>
<td>Dementia (n=466), AD (n=237); DSM-IV, NINCDS-ADRSA</td>
<td>8</td>
<td>Age, sex, education, baseline MMSE, CAD, stroke, alcohol use</td>
<td>Dementia: 1.08 (0.77–1.52); AD: 1.21 (0.76–1.91)</td>
</tr>
<tr>
<td>Szwarz et al, 2007</td>
<td>Indianapolis Ibadan Dementia Project, United States</td>
<td>1141 adults; ≥65 years</td>
<td>3</td>
<td>Dementia (n=32); DSM-III-R and ICD-10 codes (NS)</td>
<td>6</td>
<td>Age, sex, education, APOE-ε4</td>
<td>0.32 (0.07–1.42)</td>
</tr>
<tr>
<td>Zigan et al, 2007</td>
<td>No name, United States</td>
<td>123 adults; 41–78 years</td>
<td>5.5</td>
<td>AD (n=38); NS</td>
<td>3</td>
<td>NS</td>
<td>0.40 (0.14–1.17)</td>
</tr>
<tr>
<td>Wolozin et al, 2007</td>
<td>US Veteran Affairs Medical Center, United States</td>
<td>727 128 adults (94.4% men); ≥65 years</td>
<td>2.4</td>
<td>Dementia/AD (n=2647); ICD-9 code 331.0 (may not fulfill all NINCDS-ADRSA criteria)</td>
<td>8</td>
<td>Age, diabetes, obesity, hypertension, cardiovascular diseases, Charlson Comorbidity Index; no adjustment for sex but 94.4% were men</td>
<td>0.46 (0.44–0.48)*</td>
</tr>
<tr>
<td>Fischer et al, 2008</td>
<td>Vienna Transdanube Aging Study, Austria</td>
<td>479 adults; age 75 years</td>
<td>2.5</td>
<td>AD (n=90); DSM-IV, NINCDS-ADRSA</td>
<td>6</td>
<td>None</td>
<td>0.98 (0.87–1.10)</td>
</tr>
<tr>
<td>Cramer et al, 2008</td>
<td>Sacramento Area Latino Study on Aging, United States</td>
<td>1674 adults; ≥60 years</td>
<td>4.5</td>
<td>Dementia (n=130); DSM-IV, NINCDS-ADRSA</td>
<td>9</td>
<td>Age, sex (no confounding and therefore no adjustment), education, smoking, diabetes, stroke, APOE-e4, MMSE</td>
<td>0.56 (0.37–0.87)</td>
</tr>
<tr>
<td>Sparks et al, 2008</td>
<td>Alzheimer’s Disease</td>
<td>2233 adults</td>
<td>4</td>
<td>AD (n=25); DSM-IV</td>
<td>7</td>
<td>Age, sex, education, APOE-ε4</td>
<td>0.33 (0.11–0.98)</td>
</tr>
<tr>
<td>Year</td>
<td>Study Description</td>
<td>Participants</td>
<td>Outcome Measures</td>
<td>Odds Ratio (95% CI)</td>
<td>For any LLAs</td>
<td></td>
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</tr>
<tr>
<td>2008</td>
<td>Anti-inflammatory Prevention Trial, United States</td>
<td>929 adults; mean age 75 years</td>
<td>AD (n=191); NINCDS-ADRD</td>
<td>Age, sex, education</td>
<td>0.91 (0.54–1.52)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arvanitakis et al, 2008</td>
<td>Religions Orders Study, United States</td>
<td>Dementia (n=5172); AD (n=725); NS</td>
<td>Age, sex, propensity score, year of index date, first diagnosis of any disease, first use of any medication</td>
<td>Dementia: 0.81 (0.69–0.96); AD: 0.81 (0.49–1.35)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Smeeth et al, 2009</td>
<td>Health Improvement Network database, United Kingdom</td>
<td>729 529 adults; 40–80 years</td>
<td>Age, sex, education</td>
<td>0.57 (0.37–0.90)</td>
<td>1.05 (0.45–2.44)</td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>Haag et al, 2009</td>
<td>Rotterdam Study, The Netherlands</td>
<td>AD (n=582); DSM-III-R, NINCDS-ADRD</td>
<td>Age, sex, education</td>
<td>NA</td>
<td>0.42 (0.37–0.49)</td>
<td>for any LLAs</td>
</tr>
<tr>
<td></td>
<td>Solomon et al, 2010</td>
<td>FINRISK, Finland</td>
<td>Dementia (n=1561); NS</td>
<td>Age, sex, education, survey region and year, BMI, total cholesterol, systolic blood pressure</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Li et al, 2010</td>
<td>Adult Changes in Thought Study, United States</td>
<td>AD (n=263); DSM-IV, NINCDS-ADRD</td>
<td>Age, sex, cohort, race, education, BMI, smoking, CASI score, comorbid vascular diseases, use of other LLAs, APOE-ε4</td>
<td>0.62 (0.40–0.97)</td>
<td>1.28 (0.82–1.99)†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hippisley-Cox et al, 2010</td>
<td>Egton Medical Information System, United Kingdom</td>
<td>Dementia (n=8784); NS</td>
<td>Age, sex</td>
<td>0.92 (0.83–1.02) in men and 0.88 (0.81–0.96) in women*</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Beydoun et al, 2011</td>
<td>Baltimore Longitudinal Study of Aging, United States</td>
<td>Dementia (n=259); DSM-III-R, NINCDS-ADRD</td>
<td>Age, sex, race/ethnicity, education, BMI, smoking, diabetes, hypertension, SBP, CAD, dyslipidemia</td>
<td>0.41 (0.18–0.92)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ancelin et al, 2012</td>
<td>No name, France</td>
<td>Dementia (n=483), AD (n=332); DSM-IV, NINCDS-ADRD</td>
<td>Age, sex, center, education</td>
<td>Dementia: 0.81 (0.53–1.23) in men; 1.20 (0.88–1.64) in women; AD: 1.09 (0.67–1.76) in men, 1.17 (0.80–1.70) in women women</td>
<td>Dementia: 0.85 (0.53–1.36) in men, 1.08 (0.77–1.52) in women; AD: 1.04 (0.60–1.80) in men, 1.12 (0.75–1.66) in women</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Bettermann et al, 2012</td>
<td>Ginkgo Evaluation of Memory Study, United States</td>
<td>Dementia (n=324), AD (n=212); DSM-IV, NINCDS-ADRD</td>
<td>Age, sex, race, field center, education, Ginkgo biloba randomization group, APOE-ε4, stroke, CAD</td>
<td>Dementia: 0.77 (0.60–0.98); AD: 0.83 (0.61–1.12)</td>
<td>Dementia: 0.65 (0.37–1.14); AD: 0.48 (0.21–1.08)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Corrao et al, 2013</td>
<td>National Health Service, Italy</td>
<td>Dementia (n=1380); ICD-9-CM codes (&gt;10)</td>
<td>Age, sex, date of index prescription, concomitant users of other drugs.</td>
<td>0.78 (0.70–0.87)‡</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

