ARTICLE

Investigation of antihypertensive class, dementia, and cognitive decline

A meta-analysis

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Abstract

Objective

High blood pressure is one of the main modifiable risk factors for dementia. However, there is conflicting evidence regarding the best antihypertensive class for optimizing cognition. Our objective was to determine whether any particular antihypertensive class was associated with a reduced risk of cognitive decline or dementia using comprehensive meta-analysis including reanalysis of original participant data.

Methods

To identify suitable studies, MEDLINE, Embase, and PsycINFO and preexisting study consortia were searched from inception to December 2017. Authors of prospective longitudinal human studies or trials of antihypertensives were contacted for data sharing and collaboration. Outcome measures were incident dementia or incident cognitive decline (classified using the reliable change index method). Data were separated into mid and late-life (>65 years) and each antihypertensive class was compared to no treatment and to treatment with other antihypertensives. Meta-analysis was used to synthesize data.

Results

Over 50,000 participants from 27 studies were included. Among those aged >65 years, with the exception of diuretics, we found no relationship by class with incident cognitive decline or dementia. Diuretic use was suggestive of benefit in some analyses but results were not consistent across follow-up time, comparator group, and outcome. Limited data precluded meaningful analyses in those ≤65 years of age.

Conclusion

Our findings, drawn from the current evidence base, support clinical freedom in the selection of antihypertensive regimens to achieve blood pressure goals.

Clinical trials registration

The review was registered with the international prospective register of systematic reviews (PROSPERO), registration number CRD42016045454.

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Glossary

ACE-I = angiotensin-converting enzyme inhibitors; **AHM** = antihypertensive medication; **ARB** = angiotensin receptor blockers; **BB** = β-blockers; **BP** = blood pressure; **CCB** = calcium channel blockers; **CI** = confidence interval; **DSM-III-R** = *Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised*; **DSM-IV** = *Diagnostic and Statistical Manual of Mental Disorders, 4th edition*; **MMSE** = Mini-Mental State Examination; **OR** = odds ratio; **RCI** = reliable change index; **RCT** = randomized controlled trial; **SBP** = systolic blood pressure.

Dementia is a major public health problem affecting around 50 million individuals worldwide. A new case is diagnosed every 3 seconds and prevalence is estimated to rise to 131.5 million cases by 2050.[1] High blood pressure (BP) is widely recognized as one of the main modifiable risk factors for dementia.[2–5] Even though BP-lowering treatment is readily available, we lack clinical hypertension guidelines for the management of brain health. This reflects in part the conflicting evidence on the best antihypertensive class for optimizing cognitive outcomes and reducing risk of dementia, with some classes, e.g., calcium channel blockers, thought to have a pleiotropic neuroprotective effect beyond BP-lowering.[3,4,6–14] Existing meta-analyses are limited because information is lost with pooling of published results that conflate data across different age groups (mid and late-life); lack data on minimum length of exposure to antihypertensive class; adjust for differing confounders; use differing statistical measures, variable definitions of cognitive outcomes, and varied lengths of follow-up; and combine treated and untreated comparator groups.[11–14] We have conducted a two-stage individual participant data meta-analysis examining antihypertensive class using standardized measures across studies and subsequent meta-analysis. Data from 56,866 participants drawn from 27 studies were synthesized to evaluate the relationship between each antihypertensive class and incident cognitive decline and dementia.

Methods

Data sources and searches

To identify studies for inclusion in this systematic review and meta-analysis, the databases MEDLINE, MEDLINE In-Process, Embase, and PsycINFO were searched from inception to December 2017. The search terms used were (dementia or cognit* or mild cognitive impairment or Alzheimer disease or dementia vascular or dementia multi-infarct) and (antihypertensives or antihypertensive agents or diuretic or diuretics or thiazide or thiazide-like or calcium channel blocker or calcium channel blockers or calcium antagonist or angiotensin-converting enzyme inhibitor or angiotensin-converting enzyme inhibitors or ACE inhibitors or angiotensin receptor blocker or angiotensin receptor blockers or ARB or β-blocker or adrenergic β-antagonist). Details of the search strategy are given in appendix e-A (doi.org/10.5061/dryad.t9n4n3p). Reference lists and lists of studies contained within established study consortia relating to cognitive outcomes were screened for potentially relevant published articles and studies. Experts in the field were also consulted and searches were carried out for relevant trials using the following sources:

- Cochrane database from 1980 to date of search
- ISRCTN Register (international registry of trials and studies)
- ClinicalTrials.gov

