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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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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 nonsignificant 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 (≥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* ≥5 years), and number of cases (<200 *vs* ≥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 ≥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

[21]), 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.

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SUPPLEMENTARY MATERIAL

Supplementary material is available for this paper.

REFERENCES

[1] Prince M, Wimo A, Guerchet M, Ali GC, Wu YT, Prina M (2015) World Alzheimer Report 2015: The Global Impact of Dementia. Published by Alzheimer's Disease International, London.

[2] Gorelick PB (1994) Stroke prevention. An opportunity for efficient utilization of health care resources during the coming decade. *Stroke* **25**, 220-224.

[3] Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E (2011) Alzheimer's disease. *Lancet* **377**, 1019-1031.

[4] Cummings JL, Morstorf T, Zhong K (2014) Alzheimer's disease drug-development pipeline: few candidates, frequent failures. *Alzheimers Res Ther* **6**, 37.

[5] de Bruijn RF, Ikram MA (2014) Cardiovascular risk factors and future risk of Alzheimer's disease. *BMC Med* **12**, 130.

[6] Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C (2014) Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *Lancet Neurol* **13**, 788-794.

[7] Meng XF, Yu JT, Wang HF, Tan MS, Wang C, Tan CC, Tan L (2014) Midlife vascular risk factors and the risk of Alzheimer's disease: a systematic review and meta-analysis. *J Alzheimers Dis* **42**, 1295-1310.

[8] Chang-Quan H, Hui W, Chao-Min W, Zheng-Rong W, Jun-Wen G, Yong-Hong L, Yan-You L, Qing-Xiu L (2011) The association of antihypertensive medication use with risk of cognitive decline and dementia: a meta-analysis of longitudinal studies. *Int J Clin Pract* **65**, 1295-1305.

[9] Levi Marpillat N, Macquin-Mavier I, Tropeano AI, Bachoud-Levi AC, Maison P (2013) Antihypertensive classes, cognitive decline and incidence of dementia: a network meta-analysis. *J Hypertens* **31**, 1073-1082.

[10] Peters R, Booth A, Peters J (2014) A systematic review of calcium channel blocker use and cognitive decline/dementia in the elderly. *J Hypertens* **32**, 1945-1957.

[11] Song Y, Nie H, Xu Y, Zhang L, Wu Y (2013) Association of statin use with risk of dementia: a meta-analysis of prospective cohort studies. *Geriatr Gerontol Int* **13**, 817-824.

[12] McGuinness B, Craig D, Bullock R, Passmore P (2016) Statins for the prevention of dementia. *Cochrane Database Syst Rev*, CD003160.

[13] Wong WB, Lin VW, Boudreau D, Devine EB (2013) Statins in the prevention of dementia and Alzheimer's disease: a meta-analysis of observational studies and an assessment of confounding. *Pharmacoepidemiol Drug Saf* **22**, 345-358.

[14] Power MC, Weuve J, Sharrett AR, Blacker D, Gottesman RF (2015) Statins, cognition, and dementia-systematic review and methodological commentary. *Nat Rev Neurol* **11**, 220-229.

[15] Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA, Group P-P (2015) Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* **349**, g7647.

[16] The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed on 30 January 2018).

[17] DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. *Control Clin Trials* **7**, 177-188.

[18] Higgins JP, Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. *Stat Med* **21**, 1539-1558.

[19] Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. *BMJ* **315**, 629-634.
[20] (1991) Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. *JAMA* **265**, 3255-3264.
[21] Forette F, Seux ML, Staessen JA, Thijs L, Babarskiene MR, Babeanu S, Bossini A, Fagard R, Gil-Extremera B, Laks T, Kobalava Z, Sarti C, Tuomilehto J, Vanhanen H, Webster J, Yodfat Y, Birkenhager WH, Systolic Hypertension in Europe I (2002) The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study. *Arch Intern Med* **162**, 2046-2052.
[22] Lithell H, Hansson L, Skoog I, Elmfeldt D, Hofman A, Olofsson B, Trenkwalder P, Zanchetti A, Group SS (2003) The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. *J Hypertens* **21**, 875-886.
[23] Tzourio C, Anderson C, Chapman N, Woodward M, Neal B, MacMahon S, Chalmers J, Group PC (2003) Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. *Arch Intern Med* **163**, 1069-1075.
[24] Peters R, Beckett N, Forette F, Tuomilehto J, Clarke R, Ritchie C, Waldman A, Walton I, Poulter R, Ma S, Comsa M, Burch L, Fletcher A, Bulpitt C, investigators H (2008) Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. *Lancet Neurol* **7**, 683-689.
[25] Heart Protection Study Collaborative G (2002) MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* **360**, 7-22.
[26] Group AC, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F (2008) Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* **358**, 2560-2572.
[27] Ihle-Hansen H, Thommessen B, Fagerland MW, Oksengard AR, Wyller TB, Engedal K, Fure B (2014) Multifactorial vascular risk factor intervention to prevent cognitive impairment after stroke and TIA: a 12-month randomized controlled trial. *Int J Stroke* **9**, 932-938.
[28] Morris MC, Scherr PA, Hebert LE, Glynn RJ, Bennett DA, Evans DA (2001) Association of incident Alzheimer disease and blood pressure measured from 13 years before to 2 years after diagnosis in a large community study. *Arch Neurol* **58**, 1640-1646.
[29] in't Veld BA, Ruitenberg A, Hofman A, Stricker BH, Breteler MM (2001) Antihypertensive drugs and incidence of dementia: the Rotterdam Study. *Neurobiol Aging* **22**, 407-412.
[30] Lindsay J, Laurin D, Verreault R, Hebert R, Helliwell B, Hill GB, McDowell I (2002) Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging. *Am J Epidemiol* **156**, 445-453.
[31] Yasar S, Corrada M, Brookmeyer R, Kawas C (2005) Calcium channel blockers and risk of AD: the Baltimore Longitudinal Study of Aging. *Neurobiol Aging* **26**, 157-163.
[32] Peila R, White LR, Masaki K, Petrovitch H, Launer LJ (2006) Reducing the risk of dementia: efficacy of long-term treatment of hypertension. *Stroke* **37**, 1165-1170.

[33] Qiu C, Winblad B, Marengoni A, Klarin I, Fastbom J, Fratiglioni L (2006) Heart failure and risk of dementia and Alzheimer disease: a population-based cohort study. *Arch Intern Med* **166**, 1003-1008.
[34] Johnson ML, Parikh N, Kunik ME, Schulz PE, Patel JG, Chen H, Aparasu RR, Morgan RO (2012) Antihypertensive drug use and the risk of dementia in patients with diabetes mellitus. *Alzheimers Dement* **8**, 437-444.
[35] Yasar S, Xia J, Yao W, Furberg CD, Xue QL, Mercado CI, Fitzpatrick AL, Fried LP, Kawas CH, Sink KM, Williamson JD, DeKosky ST, Carlson MC, Ginkgo Evaluation of Memory Study I (2013) Antihypertensive drugs decrease risk of Alzheimer disease: Ginkgo Evaluation of Memory Study. *Neurology* **81**, 896-903.
[36] Chiu WC, Ho WC, Lin MH, Lee HH, Yeh YC, Wang JD, Chen PC, Health Data Analysis in Taiwan Research G (2014) Angiotension receptor blockers reduce the risk of dementia. *J Hypertens* **32**, 938-947.
[37] Chuang YF, Breitner JC, Chiu YL, Khachaturian A, Hayden K, Corcoran C, Tschanz J, Norton M, Munger R, Welsh-Bohmer K, Zandi PP, Cache County I (2014) Use of diuretics is associated with reduced risk of Alzheimer's disease: the Cache County Study. *Neurobiol Aging* **35**, 2429-2435.
[38] Qiu WQ, Mwamburi M, Besser LM, Zhu H, Li H, Wallack M, Phillips L, Qiao L, Budson AE, Stern R, Kowall N (2013) Angiotensin converting enzyme inhibitors and the reduced risk of Alzheimer's disease in the absence of apolipoprotein E4 allele. *J Alzheimers Dis* **37**, 421-428.
[39] Chitnis AS, Aparasu RR, Chen H, Kunik ME, Schulz PE, Johnson ML (2015) Use of Angiotensin-Converting Enzyme Inhibitors, Angiotensin Receptor Blockers, and Risk of Dementia in Heart Failure. *Am J Alzheimers Dis Other Demen*.
[40] Tully PJ, Dartigues JF, Debette S, Helmer C, Artero S, Tzourio C (2016) Dementia risk with antihypertensive use and blood pressure variability: A cohort study. *Neurology* **87**, 601-608.
[41] Ohrui T, Matsui T, Yamaya M, Arai H, Ebihara S, Maruyama M, Sasaki H (2004) Angiotensin-converting enzyme inhibitors and incidence of Alzheimer's disease in Japan. *J Am Geriatr Soc* **52**, 649-650.
[42] Sink KM, Leng X, Williamson J, Kritchevsky SB, Yaffe K, Kuller L, Yasar S, Atkinson H, Robbins M, Psaty B, Goff DC, Jr. (2009) Angiotensin-converting enzyme inhibitors and cognitive decline in older adults with hypertension: results from the Cardiovascular Health Study. *Arch Intern Med* **169**, 1195-1202.
[43] Li NC, Lee A, Whitmer RA, Kivipelto M, Lawler E, Kazis LE, Wolozin B (2010) Use of angiotensin receptor blockers and risk of dementia in a predominantly male population: prospective cohort analysis. *BMJ* **340**, b5465.
[44] Davies NM, Kehoe PG, Ben-Shlomo Y, Martin RM (2011) Associations of anti-hypertensive treatments with Alzheimer's disease, vascular dementia, and other dementias. *J Alzheimers Dis* **26**, 699-708.
[45] Hsu CY, Huang CC, Chan WL, Huang PH, Chiang CH, Chen TJ, Chung CM, Lin SJ, Chen JW, Leu HB (2013) Angiotensin-receptor blockers and risk of Alzheimer's disease in hypertension population--a nationwide cohort study. *Circ J* **77**, 405-410.
[46] Goh KL, Bhaskaran K, Minassian C, Evans SJ, Smeeth L, Douglas IJ (2015) Angiotensin receptor blockers and risk of dementia: cohort study in UK Clinical Practice Research Datalink. *Br J Clin Pharmacol* **79**, 337-350.
[47] Hwang D, Kim S, Choi H, Oh IH, Kim BS, Choi HR, Kim SY, Won CW (2016) Calcium-Channel Blockers and Dementia Risk in Older Adults- National Health Insurance Service - Senior Cohort (2002-2013). *Circ J* **80**, 2336-2342.