* Indicates statistical significance. † Indicates statistical non-significance.
<table>
<thead>
<tr>
<th>Study</th>
<th>Database</th>
<th>Sample Size</th>
<th>Age, Sex, Comorbidities</th>
<th>Charlson Comorbidity Index</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chou et al, 2014 [48]</td>
<td>National Health Insurance Research Database, Taiwan</td>
<td>33 398 adults; ≥60 years</td>
<td>AD (NS); ICD-9-CM codes 290.x, 294.1, 331.0, A210</td>
<td>Age, sex, SES, comorbidities, propensity scores</td>
<td>0.78 (0.72–0.85)</td>
</tr>
<tr>
<td>Wu et al, 2015 [49]</td>
<td>National Health Insurance Research Database, Taiwan</td>
<td>57 669 adults; ≥65 years</td>
<td>Dementia (5516); ICD-9-CM codes 290.0, 290.10–290.13</td>
<td>Age, sex, hypertension, diabetes, chronic kidney disease, stroke, TIA, cardiovascular disease, heart failure, atrial fibrillation, medication use</td>
<td>0.62 (0.41–0.92) §</td>
</tr>
<tr>
<td>Goh et al, 2015 [24]</td>
<td>Clinical Practice Research Datalink, United Kingdom</td>
<td>426 089 adults; ≥18 years</td>
<td>Dementia (n=6517); Read codes</td>
<td>Age, sex, calendar year, number of consultations, SES, BMI, smoking, diabetes, hypertension, heart failure, statin use, alcohol use</td>
<td>1.03 (0.98–1.09)</td>
</tr>
<tr>
<td>Chitnis et al, 2015 [50]</td>
<td>Medicare Advantage Prescription Drug, United States</td>
<td>8062 adults; mean age 75 years</td>
<td>Dementia (n=1135); ICD-9-CM codes (&gt;10 codes)</td>
<td>Age, sex, 44 time-independent factors such as socio-demographic and treatment factors, and comorbidities</td>
<td>0.96 (0.81–1.15)</td>
</tr>
<tr>
<td>Zissimopoulos et al, 2016 [51]</td>
<td>Medicare fee for service, United States</td>
<td>399 979 adults; ≥65 years</td>
<td>AD (NS); CD-9-CM code 331.0</td>
<td>Matched by age, sex, race/ethnicity, region, years since hyperlipidemia diagnosis, education, and health status</td>
<td>0.88 (0.83-0.93) men; 0.85 (0.82-0.89) women</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer’s disease; APOE, apolipoprotein E; BMI, body mass index; CAD, coronary artery disease; CASI, Cognitive Abilities Screening Instrument; CI, confidence interval; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases; LLA, lipid-lowering agents; MMSE, Mini-Mental State Examination; NA, not available; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke—Alzheimer’s Disease and Related Disorders Association; NOS, New-Castle Ottawa Scale (quality assessment of prospective studies); NS, not stated; RR, relative risk; SBP, systolic blood pressure; SES, socioeconomic status; TIA, transient ischemic attack.