The lead reviewer (R.P.) carried out the literature searches. All identified abstracts, or titles where abstracts were unavailable, were double-read and a list of potentially relevant evidence compiled independently by each of the 2 reviewers (R.P., J.P.). The lists were compared with differences resolved by discussion. Once the list of possible publications was agreed upon, full texts of relevant documents were independently read and assessed for relevance. To minimize the effect of publication bias, a list of potentially eligible studies was also compiled by examining those included in preexisting consortia, i.e., collaborative groups of longitudinal studies with a focus on cognitive outcomes. Publications, protocols, and web information were searched for each of the studies in the consortia to identify whether they might have suitable data for inclusion. The lead or corresponding author from each publication/study was then contacted and asked to provide raw data or aggregate data summaries, using a standard template, for use in a study-level meta-analysis.

Study selection

Inclusion criteria

- Prospective longitudinal studies or trials of antihypertensives with data on antihypertensive class, a comparator group, and with a mean follow-up ≥1 year
- Objective assessment of cognitive function on at least 2 occasions or assessment of dementia as an outcome using standard diagnostic or research criteria
- Human studies

Exclusion criteria

- Non-English publications (in the absence of resources for translation)
- Studies solely using medical record databases
- Studies in populations with cognitive impairment

Data extraction, harmonization, and reduction in risk of bias

Exposure to an antihypertensive medication (AHM) class was present if recorded over a minimum of a 12-month period, based on individual study records of antihypertensive drug use.

AHM classes were defined as calcium channel blockers (CCB), angiotensin-converting enzyme inhibitors (ACE-I), diuretics, β-blockers (BB), and angiotensin receptor blockers (ARB).

Participants with a diagnosis of dementia or cognitive impairment at baseline were excluded. Incident cognitive decline was assessed using the reliable change index (RCI) using the Chelunes method.[15] Since the cognitive data are drawn from different populations and with some variation in repeat testing times, this method allows standardization of reliable decline across cognitive tests with a fall in the RCI value greater than 1.645, i.e., changes exceeding the 90% confidence interval (CI) for RCI categorized as reliable. Follow-up cognitive testing was required to be after the minimum 1 year AHM exposure period and cognitive change was assessed subsequent to or concurrent with this. Cognitive tests were categorized as screening tests and tests of memory, executive function, attention, and speed of processing. Incident dementia was classified as present or absent. Dementia type was not considered because of the high likelihood of mixed pathology.

As the relationship between BP and cognitive function may differ in mid and late life,[3–5] data were dichotomized by age into (late-life) >65 years at baseline vs (midlife) ≤65 years. To reduce risk of bias from short follow-up, lag periods of 1 and 5 years were used such that data were separated into those with follow-up durations of ≥1 or ≥5 years. The requirement for a minimum follow-up period reduces the risk of inadvertently including prevalent cases. Where study visit frequency meant that all participants had ≥5 years follow-up, i.e., participants were only seen at intervals of 5 or more years, these were included in the latter category. The analyses for each study dataset followed the same procedure.

Data synthesis and analyses

Meta-analyses were conducted for the endpoints of both cognitive decline and dementia.

Each antihypertensive class was examined separately;

- Compared to no AHM or placebo
- Compared to other AHMs (cohort studies)

In addition, those taking any AHM (all classes) were

- Compared to no treatment (cohort studies)
- Compared to placebo (clinical trials)

Because cognitive change is insidious, classification of event dates is problematic for cognitive outcomes. To reduce bias associated with different study designs and varied duration between cognitive assessments, logistic regression models were used with incident cognitive decline or dementia as the dependent variable. Since the effect of AHM class on cognitive function is thought to be pleiotropic, models examining class were adjusted at study level for baseline systolic BP or, where this was unavailable, for the presence of hypertension at baseline, plus age, sex, and education. Adjusted results were combined to produce a pooled odds ratio (OR). Raw data relating to the number of cases and controls for each class were also combined to produce an unadjusted pooled ratio. Forest plots were used to show study level and pooled ratios.

To evaluate bias due to participant loss by AHM class, the effect of baseline AHM class on later mortality or dropout was also examined using logistic regression. These analyses were adjusted for baseline systolic BP or presence of hypertension, age, sex, and education.

Random effects models were used for meta-analyses, regardless of heterogeneity measured by I^2, since the studies were drawn from a range of populations. Where only one study was available for a particular analysis, no meta-analysis could be carried out and results were not reported. The I^2 statistic and Egger test were used to examine heterogeneity and publication bias, respectively.