[48] Jick H, Zornberg GL, Jick SS, Seshadri S, Drachman DA (2000) Statins and the risk of dementia. *Lancet* **356**, 1627-1631.
[49] Zamrini E, McGwin G, Roseman JM (2004) Association between statin use and Alzheimer's disease. *Neuroepidemiology* **23**, 94-98.
[50] Li G, Higdon R, Kukull WA, Peskind E, Van Valen Moore K, Tsuang D, van Belle G, McCormick W, Bowen JD, Teri L, Schellenberg GD, Larson EB (2004) Statin therapy and risk of dementia in the elderly: a community-based prospective cohort study. *Neurology* **63**, 1624-1628.
[51] Zandi PP, Sparks DL, Khachaturian AS, Tschanz J, Norton M, Steinberg M, Welsh-Bohmer KA, Breitner JC, Cache County Study i (2005) Do statins reduce risk of incident dementia and Alzheimer disease? The Cache County Study. *Arch Gen Psychiatry* **62**, 217-224.
[52] Rea TD, Breitner JC, Psaty BM, Fitzpatrick AL, Lopez OL, Newman AB, Hazzard WR, Zandi PP, Burke GL, Lyketsos CG, Bernick C, Kuller LH (2005) Statin use and the risk of incident dementia: the Cardiovascular Health Study. *Arch Neurol* **62**, 1047-1051.
[53] Szwast SJ, Hendrie HC, Lane KA, Gao S, Taylor SE, Unverzagt F, Murrell J, Deeg M, Ogunniyi A, Farlow MR, Hall KS (2007) Association of statin use with cognitive decline in elderly African Americans. *Neurology* **69**, 1873-1880.
[54] Zigman WB, Schupf N, Jenkins EC, Urv TK, Tycko B, Silverman W (2007) Cholesterol level, statin use and Alzheimer's disease in adults with Down syndrome. *Neurosci Lett* **416**, 279-284.
[55] Wolozin B, Wang SW, Li NC, Lee A, Lee TA, Kazis LE (2007) Simvastatin is associated with a reduced incidence of dementia and Parkinson's disease. *BMC Med* **5**, 20.
[56] Fischer P, Zehetmayer S, Jungwirth S, Weissgram S, Krampla W, Hinterberger M, Torma S, Rainer M, Huber K, Hoenigschnabl S, Gelpi E, Bauer K, Leitha T, Bauer P, Tragl KH (2008) Risk factors for Alzheimer dementia in a community-based birth cohort at the age of 75 years. *Dement Geriatr Cogn Disord* **25**, 501-507.
[57] Cramer C, Haan MN, Galea S, Langa KM, Kalbfleisch JD (2008) Use of statins and incidence of dementia and cognitive impairment without dementia in a cohort study. *Neurology* **71**, 344-350.
[58] Sparks DL, Kryscio RJ, Sabbagh MN, Connor DJ, Sparks LM, Liebsack C (2008) Reduced risk of incident AD with elective statin use in a clinical trial cohort. *Curr Alzheimer Res* **5**, 416-421.
[59] Arvanitakis Z, Schneider JA, Wilson RS, Bienias JL, Kelly JF, Evans DA, Bennett DA (2008) Statins, incident Alzheimer disease, change in cognitive function, and neuropathology. *Neurology* **70**, 1795-1802.
[60] Smeeth L, Douglas I, Hall AJ, Hubbard R, Evans S (2009) Effect of statins on a wide range of health outcomes: a cohort study validated by comparison with randomized trials. *Br J Clin Pharmacol* **67**, 99-109.
[61] Haag MD, Hofman A, Koudstaal PJ, Stricker BH, Breteler MM (2009) Statins are associated with a reduced risk of Alzheimer disease regardless of lipophilicity. The Rotterdam Study. *J Neurol Neurosurg Psychiatry* **80**, 13-17.
[62] Li G, Shofer JB, Rhew IC, Kukull WA, Peskind ER, McCormick W, Bowen JD, Schellenberg GD, Crane PK, Breitner JC, Larson EB (2010) Age-varying association between statin use and incident Alzheimer's disease. *J Am Geriatr Soc* **58**, 1311-1317.
[63] Hippisley-Cox J, Coupland C (2010) Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. *BMJ* **340**, c2197.

[64] Beydoun MA, Beason-Held LL, Kitner-Triolo MH, Beydoun HA, Ferrucci L, Resnick SM, Zonderman AB (2011) Statins and serum cholesterol's associations with incident dementia and mild cognitive impairment. *J Epidemiol Community Health* **65**, 949-957.
[65] Ancelin ML, Carriere I, Barberger-Gateau P, Auriacombe S, Rouaud O, Fourlanos S, Berr C, Dupuy AM, Ritchie K (2012) Lipid lowering agents, cognitive decline, and dementia: the three-city study. *J Alzheimers Dis* **30**, 629-637.
[66] Bettermann K, Arnold AM, Williamson J, Rapp S, Sink K, Toole JF, Carlson MC, Yasar S, Dekosky S, Burke GL (2012) Statins, risk of dementia, and cognitive function: secondary analysis of the ginkgo evaluation of memory study. *J Stroke Cerebrovasc Dis* **21**, 436-444.
[67] Corrao G, Ibrahim B, Nicotra F, Zambon A, Merlino L, Pasini TS, Catapano AL, Mancia G (2013) Long-term use of statins reduces the risk of hospitalization for dementia. *Atherosclerosis* **230**, 171-176.
[68] Chou CY, Chou YC, Chou YJ, Yang YF, Huang N (2014) Statin use and incident dementia: a nationwide cohort study of Taiwan. *Int J Cardiol* **173**, 305-310.
[69] Wu CK, Yang YH, Lin TT, Tsai CT, Hwang JJ, Lin JL, Chen PC, Chiang FT, Lin LY (2015) Statin use reduces the risk of dementia in elderly patients: a nationwide data survey and propensity analysis. *J Intern Med* **277**, 343-352.
[70] Chitnis AS, Aparasu RR, Chen H, Kunik ME, Schulz PE, Johnson ML (2015) Use of Statins and Risk of Dementia in Heart Failure: A Retrospective Cohort Study. *Drugs Aging* **32**, 743-754.
[71] Zissimopoulos JM, Barthold D, Brinton RD, Joyce G (2017) Sex and Race Differences in the Association Between Statin Use and the Incidence of Alzheimer Disease. *JAMA Neurol* **74**, 225-232.
[72] Reitz C, Tang MX, Luchsinger J, Mayeux R (2004) Relation of plasma lipids to Alzheimer disease and vascular dementia. *Arch Neurol* **61**, 705-714.
[73] Solomon A, Sippola R, Soininen H, Wolozin B, Tuomilehto J, Laatikainen T, Kivipelto M (2010) Lipid-lowering treatment is related to decreased risk of dementia: a population-based study (FINRISK). *Neurodegener Dis* **7**, 180-182.
[74] Zandi PP, Anthony JC, Hayden KM, Mehta K, Mayer L, Breitner JC, Cache County Study I (2002) Reduced incidence of AD with NSAID but not H2 receptor antagonists: the Cache County Study. *Neurology* **59**, 880-886.
[75] Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, Breteler MM (1999) Diabetes mellitus and the risk of dementia: The Rotterdam Study. *Neurology* **53**, 1937-1942.
[76] Xu WL, Qiu CX, Wahlin A, Winblad B, Fratiglioni L (2004) Diabetes mellitus and risk of dementia in the Kungsholmen project: a 6-year follow-up study. *Neurology* **63**, 1181-1186.
[77] Huang CC, Chung CM, Leu HB, Lin LY, Chiu CC, Hsu CY, Chiang CH, Huang PH, Chen TJ, Lin SJ, Chen JW, Chan WL (2014) Diabetes mellitus and the risk of Alzheimer's disease: a nationwide population-based study. *PLoS One* **9**, e87095.
[78] Heneka MT, Fink A, Doblhammer G (2015) Effect of pioglitazone medication on the incidence of dementia. *Ann Neurol* **78**, 284-294.
[79] Parikh NM, Morgan RO, Kunik ME, Chen H, Aparasu RR, Yadav RK, Schulz PE, Johnson ML (2011) Risk factors for dementia in patients over 65 with diabetes. *Int J Geriatr Psychiatry* **26**, 749-757.
[80] Orkaby AR, Cho K, Cormack J, Gagnon DR, Driver JA (2017) Metformin vs sulfonylurea use and risk of dementia in US veterans aged >/=65 years with diabetes. *Neurology* **89**, 1877-1885.