*Results for simvastatin were used in the main meta-analysis because simvastatin was the most frequently prescribed statin. Results for other statins were used in subgroup analyses by type of statins.

†The risk estimate was obtained by combining the reported risk estimates for those <80 years and ≥80 years of age.

‡The risk estimate was obtained by combining the reported risk estimates for prescriptions of 7–24 months, 25–48 months, and >48 months.

§The risk estimate was obtained by combining the reported risk estimates for the three groups of accumulated dose.

ǁThe risk estimate was obtained by combining the reported risk estimates for current and former users.
Table S6: Combined relative risks of dementia and Alzheimer’s disease for statin use vs nonuse in prospective studies, stratified by duration of follow-up, number of cases, degree of adjustment for potential confounders, and statin type

<table>
<thead>
<tr>
<th>Study quality (NOS)</th>
<th>Dementia</th>
<th></th>
<th>Alzheimer’s disease</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of studies*</td>
<td>Combined RR (95% CI)</td>
<td>$I^2$†</td>
<td>No. of studies*</td>
<td>Combined RR (95% CI)</td>
</tr>
<tr>
<td>0–7</td>
<td>11</td>
<td>0.87 (0.78–0.97)</td>
<td>79%</td>
<td>6</td>
</tr>
<tr>
<td>8–9</td>
<td>8</td>
<td>0.73 (0.52–1.01)</td>
<td>90%</td>
<td>7</td>
</tr>
</tbody>
</table>

Duration of follow-up

<table>
<thead>
<tr>
<th>No. of cases</th>
<th>Dementia</th>
<th></th>
<th>Alzheimer’s disease</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;200</td>
<td>4</td>
<td>0.72 (0.50–1.04)</td>
<td>33%</td>
<td>6</td>
</tr>
<tr>
<td>≥200</td>
<td>15</td>
<td>0.78 (0.63–0.98)</td>
<td>98%</td>
<td>6</td>
</tr>
</tbody>
</table>

Statin type§

<table>
<thead>
<tr>
<th>Statin type</th>
<th>No. of studies</th>
<th>Combined RR (95% CI)</th>
<th>$I^2$†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>5</td>
<td>0.84 (0.80–0.89)</td>
<td>39%</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>3</td>
<td>0.90 (0.76–1.06)</td>
<td>0%</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>2</td>
<td>0.95 (0.88–1.03)</td>
<td>0%</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>4</td>
<td>0.90 (0.78–1.04)</td>
<td>52%</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>5</td>
<td>0.72 (0.57–0.91)</td>
<td>68%</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>5</td>
<td>0.78 (0.58–1.04)</td>
<td>99%</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer’s disease; CI, confidence interval; NOS, Newcastle Ottawa Scale; RR, relative risk.