Finally, to broadly examine the role of study-level characteristics, study OR for the comparison between AHM and no treatment or placebo were plotted against the primary decade of recruitment and percentage of participants who were female, and additional multilevel regression models were run with study OR as the dependent variable. In addition, because of potential differences in the relationship between hypertension and cognitive outcomes by sex, analyses comparing AHM to no treatment or placebo were rerun separately for male and female participants.

Standard protocol approvals, registrations, and patient consents

The review was registered with the international prospective register of systematic reviews (PROSPERO), registration number CRD42016045454. Ethical approval was obtained from the Science and Medical Human Research Medical Committee (DERC). Australian National University approval (reference 2016/500) was granted September 23, 2016. Analyses were carried out using SAS v9.3 and StatsDirect v3.0.198.

Data availability

Data availability depends on agreement from each of the participating studies subject to their regulatory requirements and appropriate data sharing arrangements.

Results

Study characteristics

A pool of 2,429 abstracts was screened and 82 articles were examined at the full-text stage. Of these, articles reporting on 27 studies were retained. Thirty-seven additional potential studies were identified from consortia and expert recommendation (figure e-1, doi.org/10.5061/dryad.t9n4n3p). Of the 64

studies, 5 held no relevant data or indicated that data were no longer maintained[16–20]; 27 studies[7–9,21–46] contributed data (table e-1, doi.org/10.5061/dryad.t9n4n3p); and 28 studies did not participate. Reasons for nonparticipation included a lack of valid email contact or no response to inquiries and 4 declined to provide data. There were no evident differences in study design, proportion of study type, population, or region of recruitment between the studies that agreed and those that did not participate. Of those where data were unavailable, 20 were observational studies, 8 were trials, and populations were from Europe, America, Asia, and Australia.

Of the 27 that agreed, 21 were observational cohort studies (14 population-based and 7 selected cohorts), 6 were trials; 2[22,36] were clinical trials treated as cohort studies (where the randomized intervention was not an antihypertensive agent and where randomized groups had no significant effect on cognitive outcomes) and 4[7–9,39] were randomized controlled trials (RCTs) of antihypertensive treatment. Studies represented populations from Europe,[7,8,24,27,28,31–38,40–45] America,[21–23,26,29,39,42] Australia,[25,30,43] and Asia.[8,9,46] In total, there were 43,049 participants from cohort studies and 13,817 from clinical trials with ≥1 year follow-up and without prevalent dementia at baseline (table e-1, doi.org/10.5061/dryad.t9n4n3p). Mean baseline age in the sampled studies ranged from 57.0 (SD ±5.2)[24] to 93.0 (SD ±2.6)[26] years with the mean age of participants in the majority of participating studies[7,21–23,26,27,29,31,33,37,39–43] in the range 70 to 79 years. Mean baseline systolic BP (SBP) was in the normotensive range (≤140 mm Hg) for 8 studies,[21–26,44–46] between 140 and 159 mm Hg for 13 studies,[8,27–38,43] and ≥160 mm Hg for 3 studies.[7,9,39] For 3 studies,[40–42] baseline BP was not available. Twenty-four studies[7–9,21–23,25–31,33–45] contributed data on those aged >65 years at baseline, and 9[7,8,24,25,28,32,39,44–46] had some data on those aged ≤65 years at baseline. Twenty-four studies[7–9,21–31,33–38,40,41,43–46] reported results for cognitive decline from the most commonly used screening test, the Mini-Mental State Examination (MMSE), and 17[7–9,22,26–29,31,33,34,36,37,39,41,42] reported results for incident dementia. Diagnosis of dementia was based on DSM-III-R or DSM-IV (n = 15),[7–9,22,24,26–29,31,33,34,36,37,39,41,42] Clinical Dementia Rating scale score ≥1 (n = 1),[23] or derived from standard diagnostic evaluation used in Finland (n = 1).[24] Ten studies[21,23,25,27,29,31–34,42,43] provided results of neuropsychological testing. Due to variation in the timing of study visits, baseline age, and data on exposure to antihypertensive class, and cognitive test or dementia outcome, the number of studies combined in each meta-analysis varied.