[81] Matz K, Teuschl Y, Firlinger B, Dachenhausen A, Keindl M, Seyfang L, Tuomilehto J, Brainin M (2015) Multidomain Lifestyle Interventions for the Prevention of Cognitive Decline After Ischemic Stroke: Randomized Trial. *Stroke* **46**, 2874-2880.
[82] Pase MP, Satizabal CL, Seshadri S (2017) Role of Improved Vascular Health in the Declining Incidence of Dementia. *Stroke* **48**, 2013-2020.
[83] Debette S, Markus HS (2010) The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. *BMJ* **341**, c3666.
[84] Dufouil C, Chalmers J, Coskun O, Besancon V, Bousser MG, Guillon P, MacMahon S, Mazoyer B, Neal B, Woodward M, Tzourio-Mazoyer N, Tzourio C, Investigators PMS (2005) Effects of blood pressure lowering on cerebral white matter hyperintensities in patients with stroke: the PROGRESS (Perindopril Protection Against Recurrent Stroke Study) Magnetic Resonance Imaging Substudy. *Circulation* **112**, 1644-1650.
[85] Tsukuda K, Mogi M, Li JM, Iwanami J, Min LJ, Sakata A, Fujita T, Iwai M, Horiuchi M (2008) Diabetes-associated cognitive impairment is improved by a calcium channel blocker, nifedipine. *Hypertension* **51**, 528-533.
[86] Paris D, Bachmeier C, Patel N, Quadros A, Volmar CH, Laporte V, Ganey J, Beaulieu-Abdelahad D, Ait-Ghezala G, Crawford F, Mullan MJ (2011) Selective antihypertensive dihydropyridines lower Abeta accumulation by targeting both the production and the clearance of Abeta across the blood-brain barrier. *Mol Med* **17**, 149-162.
[87] Lovell MA, Abner E, Kryscio R, Xu L, Fister SX, Lynn BC (2015) Calcium Channel Blockers, Progression to Dementia, and Effects on Amyloid Beta Peptide Production. *Oxid Med Cell Longev* **2015**, 787805.
[88] Proitsi P, Lupton MK, Velayudhan L, Newhouse S, Fogh I, Tsolaki M, Daniilidou M, Pritchard M, Kloszewska I, Soininen H, Mecocci P, Vellas B, Alzheimer's Disease Neuroimaging I, Williams J, Consortium G, Stewart R, Sham P, Lovestone S, Powell JF (2014) Genetic predisposition to increased blood cholesterol and triglyceride lipid levels and risk of Alzheimer disease: a Mendelian randomization analysis. *PLoS Med* **11**, e1001713.
[89] Larsson SC, Traylor M, Malik R, Dichgans M, Burgess S, Markus HS (2017) Modifiable pathways in Alzheimer's disease: Mendelian randomisation analysis. *BMJ* **359**, j5375.
[90] van der Most PJ, Dolga AM, Nijholt IM, Luiten PG, Eisel UL (2009) Statins: mechanisms of neuroprotection. *Prog Neurobiol* **88**, 64-75.
[91] Group SR, Wright JT, Jr., Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, Reboussin DM, Rahman M, Oparil S, Lewis CE, Kimmel PL, Johnson KC, Goff DC, Jr., Fine LJ, Cutler JA, Cushman WC, Cheung AK, Ambrosius WT (2015) A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med* **373**, 2103-2116.

Table 1

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

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

*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.

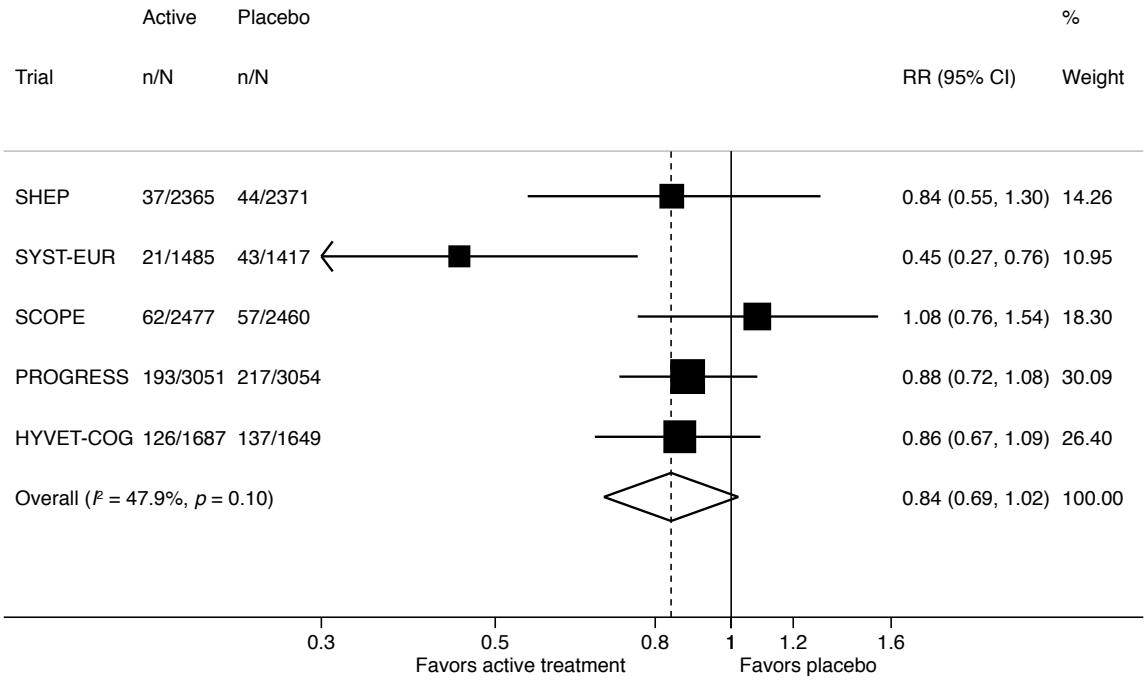

Fig. 1. Relative risks of dementia for antihypertensive treatment *vs* placebo in individual randomized controlled trials and all trials combined. Trials are ordered by year of publication. Squares represent trial-specific relative risk (RR) (size of the square reflects the trial-specific statistical 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.

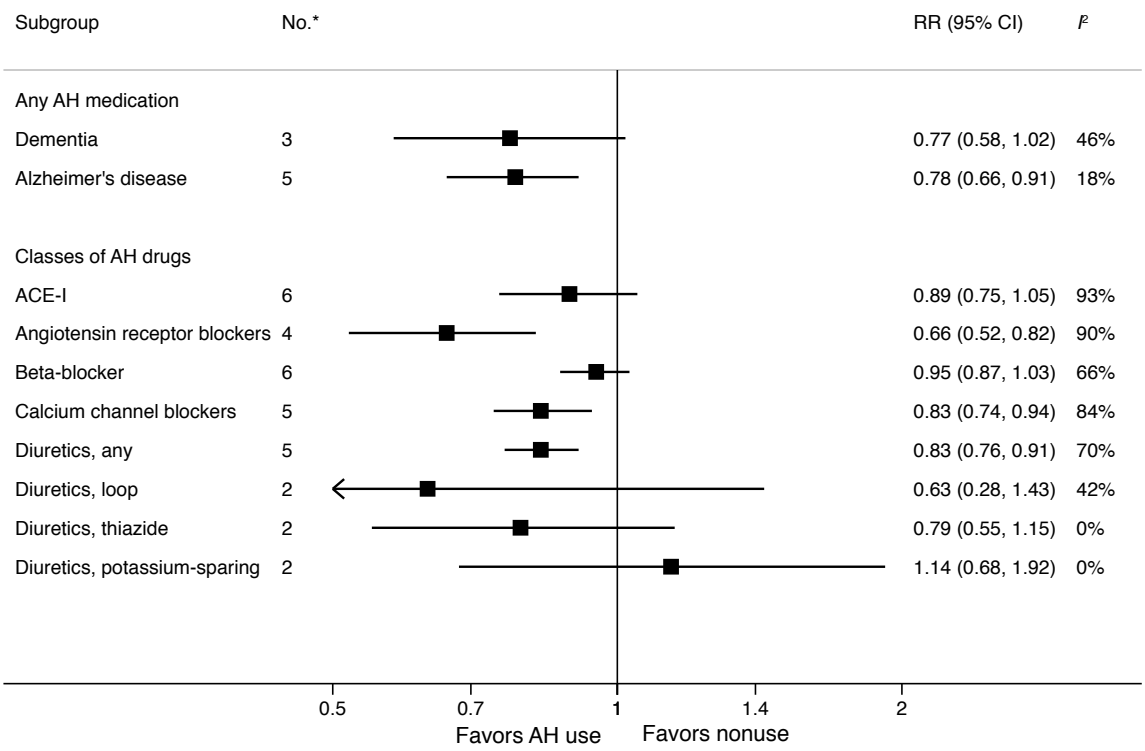

Fig. 2. Combined relative risks of dementia and Alzheimer's disease for use of any antihypertensive drug and classes of antihypertensive drugs *vs* nonuse in prospective studies. Results for antihypertensive drug classes are for dementia or Alzheimer's disease. *Number of studies in each subgroup. ACE-I, angiotensin-converter enzyme inhibitor; AH, anti-hypertensive; CI, confidence interval; RR, relative risk.