*The number of studies may not sum up to the total number of studies because of lack of information on duration of follow-up or number of cases. Hippisley-Cox et al 2010 [43], Ancelin et al [45], and Zissimopoulos [51] reported results stratified by sex; for these two studies, results for men and women were counted as two separate studies.

†Describes the proportion of total variation in study estimates that is due to heterogeneity. $I^2$ values of <30%, 30%–75%, and >75% were considered no or marginal, moderate, and notable heterogeneity, respectively.

‡Defined as adjustment for age, sex (if applicable), and at least five additional major risk factors (e.g., education, smoking, physical inactivity, obesity, diabetes, blood pressure or hypertension, cholesterol concentration or hyperlipidemia, cardiovascular diseases, depression, APOE-ε4) or Charlson Comorbidity Index.

§The outcome for these analyses was either all-cause dementia or Alzheimer’s disease.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study name, country</th>
<th>Participants; baseline age</th>
<th>Mean follow-up, years</th>
<th>Outcome (No. of cases); diagnostic criteria</th>
<th>Antidiabetic therapy</th>
<th>NOS score</th>
<th>Adjustments</th>
<th>Adjusted RR (95% CI) of dementia or AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ott et al, 1999</td>
<td>Rotterdam Study, The Netherlands</td>
<td>6370 adults; ≥55 years</td>
<td>2.1</td>
<td>Dementia (n=126); DSM-III-R</td>
<td>Any oral antidiabetic medication, insulin therapy, no drugs</td>
<td>7</td>
<td>Age, sex</td>
<td>Compared with nondiabetics, the RRs were 2.4 (1.4–4.1) for oral antidiabetic therapy and 4.3 (1.7–10.5) for insulin therapy</td>
</tr>
<tr>
<td>Xu et al, 2004</td>
<td>Kungsholmen Project, Sweden</td>
<td>1301 adults; ≥75 years</td>
<td>4.3</td>
<td>Dementia (n=350); AD (n=260); DSM-III-R, NINCDS-ADRA</td>
<td>Any oral antidiabetic medication</td>
<td>8</td>
<td>Age, sex, education, BMI, heart disease, stroke, blood pressure, antihypertensive drugs</td>
<td>Compared with nondiabetics, the RRs for oral antidiabetic therapy were 1.7 (1.0–2.8) for dementia and 1.4 (0.7–2.7) for AD</td>
</tr>
<tr>
<td>Fischer et al, 2008</td>
<td>Vienna Transdanube Aging Study, Austria</td>
<td>479 adults; age 75 years</td>
<td>2.5</td>
<td>AD (n=90); DSM-IV, NINCDS-ADRA</td>
<td>Insulin therapy</td>
<td>6</td>
<td>None</td>
<td>Compared with nondiabetics, the RRs were 1.78 (0.55–5.74) for insulin therapy</td>
</tr>
<tr>
<td>Parikh et al, 2011</td>
<td>Veterans Administration, United States</td>
<td>377 838 diabetes patients; ≥65 years</td>
<td>2</td>
<td>Dementia (14 580); ICD-9-CM codes 250.xx, 357.2, 362.0, 366.41</td>
<td>Any oral antidiabetic medication, insulin</td>
<td>7</td>
<td>NS</td>
<td>Compared with nonuse, the RRs were 0.94 (0.91–0.97) for oral antidiabetic therapy and 1.02 (0.98–1.07) for insulin therapy</td>
</tr>
<tr>
<td>Huang et al, 2014</td>
<td>National Health Insurance Research Database, Taiwan (only diabetic patients)</td>
<td>71 433 diabetes patients; mean age 59 years</td>
<td>5.5</td>
<td>AD (n=346); ICD-9-CM code 331.0</td>
<td>Metformin, sulfonylureas, thiazolidinediones, α-glucosidase blockers, nonsulfonylurea insulin secretagogue, insulin</td>
<td>9</td>
<td>None</td>
<td>Compared with nonuse, the RR was 0.92 (0.13–6.60) for thiazolidinediones and 1.53 (0.98–2.39) for insulin therapy</td>
</tr>
<tr>
<td>Heneka et al, 2015</td>
<td>Allgemeine Ortskrankenkasse, Germany</td>
<td>145 928 adults; ≥60 years</td>
<td>4.3</td>
<td>Dementia (n=13 177); ICD-10 codes G30, G31.0, G31.82, G23.1, F00, F01, F02, F03 or F05.1</td>
<td>Metformin, thiazolidinediones</td>
<td>9</td>
<td>None</td>
<td>Compared with nonuse, the RR was 0.97 (0.91–1.03) for metformin, 0.84 (0.60–1.19) for rosiglitazone and 1.61 (1.46–1.77) for insulin therapy</td>
</tr>
<tr>
<td>Orkaby et al, 2017</td>
<td>Veterans Administration, United States</td>
<td>28 640 diabetes patients; ≥65 years</td>
<td>5.0</td>
<td>Dementia (n=4906); ICD-9 codes 290.x, 291.2, 294.1,294.11, 331.x, 333.0, 333.4, 797, 332.0, 294.8, 046.1, 046.3</td>
<td>Metformin vs. sulfonylureas</td>
<td>9</td>
<td>Propensity score model with 23 variables: race, sex, BMI, HbA1c, renal function, and comorbidities; stratified by age</td>
<td>Compared with sulfonylureas, the RR for metformin use was 0.89 (0.79–0.99) for those &lt;75 years of age and 0.96 (0.87–1.05) for those ≥75 years of age</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer’s disease; CI, confidence interval; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases; NOS, New-Castle Ottawa Scale (quality assessment of prospective studies); RR, relative risk.
**Figure S1:** Newcastle-Ottawa Scale for prospective studies: Details of how the criteria were applied