Late-life >65 years, incident dementia

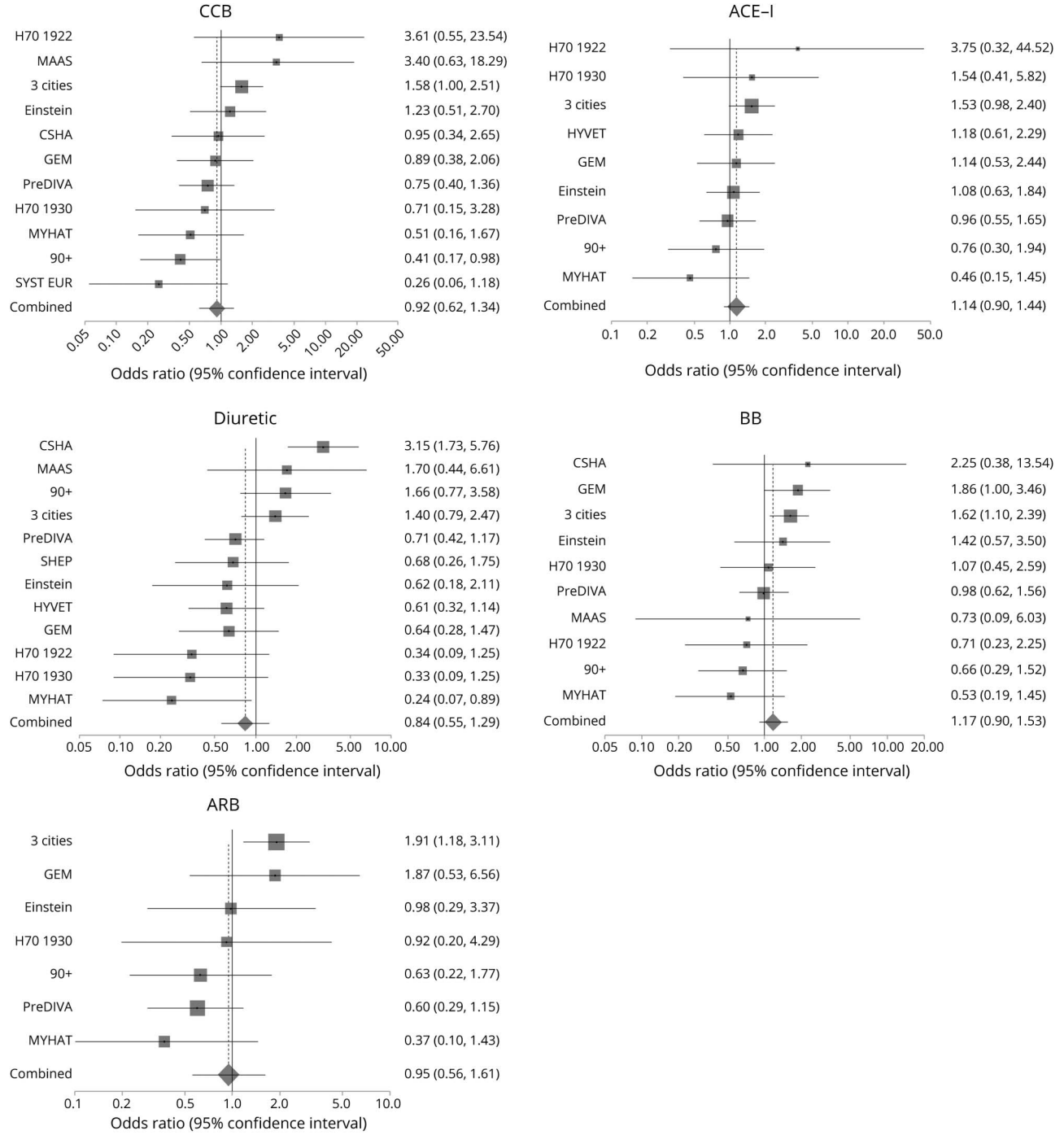
For those aged >65 years, we evaluated the effect of antihypertensive class compared to no antihypertensive treatment or placebo for incident dementia. After adjustment for age, sex, baseline SBP, and education, there was no association between CCB, ACE-I, BB, or ARB use and risk of developing dementia compared to those without treatment or with placebo and among studies with ≥5-year or ≥1-year follow-up (for ≥5-year follow-up, see table 1 and figure 1, and for ≥1-year follow-up, table e-2, doi.org/10.5061/dryad.t9n4n3p; and figure e-2, doi.org/10.5061/dryad.t9n4n3p; for full-size forest plots, see appendix e-B, doi.org/10.5061/dryad.t9n4n3p). Exposure to diuretics was associated with a statistically significant lower risk of incident dementia only in those with ≥1-year follow-up (OR 0.83; 95% CI 0.72–0.96), but not statistically significant in those with ≥5 years of follow-up (OR 0.84; 95% CI 0.55–1.29). Unadjusted results showed a similar association (table e-3, doi.org/10.5061/dryad.t9n4n3p).