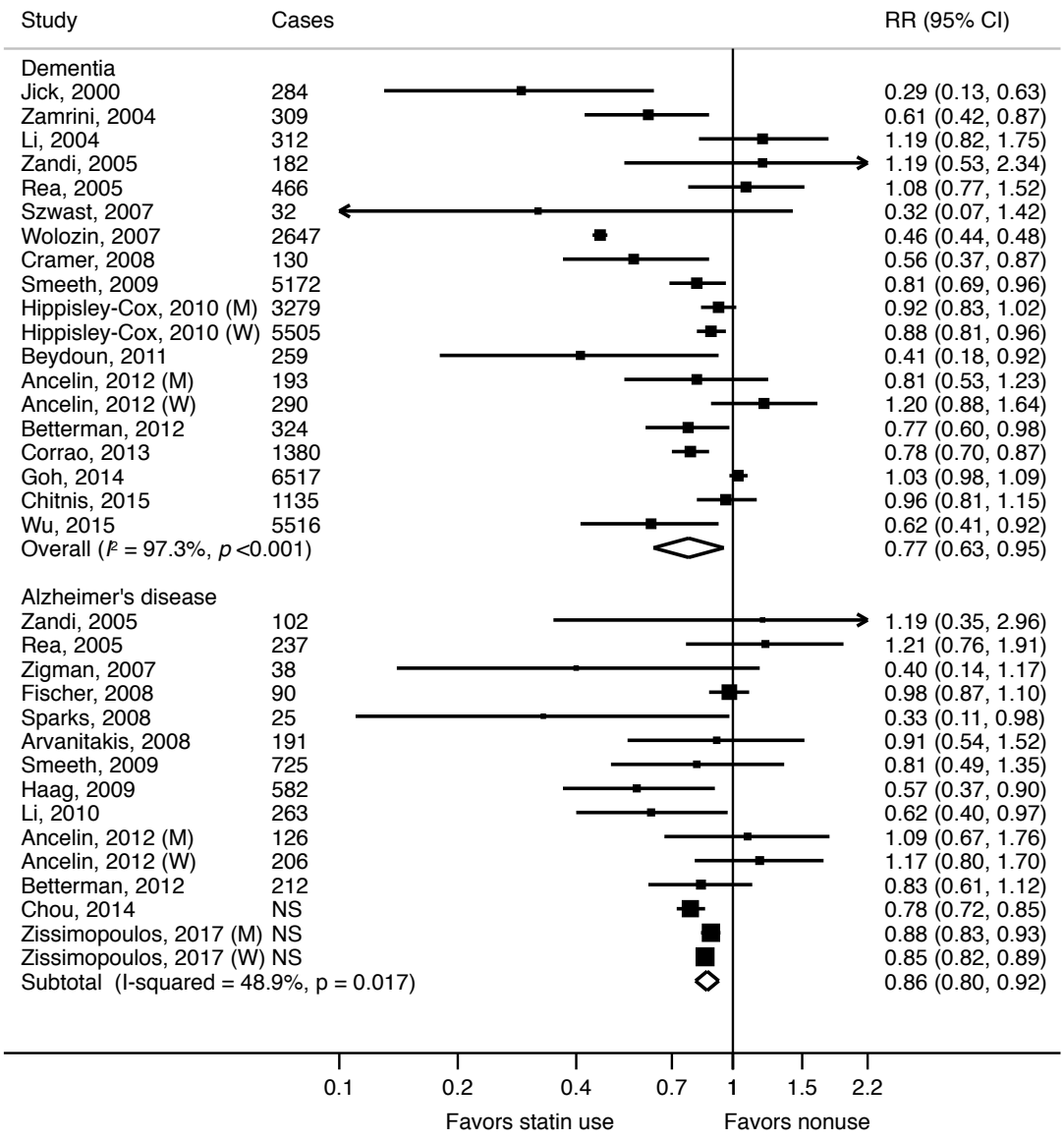

Fig. 3. Relative risks of dementia and Alzheimer's disease for statin use *vs* nonuse in individual prospective studies and all studies combined. *First author's last name and year of publication. Studies are ordered by year of publication. NS, not specified; M, men; W, women. Squares represent study-specific 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.

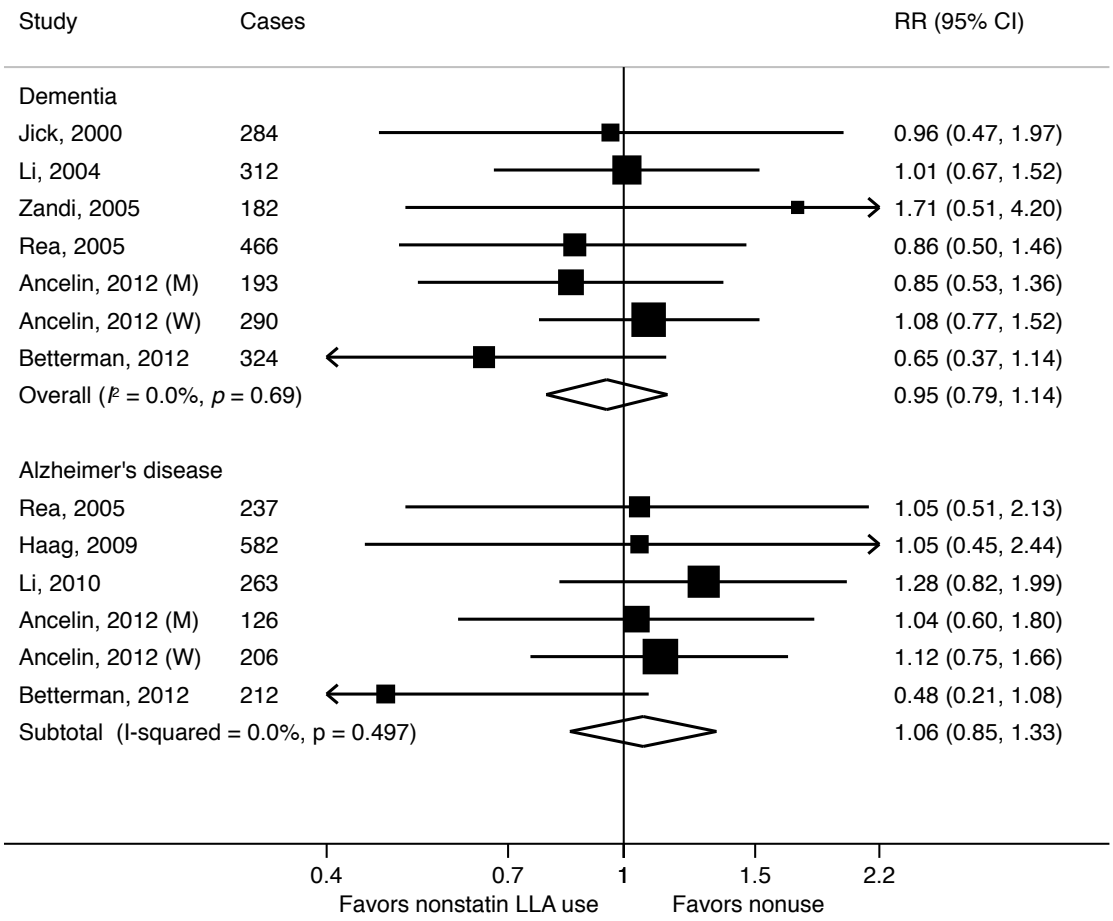

Fig. 4. Forest plot of prospective studies of nonstatin lipid-lowering agent use vs nonuse in relation to incidence of dementia and Alzheimer's disease. *First author's last name and year of publication. LLA, lipid-lowering agent; M, men; W, women. Squares represent study-specific relative risks (RR) (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

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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 S2: Randomized controlled trials of hypertension treatment and incidence of dementia

Reference	Trial name, country	Participant characteristics	Mean Follow-up, years	No. of dementia cases; diagnostic criteria	Antihypertensive medication	ΔSBP/DBP (active–placebo)	RR (95% CI) of dementia
SHEP Research Group, 1991 [1]	SHEP, United States	4736 adults (43% men) ≥60 years of age; SBP 160–219 mmHg, DBP <90 mmHg; no history of major CVDs	5	81; expert diagnosis evaluation (Short-Care Test)	Diuretic (chlorthalidone) ± β-blocker (atenolol) *vs* placebo	–11.1/3.4 mmHg	0.84 (0.55–1.30)*
Forette et al, 2002 [2]	SYST-EUR, 19 countries	2902 adults (34% men) ≥60 years of age; SBP 160–219 mmHg, DBP <95 mmHg	3.9	64; DSM-III-R and results of CT scan	CCB (nitrendipine) ± diuretic (hydrochlorothiazide), ACE-I (enalapril) or both drugs *vs* placebo	–7.0/3.2 mmHg	0.45 (0.27–0.76)
Lithell et al, 2003 [3]	SCOPE, 15 countries	4937 adults (36% men) 70–89 years of age; SBP 160–179 mmHg, DBP 90–99 mmHg; MMSE score ≥24	3.7	119; modified ICD-10 research criteria	ARB (candecertan) ± diuretic (hydrochlorothiazide) *vs* placebo	–3.2/1.6 mmHg	1.08 (0.76–1.54)*
Tzourio et al, 2003 [4]	PROGRESS, 10 countries	6105 adults (70% men), mean age 64 years; prior stroke or transient ischemic attack	3.9	410; DSM-IV	ACE-I (perindopril) ± diuretic (indapamide) *vs* placebo	–9/4 mmHg	0.88 (0.72–1.08)
Peters et al, 2008 [5]	HYVET-COG, 13 countries	3336 adults (40% men) ≥80 years of age; SBP 160–200 mmHg, DBP <110 mmHg	2.2	263; DSM-IV and results of CT scan	Diuretic (indapamide) ± ACE-I (perindopril) *vs* placebo	–15/5.9 mmHg	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]

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 S3: Prospective studies of antihypertensive medication use *vs* nonuse and incidence of dementia and Alzheimer's disease

Reference	Study name, country	Participants; baseline age	Mean follow-up, years	Outcome (No. of cases); diagnostic criteria	NOS score	Adjustments	Adjusted RR (95% CI) of dementia or AD for AH drug use *vs* nonuse
Morris et al, 2001 [6]	East Boston Study, United States	634 adults; ≥65 years	4	AD (n=99); NINCDS-ADRDA	7	Age, sex, education	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
in't Veld, et al, 2001 [7]	Rotterdam Study, The Netherlands	7046 adults; ≥55 years	2.2	Dementia (n=118), AD (n=82); DSM-III-R, NINCDS-ADRDA	8	Age, sex, education, living situation, BMI, smoking, diabetes, stroke, PAD, DBP, SBP, baseline MMSE	Any AH, dementia: 0.67 (0.45–1.00); AD: 0.77 (0.49–1.24)
Lindsay et al, 2002 [8]	Canadian Study of Health and Aging, Canada	4088 adults; ≥65 years	5	AD (n=194); NINCDS-ADRDA	7	Age, sex, education	Any AH, 0.91 (0.64–1.30)
Yasar et al, 2005 [9]	Baltimore Longitudinal Study of Aging, United States	1092 adults; ≥60 years	11	AD (n=115); DSM-III-R, NINCDS-ADRDA	7	Age, sex, education, smoking, blood pressure, heart disease	CCB, 0.63 (0.31–1.28) [0.30 (0.07–1.25) for dihydropyridine and 0.82 (0.37–1.83) for nondihydro-pyridine]
Peila et al, 2006 [10]	Honolulu Asia Aging Study, United States	1294 men; ≥72 years	5	Dementia (n=108), AD (n=65); DSM-III-R, DSM-IV, NINCDS-ADRDA	8	Age, sex (all men), education, APOE-ε4 status, blood pressure, BMI, smoking status, coronary heart disease	Any AH, dementia: 0.59 (0.35–1.00)*; AD: 0.48 (0.29–0.78)*
Qiu et al, 2006 [11]	Kungsholmen Project, Sweden	1301 adults; 75–101 years	5	Dementia (n=440), AD (n=333); DSM-III-R, NINCDS-ADRDA	9	Age, sex, education, follow-up survival status, BMI, diabetes, heart failure, stroke, pulse rate, SBP, DBP, baseline MMSE	Any AH, dementia: 0.92 (0.75–1.13); AD: 0.84 (0.67–1.07)
Johnson et al, 2012 [12]	Cohort from Veterans Administration, United States	377 838 adults; ≥65 years	2	Dementia (n=14 580); ICD-9-CM codes	6	Age, sex, ethnicity, comorbidities, co-medications	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)
Qui et al, 2013 [13]	National Alzheimer's Disease Coordinating Center, United States	4830 adults; mean age 76 years	3.4	AD (n=1331); DSM-IV, NINCDS-ADRDA	6	Age, sex, ethnicity, education, smoking, drinking, follow-up time, diabetes, hypertension, stroke, heart failure, mild cognitive impairment	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]
Yasar et al, 2013 [14]	Ginkgo Evaluation of Memory Study, United States	1928 adults; ≥75 years	5.6	AD (n=290); DSM-IV, NINCDS-ADRDA	9	Age, sex, education, income, BMI, SBP, DBP, vascular diseases, mild cognitive impairment	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)
Chiu et al, 2014 [15]	National Health Insurance Research	140 140 adults; >50	10.3	Dementia (n=11 075); ICD-9 codes 290.0–	8	Age, sex, income, urbanization, hypertension, coronary heart disease, diabetes,	ACE-I, dementia: 1.14 (1.08–1.19); AD: 1.11 (0.98–1.26)