### Selection

1) *Representativeness of the exposed cohort*
   - Star assigned if exposed cohort was truly or somewhat representative of the average medication users in the community (i.e., the sample was random or covered all individuals residing in one or a few geographical areas).

2) *Selection of the non-exposed cohort*
   - Star assigned where non-exposed participants were drawn from the same population as the exposed participants.

3) *Ascertainment of exposure*
   - Star assigned if medication use had been assessed using a structured interview or a prescription database.

4) *Demonstration that outcome of interest was not present at the start of study*
   - Star assigned to studies that excluded participants with dementia and/or Alzheimer’s disease at baseline.

### Comparability

1) *Comparability of cohorts on the basis of the design or analysis*
   - One star assigned to studies that adjusted for age and sex (if applicable) in the analysis.
   - Second star assigned to studies that further adjusted for at least five other major risk factors (e.g., education, smoking, physical inactivity, obesity, diabetes, blood pressure or hypertension, cholesterol concentration or hyperlipidemia, cardiovascular diseases, depression, APOE-ε4) or Charlson Comorbidity Index.

### Outcome

1) *Assessment of outcome*
   - Star assigned where an assessment for possible or probable dementia or Alzheimer’s disease was made in accordance with internationally accepted diagnostic criteria (NINCDS-ADRDA, DSM-III-R, or DSM-IV) or based on ICD codes for dementia or Alzheimer’s disease.

2) *Was follow-up long enough for outcomes to occur?*
   - Star assigned where follow-up was at least 5 years.

3) *Adequacy of follow up of cohorts*
   - Star assigned where the loss to follow-up had been estimated and reported in the article, and where loss was no more than 20% of those included in the final analysis.
Abbreviations: AD, Alzheimer’s disease; VRF, vascular risk factor. *The number of studies on different treatments and interventions does not sum up to the total number because two articles provided results on two treatments. The PubMed search was until 1 January 2018.
References