	Database, Taiwan	years		290.4, 294.1, 331.0		hypercholesterolemia, depressive disorder, heart failure, chronic kidney disease, stroke	ARB, dementia: 0.59 (0.56–0.62); AD: 0.61 (0.54–0.68)‡ BB, dementia: 1.00 (0.95–1.04); AD: 1.18 (1.05–1.33) CCB, dementia: 0.81 (0.77–0.84); AD: 0.76 (0.68–0.86) Diuretic, dementia: 0.87 (0.83–0.91); AD: 0.78 (0.68–0.90)
Chuang et al, 2014 [16]	Cache County Study, United States	3227 adults; ≥65 years	7.1	AD (n=325); DSM-III-R, NINCDS-ADRDA	8	Age, sex, education, APOE-ε4 status, smoking and drinking habits, history of high cholesterol, diabetes, stroke, coronary artery bypass graft, and myocardial infarction	Any AH, 0.76 (0.60–0.96) ACE-I, 0.95 (0.71–1.29) BB, 0.90 (0.67–1.21) CCB, 0.75 (0.55–1.04) [0.75 0.48–1.17) for dihydropyridine and 0.88 (0.60–1.30) for non-dihydropyridine] Diuretic (any), 0.72 (0.56–0.93) [0.98 (0.67–1.43) for loop, 0.70 (0.53–0.93) for thiazide, and 0.69 (0.48–0.99) for potassium-sparing]
Chitnis et al, 2015 [17]	Medicare Advantage Prescription Drug, United States	8062 adults; mean age 75 years	3	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	7	43 time-independent factors (e.g., sociodemographic, treatment, and clinical factors) and time-dependent factors updated monthly (e.g., exposure groups, duration of use, medication possession ratio, and hospitalization)	ACE-I/ARB, 0.90 (0.70–1.16) for current use and 0.89 (0.71–1.10) for former use
Tully et al., 2016 [18]	3C Study, France	6537 adults; ≥65 years	8.4	Dementia (n=446); NINCDS-ADRDA	9	Age, sex, center, education, BMI, CVD, diabetes, hypercholesterolemia, Center for Epidemiologic Studies Depression Scale, chronic kidney disease, APOE4, SBP, DBP	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

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 S4: Prospective studies comparing different classes of antihypertensive drugs and incidence of dementia and Alzheimer's disease

Reference	Study name, country	Participants; baseline age	Mean follow-up, years	Outcome (No. of cases); diagnostic criteria	NOS score	Adjustments	Adjusted RR (95% CI) of dementia or AD comparing different AH drug classes
Ohrui et al, 2004 [19]	No name, Japan	4124 adults; ≥65 years	8	AD (n=90); NS	1	NS	No difference in AD risk for ACE-I, BB, CCB, or diuretics; however, among ACE-I users, the use of ACE-Is that inhibit brain ACE, compared with other ACE-Is, was associated with a lower risk of AD (0.25; 0.08–0.75)
Sink et al, 2009 [20]	Cardiovascular Health Study, United States	1054 adults; ≥65 years	6	Dementia (n=158); DSM-IV, NINCDS-ADRDA	8	Age, sex, race, education, income, smoking, alcohol, diabetes, coronary artery disease, serum creatinine, serum low-density lipoprotein, MMSE, depression	ACE-I *vs* other AH medications, 1.05 (0.91–1.21)
Li et al, 2010 [21]	US Veterans Affairs Health System, United States	799 069 (dementia); 819 491 (AD); ≥65 years	4	Dementia (NS), AD (NS); ICD-9 codes (NS)	6	Age, sex (98% men), diabetes, stroke, cardiovascular disease	ARB *vs* ACE-I, dementia: 0.81 (0.73–0.90); AD: 0.81 (0.68–0.96) ARB *vs* cardiovascular comparator (BB or CCB): dementia: 0.76 (0.69–0.84); AD: 0.84 (0.71–1.00)
Davies et al, 2011 [22]	General Practice Research Database, United Kingdom	9197 cases and 39 166 controls; ≥60 years	NS	Dementia (n=9197), AD (n=5797); NS	6	Age, sex, region, diabetes, stroke, coronary artery disease, blood pressure, number of consultations	ARB *vs* other AH medications, dementia: 0.55 (0.49–0.62); AD: 0.47 (0.37–0.58) ACE-I *vs* other AH medications, dementia: 0.80 (0.76–0.84); AD: 0.76 (0.69–0.84)
Hsu et al, 2013 [23]	National Health Insurance Research Database, Taiwan	32 911 adults; mean age 58 years	5.2	Dementia (n=1031); ICD-9 codes 290.0, 290.20, 290.21, 290.3, 331.0	9	Age, sex, diabetes, coronary artery disease, arrhythmia, hypertension, hyperlipidemia	ARB *vs* other AH medications, 1.00 (0.88–1.13)
Goh et al., 2015 [24]	Clinical Practice Research Datalink, United Kingdom	426 089 adults; ≥18 years	4.3	Dementia (n=6517); Read codes	6	Age, sex, calendar year, SES, number of consultations, BMI, smoking, diabetes, hypertension, heart failure, statin use, alcohol use	ARB *vs* ACE-I, 0.92 (0.85–1.00)
Hwang et al, 2017 [25]	National Health Insurance Service Senior Cohort, Korea	18 423 adults; ≥60 years	9.6	Dementia (4005); AD (1987); ICD-10 codes F00-F07, G20-G26, G30-G32	9	Age, sex, BMI, income, urbanization, smoking, alcohol, blood pressure, hypertensive drugs, CAD, diabetes, hypercholesterolemia,	CCB *vs* non-CCB, dementia: 0.81 (0.75-0.87); AD: 0.80 (0.72-0.88)

Abbreviations: AD, Alzheimer's disease; ACE-I, angiotensin converting enzyme-inhibitor; AH, antihypertensive; ARB, angiotensin receptor blocker; BB, β-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

Reference	Study name, country	Participants; baseline age	Mean Follow-up, years	Outcome (No. of cases); diagnostic criteria	NOS score	Adjustments	Adjusted RR (95% CI)	
							Statins	Non-statin LLAs
Jick et al, 2000 [26]	General Practice Research Database, United Kingdom	284 cases and 1080 controls; ≥50 years	NS	Dementia (n=284); NS	5	Age, sex, calendar time, practice, BMI, smoking, diabetes, years of recorded history in database, hypertension, CAD, coronary artery bypass surgery, TIA	0.29 (0.13–0.63)	0.96 (0.47–1.97)
Reitz et al, 2004 [27]	Washington Heights, United States	1168 adults; ≥65 years	4.4	AD (n=119); DSM-III-R, NINCDS-ADRDA	8	Age, sex, education, race, BMI, diabetes, hypertension, heart disease, APOE-ε4	NA	0.61 (0.42–0.87) for any LLAs
Zamrini et al, 2004 [28]	US Veterans Affairs Medical Center, United States	309 male cases, 3088 male controls; ≥50 years	NS	AD (n=309); ICD-9-CM codes 290.0, 290.10, 290.13, 290.20, 290.21, 290.3, 331.0	6	Age, sex (all men), diabetes, lipid metabolism disorders, hypertension, CAD, cerebrovascular disease, arterial disease	0.61 (0.42–0.87)	NA
Li et al, 2004 [29]	Adult Changes in Thought Study, United States	2356 adults; ≥65 years	5.6	Dementia (n=312); DSM-IV, NINCDS-ADRDA	9	Age, education, APOE-ε4, use of other LLAs or statins; no adjustments for sex, BMI, and comorbidities because of lack of association with dementia/AD	1.19 (0.82–1.75)	1.01 (0.67–1.52)
Zandi et al, 2005 [30]	Cache County Study, United States	3308 adults; ≥65 years	3	Dementia (n=182), AD (n=102); DSM-III-R, NINCDS-ADRDA	8	Age, sex, education, diabetes, hypertension, APOE-ε4, age*ε4 interaction	Dementia: 1.19 (0.53–2.34); AD: 1.19 (0.35–2.96)	Dementia: 1.71 (0.51–4.20)
Rea et al, 2005 [31]	Cardiovascular Health Study, United States	2798 adults; ≥65 years	5.4	Dementia (n=466), AD (n=237); DSM-IV, NINCDS-ADRDA	8	Age, sex, education, baseline MMSE, CAD, stroke, alcohol use	Dementia: 1.08 (0.77–1.52); AD: 1.21 (0.76–1.91)	Dementia: 0.86 (0.50–1.46); AD: 1.05 (0.51–2.13)
Szwast, et al, 2007 [32]	Indianapolis Ibadan Dementia Project, United States	1141 adults; ≥65 years	3	Dementia (n=32); DSM-III-R and ICD-10 codes (NS)	6	Age, sex, education, APOE-ε4	0.32 (0.07–1.42)	NA
Zigman et al, 2007 [33]	No name, United States	123 adults; 41–78 years	5.5	AD (n=38); NS	3	NS	0.40 (0.14–1.17)	NA
Wolozin et al, 2007 [34]	US Veteran Affairs Medical Center, United States	727 128 adults (94.4% men); ≥65 years	2.4	Dementia/AD (n=2647); ICD-9 code 331.0 (may not fulfill all NINCDS-ADRDA criteria)	8	Age, diabetes, obesity, hypertension, cardiovascular diseases, Charlson Comorbidity Index; no adjustment for sex but 94.4% were men	0.46 (0.44–0.48)*	NA
Fischer et al, 2008 [35]	Vienna Transdanube Aging Study, Austria	479 adults; age 75 years	2.5	AD (n=90); DSM-IV, NINCDS-ADRDA	6	None	0.98 (0.87–1.10)	NA
Cramer et al, 2008 [36]	Sacramento Area Latino Study on Aging, United States	1674 adults; ≥60 years	4.5	Dementia (n=130); DSM-IV, NINCDS-ADRDA	9	Age, sex (no confounding and therefore no adjustment), education, smoking, diabetes, stroke, APOE-ε4, MMSE	0.56 (0.37–0.87)	NA
Sparks et al,	Alzheimer's Disease	2233 adults;	4	AD (n=25); DSM-IV,	7	Age, sex, education, APOE-ε4	0.33 (0.11–0.98)	0.33 (0.12–0.89)

2008 [37]	Anti-inflammatory Prevention Trial, United States	≥70 years		NINCDS-ADRDA			NA	for any LLAs
Arvanitakis et al, 2008 [38]	Religious Orders Study, United States	929 adults; mean age 75 years	12	AD (n=191); NINCDS-ADRDA	8	Age, sex, education	0.91 (0.54–1.52)	NA
Smeeth et al, 2009 [39]	Health Improvement Network database, United Kingdom	729 529 adults; 40–80 years	4.4	Dementia (n=5172), AD (n=725); NS	6	Age, sex, propensity score, year of index date, first diagnosis of any disease, first use of any medication	Dementia: 0.81 (0.69–0.96); AD: 0.81 (0.49–1.35)	NA
Haag et al, 2009 [40]	Rotterdam Study, The Netherlands	6992 adults; ≥55 years	9	AD (n=582); DSM-III-R, NINCDS-ADRDA	9	Age, sex, education, BMI, smoking, diabetes, SBP, cholesterol, cardiovascular and cerebrovascular disease, non-statin LLAs or statins	0.57 (0.37–0.90)	1.05 (0.45–2.44)
Solomon et al, 2010 [41]	FINRISK, Finland	17 597 adults; mean age 67–72 years	NS	Dementia (n=1561); NS	8	Age, sex, education, survey region and year, BMI, total cholesterol, systolic blood pressure	NA	0.42 (0.37–0.49) for any LLAs
Li et al, 2010 [42]	Adult Changes in Thought Study, United States	3099 adults; ≥65 years	6.1	AD (n=263); DSM-IV, NINCDS-ADRDA	9	Age, sex, cohort, race, education, BMI, smoking, CASI score, comorbid vascular diseases, use of other LLAs, APOE-ε4	0.62 (0.40–0.97)	1.28 (0.82–1.99)†
Hippisley-Cox et al, 2010 [43]	Egton Medical Information System, United Kingdom	2 004 692 adults; 30–84 years	7	Dementia (n=8784); NS	5	Age, sex	0.92 (0.83–1.02) in men and 0.88 (0.81–0.96) in women*	NA
Beydoun et al, 2011 [44]	Baltimore Longitudinal Study of Aging, United States	1604 adults; ≥50 years	24.9	Dementia (n=259); DSM-IIII-R, NINCDS-ADRDA	9	Age, sex, race/ethnicity, education, BMI, smoking, diabetes, hypertension, SBP, CAD, dyslipidemia	0.41 (0.18–0.92)	NA
Ancelin et al, 2012 [45]	No name, France	7056 adults; ≥65 years	6.7	Dementia (n=483), AD (n=332); DSM-IV, NINCDS-ADRDA	7	Age, sex, center, education	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	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
Bettermann et al, 2012 [46]	Ginkgo Evaluation of Memory Study, United States	2587 adults; ≥65 years	5.6	Dementia (n=324), AD (n=212); DSM-IV, NINCDS-ADRDA	9	Age, sex, race, field center, education, Ginkgo biloba randomization group, APOE-ε4, stroke, CAD	Dementia: 0.77 (0.60–0.98); AD: 0.83 (0.61–1.12)	Dementia: 0.65 (0.37–1.14); AD: 0.48 (0.21–1.08)
Corrao et al, 2013 [47]	National Health Service, Italy	152 729 adults; ≥40 years	NS	Dementia (n=1380); ICD-9-CM codes (>10	7	Age, sex, date of index prescription, concomitant users of other drugs,	0.78 (0.70–0.87)‡	NA

				codes)		Charlson Comorbidity Index		
Chou et al, 2014 [48]	National Health Insurance Research Database, Taiwan	33 398 adults; ≥60 years	5	AD (NS); ICD-9-CM codes 290.x, 294.1, 331.0, A210	9	Age, sex, SES, comorbidities, propensity scores	0.78 (0.72–0.85)	NA
Wu et al, 2015 [49]	National Health Insurance Research Database, Taiwan	57 669 adults; ≥65 years	11.8	Dementia (5516); ICD-9-CM codes 290.0, 290.10–290.13	9	Age, sex, hypertension, diabetes, chronic kidney disease, stroke, TIA, cardiovascular disease, heart failure, atrial fibrillation, medication use	0.62 (0.41–0.92)§	NA
Goh et al, 2015 [24]	Clinical Practice Research Datalink, United Kingdom	426 089 adults; ≥18 years	4.3	Dementia (n=6517); Read codes	6	Age, sex, calendar year, number of consultations, SES, BMI, smoking, diabetes, hypertension, heart failure, statin use, alcohol use	1.03 (0.98–1.09)	NA
Chitnis et al, 2015 [50]	Medicare Advantage Prescription Drug, United States	8062 adults; mean age 75 years	1.8	Dementia (n=1135); ICD-9-CM codes (>10 codes)	6	Age, sex, 44 time-independent factors such as socio-demographic and treatment factors, and comorbidities	0.96 (0.81–1.15)‖	NA
Zissimopoulos et al, 2016 [51]	Medicare fee for service, United States	399 979 adults; ≥65 years	7.2	AD (NS); CD-9-CM code 331.0	9	Matched by age, sex, race/ethnicity, region, years since hyperlipidemia diagnosis, education, and health status	0.88 (0.83-0.93) men; 0.85 (0.82-0.89) women	NA

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.

‖The 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

	Dementia			Alzheimer's disease		
	No. of studies*	**Combined RR (95% CI)**	I^2†	**No. of studies***	**Combined RR (95% CI)**	I^2†
Study quality (NOS)						
0–7	11	0.87 (0.78–0.97)	79%	6	0.93 (0.74–1.16)	38%
8–9	8	0.73 (0.52–1.01)	90%	7	0.79 (0.69–0.91)	20%
Duration of follow-up						
<5 years	7	0.74 (0.49–1.13)	99%	4	0.88 (0.65–1.19)	31%
≥5 years	9	0.90 (0.80–1.00)	48%	9	0.84 (0.71–0.98)	44%
No. of cases						
<200	4	0.72 (0.50–1.04)	33%	6	0.91 (0.72–1.16)	27%
≥200	15	0.78 (0.63–0.98)	98%	6	0.84 (0.66–1.07)	51%
Statin type§						
Atorvastatin	5	0.84 (0.80–0.89)	39%	---	---	---
Fluvastatin	3	0.90 (0.76–1.06)	0%	---	---	---
Lovastatin	2	0.95 (0.88–1.03)	0%	---	---	---
Pravastatin	4	0.90 (0.78–1.04)	52%	---	---	---
Rosuvastatin	5	0.72 (0.57–0.91)	68%	---	---	---
Simvastatin	5	0.78 (0.58–1.04)	99%	---	---	---

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 last 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 S7: Prospective studies of type 2 diabetes therapy and risk of dementia and Alzheimer's disease

Reference	Study name, country	Participants; baseline age	Mean follow-up, years	Outcome (No. of cases); diagnostic criteria	Antidiabetic therapy	NOS score	Adjustments	Adjusted RR (95% CI) of dementia or AD
Ott et al, 1999 [52]	Rotterdam Study, The Netherlands	6370 adults; ≥55 years	2.1	Dementia (n=126); DSM-III-R	Any oral antidiabetic medication, insulin therapy, no drugs	7	Age, sex	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
Xu et al, 2004 [53]	Kungsholmen Project, Sweden	1301 adults; ≥75 years	4.3	Dementia (n=350), AD (n=260); DSM-III-R, NINCDS-ADRDA	Any oral antidiabetic medication	8	Age, sex, education, BMI, heart disease, stroke, blood pressure, antihypertensive drugs	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
Fischer et al, 2008 [35]	Vienna Transdanube Aging Study, Austria	479 adults; age 75 years	2.5	AD (n=90); DSM-IV, NINCDS-ADRDA	Insulin therapy	6	None	Compared with nondiabetics, the RRs were 1.78 (0.55–5.74) for insulin therapy
Parikh et al, 2011 [54]	Veterans Administration, United States	377 838 diabetes patients; ≥65 years	2	Dementia (14 580); ICD-9-CM codes 250.xx, 357.2, 362.0, 366.41	Any oral antidiabetic medication, insulin	7	NS	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
Huang et al, 2014 [55]	National Health Insurance Research Database, Taiwan (only diabetic patients)	71 433 diabetes patients; mean age 59 years	5.5	AD (n=346); ICD-9-CM code 331.0	Metformin, sulfonylureas, thiazolidinediones, α-glucosidase blockers, nonsulfonylurea insulin secretagouge, insulin	9	Age, sex, geographic area, urbanization, hypertension, hyperlipidemia, stroke, coronary artery disease, arrhythmia, heart failure, depression	Compared with nonuse, the RR was 0.92 (0.13–6.60) for thiazolidinediones and 1.53 (0.98–2.39) for insulin therapy
Heneka et al, 2015 [56]	Allgemeine Ortskrankenkassen, Germany	145 928 adults; ≥60 years	4.3	Dementia (n=13 177); ICD-10 codes G30, G31.0, G31.82, G23.1, F00, F01, F02, F03 or F05.1	Metformin, thiazolidinediones	9	None	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
Orkaby et al, 2017 [57]	Veterans Administration, United States	28 640 diabetes patients; ≥65 years	5.0	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	Metformin *vs.* sulfonylureas	9	Propensity score model with 23 variables: race, sex, BMI, HbA1c, renal function, and comorbidities; stratified by age	Compared with sulfonylureas, the RR for metformin use was 0.89 (0.79–0.99) for those <75 years of age and 0.96 (0.87–1.05) for those ≥75 years of age

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.

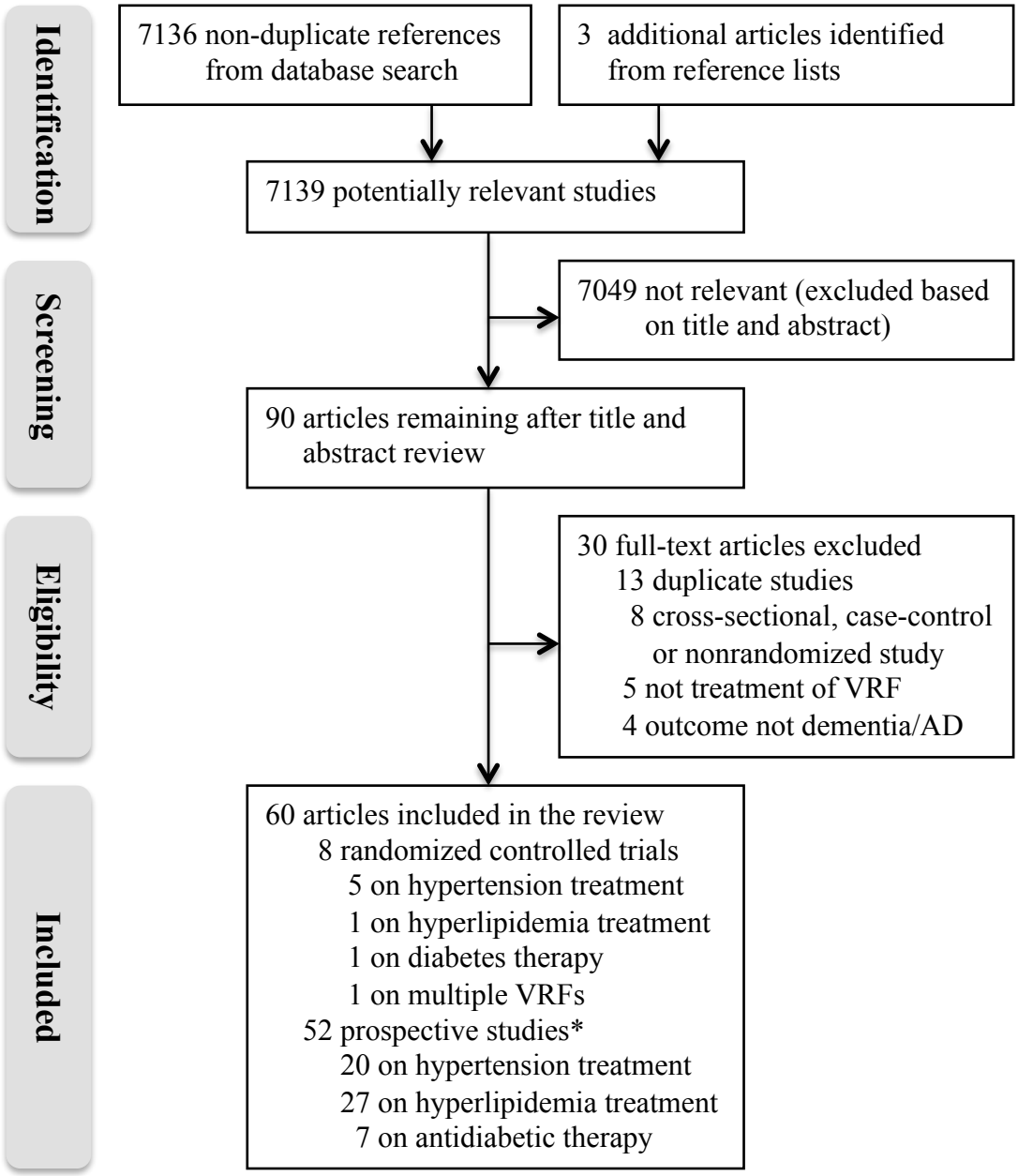

Figure S2: Flow diagram of study selection process for the systematic review

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

[1] (1991) Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. *JAMA* **265**, 3255-3264.

[2] Forette F, Seux ML, Staessen JA, Thijs L, Babarskiene MR, Babeanu S, Bossini A, Fagard R, Gil-Extremera B, Laks T, Kobalava Z, Sarti C, Tuomilehto J, Vanhanen H, Webster J, Yodfat Y, Birkenhager WH, Systolic Hypertension in Europe I (2002) The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study. *Arch Intern Med* **162**, 2046-2052.

[3] Lithell H, Hansson L, Skoog I, Elmfeldt D, Hofman A, Olofsson B, Trenkwalder P, Zanchetti A, Group SS (2003) The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. *J Hypertens* **21**, 875-886.

[4] Tzourio C, Anderson C, Chapman N, Woodward M, Neal B, MacMahon S, Chalmers J, Group PC (2003) Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. *Arch Intern Med* **163**, 1069-1075.

[5] Peters R, Beckett N, Forette F, Tuomilehto J, Clarke R, Ritchie C, Waldman A, Walton I, Poulter R, Ma S, Comsa M, Burch L, Fletcher A, Bulpitt C, investigators H (2008) Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. *Lancet Neurol* **7**, 683-689.

[6] Morris MC, Scherr PA, Hebert LE, Glynn RJ, Bennett DA, Evans DA (2001) Association of incident Alzheimer disease and blood pressure measured from 13 years before to 2 years after diagnosis in a large community study. *Arch Neurol* **58**, 1640-1646.

[7] in't Veld BA, Ruitenberg A, Hofman A, Stricker BH, Breteler MM (2001) Antihypertensive drugs and incidence of dementia: the Rotterdam Study. *Neurobiol Aging* **22**, 407-412.

[8] Lindsay J, Laurin D, Verreault R, Hebert R, Helliwell B, Hill GB, McDowell I (2002) Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging. *Am J Epidemiol* **156**, 445-453.

[9] Yasar S, Corrada M, Brookmeyer R, Kawas C (2005) Calcium channel blockers and risk of AD: the Baltimore Longitudinal Study of Aging. *Neurobiol Aging* **26**, 157-163.

[10] Peila R, White LR, Masaki K, Petrovitch H, Launer LJ (2006) Reducing the risk of dementia: efficacy of long-term treatment of hypertension. *Stroke* **37**, 1165-1170.

[11] Qiu C, Winblad B, Marengoni A, Klarin I, Fastbom J, Fratiglioni L (2006) Heart failure and risk of dementia and Alzheimer disease: a population-based cohort study. *Arch Intern Med* **166**, 1003-1008.

[12] Johnson ML, Parikh N, Kunik ME, Schulz PE, Patel JG, Chen H, Aparasu RR, Morgan RO (2012) Antihypertensive drug use and the risk of dementia in patients with diabetes mellitus. *Alzheimers Dement* **8**, 437-444.

[13] Qiu WQ, Mwamburi M, Besser LM, Zhu H, Li H, Wallack M, Phillips L, Qiao L, Budson AE, Stern R, Kowall N (2013) Angiotensin converting enzyme inhibitors and the reduced risk of Alzheimer's disease in the absence of apolipoprotein E4 allele. *J Alzheimers Dis* **37**, 421-428.

[14] Yasar S, Xia J, Yao W, Furberg CD, Xue QL, Mercado CI, Fitzpatrick AL, Fried LP, Kawas CH, Sink KM, Williamson JD, DeKosky ST, Carlson MC, Ginkgo Evaluation of Memory Study I (2013) Antihypertensive drugs decrease risk of Alzheimer disease: Ginkgo Evaluation of Memory Study. *Neurology* **81**, 896-903.

[15] Chiu WC, Ho WC, Lin MH, Lee HH, Yeh YC, Wang JD, Chen PC, Health Data Analysis in Taiwan Research G (2014) Angiotension receptor blockers reduce the risk of dementia. *J Hypertens* **32**, 938-947.
[16] Chuang YF, Breitner JC, Chiu YL, Khachaturian A, Hayden K, Corcoran C, Tschanz J, Norton M, Munger R, Welsh-Bohmer K, Zandi PP, Cache County I (2014) Use of diuretics is associated with reduced risk of Alzheimer's disease: the Cache County Study. *Neurobiol Aging* **35**, 2429-2435.
[17] Chitnis AS, Aparasu RR, Chen H, Kunik ME, Schulz PE, Johnson ML (2015) Use of Angiotensin-Converting Enzyme Inhibitors, Angiotensin Receptor Blockers, and Risk of Dementia in Heart Failure. *Am J Alzheimers Dis Other Demen*.
[18] Tully PJ, Dartigues JF, Debette S, Helmer C, Artero S, Tzourio C (2016) Dementia risk with antihypertensive use and blood pressure variability: A cohort study. *Neurology* **87**, 601-608.
[19] Ohrui T, Matsui T, Yamaya M, Arai H, Ebihara S, Maruyama M, Sasaki H (2004) Angiotensin-converting enzyme inhibitors and incidence of Alzheimer's disease in Japan. *J Am Geriatr Soc* **52**, 649-650.
[20] Sink KM, Leng X, Williamson J, Kritchevsky SB, Yaffe K, Kuller L, Yasar S, Atkinson H, Robbins M, Psaty B, Goff DC, Jr. (2009) Angiotensin-converting enzyme inhibitors and cognitive decline in older adults with hypertension: results from the Cardiovascular Health Study. *Arch Intern Med* **169**, 1195-1202.
[21] Li NC, Lee A, Whitmer RA, Kivipelto M, Lawler E, Kazis LE, Wolozin B (2010) Use of angiotensin receptor blockers and risk of dementia in a predominantly male population: prospective cohort analysis. *BMJ* **340**, b5465.
[22] Davies NM, Kehoe PG, Ben-Shlomo Y, Martin RM (2011) Associations of anti-hypertensive treatments with Alzheimer's disease, vascular dementia, and other dementias. *J Alzheimers Dis* **26**, 699-708.
[23] Hsu CY, Huang CC, Chan WL, Huang PH, Chiang CH, Chen TJ, Chung CM, Lin SJ, Chen JW, Leu HB (2013) Angiotensin-receptor blockers and risk of Alzheimer's disease in hypertension population--a nationwide cohort study. *Circ J* **77**, 405-410.
[24] Goh KL, Bhaskaran K, Minassian C, Evans SJ, Smeeth L, Douglas IJ (2015) Angiotensin receptor blockers and risk of dementia: cohort study in UK Clinical Practice Research Datalink. *Br J Clin Pharmacol* **79**, 337-350.
[25] Hwang D, Kim S, Choi H, Oh IH, Kim BS, Choi HR, Kim SY, Won CW (2016) Calcium-Channel Blockers and Dementia Risk in Older Adults- National Health Insurance Service - Senior Cohort (2002-2013). *Circ J* **80**, 2336-2342.
[26] Jick H, Zornberg GL, Jick SS, Seshadri S, Drachman DA (2000) Statins and the risk of dementia. *Lancet* **356**, 1627-1631.
[27] Reitz C, Tang MX, Luchsinger J, Mayeux R (2004) Relation of plasma lipids to Alzheimer disease and vascular dementia. *Arch Neurol* **61**, 705-714.
[28] Zamrini E, McGwin G, Roseman JM (2004) Association between statin use and Alzheimer's disease. *Neuroepidemiology* **23**, 94-98.
[29] Li G, Higdon R, Kukull WA, Peskind E, Van Valen Moore K, Tsuang D, van Belle G, McCormick W, Bowen JD, Teri L, Schellenberg GD, Larson EB (2004) Statin therapy and risk of dementia in the elderly: a community-based prospective cohort study. *Neurology* **63**, 1624-1628.
[30] Zandi PP, Sparks DL, Khachaturian AS, Tschanz J, Norton M, Steinberg M, Welsh-Bohmer KA, Breitner JC, Cache County Study i (2005) Do statins reduce risk of incident dementia and Alzheimer disease? The Cache County Study. *Arch Gen Psychiatry* **62**, 217-224.
[31] Rea TD, Breitner JC, Psaty BM, Fitzpatrick AL, Lopez OL, Newman AB, Hazzard WR, Zandi PP, Burke GL, Lyketsos CG, Bernick C, Kuller LH (2005) Statin use and

the risk of incident dementia: the Cardiovascular Health Study. *Arch Neurol* **62**, 1047-1051.

[32] Szwast SJ, Hendrie HC, Lane KA, Gao S, Taylor SE, Unverzagt F, Murrell J, Deeg M, Ogunniyi A, Farlow MR, Hall KS (2007) Association of statin use with cognitive decline in elderly African Americans. *Neurology* **69**, 1873-1880.

[33] Zigman WB, Schupf N, Jenkins EC, Urv TK, Tycko B, Silverman W (2007) Cholesterol level, statin use and Alzheimer's disease in adults with Down syndrome. *Neurosci Lett* **416**, 279-284.

[34] Wolozin B, Wang SW, Li NC, Lee A, Lee TA, Kazis LE (2007) Simvastatin is associated with a reduced incidence of dementia and Parkinson's disease. *BMC Med* **5**, 20.

[35] Fischer P, Zehetmayer S, Jungwirth S, Weissgram S, Krampla W, Hinterberger M, Torma S, Rainer M, Huber K, Hoenigschnabl S, Gelpi E, Bauer K, Leitha T, Bauer P, Tragl KH (2008) Risk factors for Alzheimer dementia in a community-based birth cohort at the age of 75 years. *Dement Geriatr Cogn Disord* **25**, 501-507.

[36] Cramer C, Haan MN, Galea S, Langa KM, Kalbfleisch JD (2008) Use of statins and incidence of dementia and cognitive impairment without dementia in a cohort study. *Neurology* **71**, 344-350.

[37] Sparks DL, Kryscio RJ, Sabbagh MN, Connor DJ, Sparks LM, Liebsack C (2008) Reduced risk of incident AD with elective statin use in a clinical trial cohort. *Curr Alzheimer Res* **5**, 416-421.

[38] Arvanitakis Z, Schneider JA, Wilson RS, Bienias JL, Kelly JF, Evans DA, Bennett DA (2008) Statins, incident Alzheimer disease, change in cognitive function, and neuropathology. *Neurology* **70**, 1795-1802.

[39] Smeeth L, Douglas I, Hall AJ, Hubbard R, Evans S (2009) Effect of statins on a wide range of health outcomes: a cohort study validated by comparison with randomized trials. *Br J Clin Pharmacol* **67**, 99-109.

[40] Haag MD, Hofman A, Koudstaal PJ, Stricker BH, Breteler MM (2009) Statins are associated with a reduced risk of Alzheimer disease regardless of lipophilicity. The Rotterdam Study. *J Neurol Neurosurg Psychiatry* **80**, 13-17.

[41] Solomon A, Sippola R, Soininen H, Wolozin B, Tuomilehto J, Laatikainen T, Kivipelto M (2010) Lipid-lowering treatment is related to decreased risk of dementia: a population-based study (FINRISK). *Neurodegener Dis* **7**, 180-182.

[42] Li G, Shofer JB, Rhew IC, Kukull WA, Peskind ER, McCormick W, Bowen JD, Schellenberg GD, Crane PK, Breitner JC, Larson EB (2010) Age-varying association between statin use and incident Alzheimer's disease. *J Am Geriatr Soc* **58**, 1311-1317.

[43] Hippisley-Cox J, Coupland C (2010) Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. *BMJ* **340**, c2197.

[44] Beydoun MA, Beason-Held LL, Kitner-Triolo MH, Beydoun HA, Ferrucci L, Resnick SM, Zonderman AB (2011) Statins and serum cholesterol's associations with incident dementia and mild cognitive impairment. *J Epidemiol Community Health* **65**, 949-957.

[45] Ancelin ML, Carriere I, Barberger-Gateau P, Auriacombe S, Rouaud O, Fourlanos S, Berr C, Dupuy AM, Ritchie K (2012) Lipid lowering agents, cognitive decline, and dementia: the three-city study. *J Alzheimers Dis* **30**, 629-637.

[46] Bettermann K, Arnold AM, Williamson J, Rapp S, Sink K, Toole JF, Carlson MC, Yasar S, Dekosky S, Burke GL (2012) Statins, risk of dementia, and cognitive function: secondary analysis of the ginkgo evaluation of memory study. *J Stroke Cerebrovasc Dis* **21**, 436-444.

[47] Corrao G, Ibrahim B, Nicotra F, Zambon A, Merlino L, Pasini TS, Catapano AL, Mancia G (2013) Long-term use of statins reduces the risk of hospitalization for dementia. *Atherosclerosis* **230**, 171-176.
[48] Chou CY, Chou YC, Chou YJ, Yang YF, Huang N (2014) Statin use and incident dementia: a nationwide cohort study of Taiwan. *Int J Cardiol* **173**, 305-310.
[49] Wu CK, Yang YH, Lin TT, Tsai CT, Hwang JJ, Lin JL, Chen PC, Chiang FT, Lin LY (2015) Statin use reduces the risk of dementia in elderly patients: a nationwide data survey and propensity analysis. *J Intern Med* **277**, 343-352.
[50] Chitnis AS, Aparasu RR, Chen H, Kunik ME, Schulz PE, Johnson ML (2015) Use of Statins and Risk of Dementia in Heart Failure: A Retrospective Cohort Study. *Drugs Aging* **32**, 743-754.
[51] Zissimopoulos JM, Barthold D, Brinton RD, Joyce G (2017) Sex and Race Differences in the Association Between Statin Use and the Incidence of Alzheimer Disease. *JAMA Neurol* **74**, 225-232.
[52] Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, Breteler MM (1999) Diabetes mellitus and the risk of dementia: The Rotterdam Study. *Neurology* **53**, 1937-1942.
[53] Xu WL, Qiu CX, Wahlin A, Winblad B, Fratiglioni L (2004) Diabetes mellitus and risk of dementia in the Kungsholmen project: a 6-year follow-up study. *Neurology* **63**, 1181-1186.
[54] Parikh NM, Morgan RO, Kunik ME, Chen H, Aparasu RR, Yadav RK, Schulz PE, Johnson ML (2011) Risk factors for dementia in patients over 65 with diabetes. *Int J Geriatr Psychiatry* **26**, 749-757.
[55] Huang CC, Chung CM, Leu HB, Lin LY, Chiu CC, Hsu CY, Chiang CH, Huang PH, Chen TJ, Lin SJ, Chen JW, Chan WL (2014) Diabetes mellitus and the risk of Alzheimer's disease: a nationwide population-based study. *PLoS One* **9**, e87095.
[56] Heneka MT, Fink A, Doblhammer G (2015) Effect of pioglitazone medication on the incidence of dementia. *Ann Neurol* **78**, 284-294.
[57] Orkaby AR, Cho K, Cormack J, Gagnon DR, Driver JA (2017) Metformin vs sulfonylurea use and risk of dementia in US veterans aged >/=65 years with diabetes. *Neurology* **89**, 1877-1885.