Table 1 Combined risk ratios for each antihypertensive class compared to no treatment or placebo for participants aged >65 years with ≥5 years follow-up

	Antihypertensive class				
	CCB	**ACE-I**	**ARB**	**Diuretic**	**BB**
Risk of developing dementia, pooled OR (95% CI)[a]	0.92 (0.62–1.34)	1.14 (0.90–1.44)	0.95 (0.56–1.61)	0.84 (0.55–1.29)	1.17 (0.90–1.53)
No. of cohorts included	11	9	7	12	10
I^2 measure of heterogeneity, %	42	0	51.6	67.7	18.9
Publication bias, Egger test	$p = 0.5284$	$p = 0.7046$	$p = 0.2432$	$p = 0.1609$	$p = 0.2671$
Risk of developing cognitive decline as measured using the MMSE, pooled OR (95% CI)[a]	0.87 (0.66–1.15)	0.92 (0.66–1.29)	0.96 (0.67–1.39)	0.81 (0.59–1.12)	0.97 (0.70–1.35)
No. of cohorts included	16	11	8	16	13
I^2 measure of heterogeneity, %	0	12.1	0	33.7	32.8
Publication bias, Egger test	$p = 0.6726$	$p = 0.9241$	$p = 0.17$	$p = 0.4881$	$p = 0.8862$

Abbreviations: ACE-I = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; BB = β-blockers; CCB = calcium channel blockers; CI = confidence interval; MMSE = Mini-Mental State Examination; OR = odds ratio.
[a] Adjusted for sex, age, baseline systolic blood pressure, and education. Additional adjustment for ethnic group in the Einstein Aging Study.

Figure 1 Forest plots showing odds ratios for risk of developing dementia by exposure to each antihypertensive class compared to no treatment in participants aged over 65 years with ≥5 years follow-up



[a]Adjusted for sex, age, baseline systolic blood pressure, and education. Additional adjustment for ethnic group in the Einstein Aging Study. ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = β-blocker; CCB = calcium channel blocker; CSHA = Canadian Study of Health and Ageing; GEM = Ginkgo Evaluation and Memory trial; HYVET = Hypertension in the Very Elderly Trial; MAAS = Maastricht Ageing Study; MYHAT = Monongahela Valley Independent Elders Survey; PreDIVA = Prevention of Dementia by Intensive Vascular Care; *Syst-Eur* = Systolic Hypertension in Europe.

An additional comparison between each antihypertensive class and those receiving any other antihypertensive treatment (cohort studies only) found no association between antihypertensive class, CCB, ACE-I, BB, ARB, or diuretic and risk of developing dementia in those with ≥5-year or ≥1-year follow-up (table 2 and table e-4, doi.org/10.5061/dryad.t9n4n3p).

Late life, >65 years, incident cognitive decline

We evaluated the effect of antihypertensive class compared to no antihypertensive treatment or placebo for incident cognitive decline. For incident cognitive decline using the RCI of the MMSE, results were not statistically significant for those with ≥5-year or ≥1-year follow-up for any drug

Table 2 Pooled odds ratios (ORs) for risk of dementia and cognitive decline comparing exposure to each antihypertensive drug class with exposure to other drug classes in participants with ≥5 years follow-up and aged >65 years

	Antihypertensive class				
	CCB	**ACE-I**	**ARB**	**Diuretic**	**BB**
Risk of developing dementia, pooled OR (95% CI)[a]	0.76 (0.48–1.20)	1.01 (0.74–1.37)	0.93 (0.63–1.37)	0.75 (0.41–1.37)	1.13 (0.86–1.48)
No. of cohorts included	9	7	6	9	9
I^2 measure of heterogeneity, %	43.3	0	7.9	63.9	0
Publication bias, Egger test	$p = 0.5318$	$p = 0.0362$	$p = 0.8833$	$p = 0.399$	$p = 0.2906$
Risk of developing cognitive decline as measured using the MMSE, pooled OR (95% CI)[a]	0.83 (0.61–1.12)	0.93 (0.67–1.28)	1.14 (0.76–1.72)	0.69 (0.51–0.92)	1.14 (0.87–1.48)
No. of cohorts included	12	9	6	12	11
I^2 measure of heterogeneity, %	0	0	0	0	0
Publication bias, Egger test	$p = 0.3596$	$p = 0.7415$	$p = 0.2331$	$p = 0.3748$	$p = 0.7175$

ACE-I = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; BB = β-blockers; CCB = calcium channel blockers; CI = confidence interval; MMSE = Mini-Mental State Examination.
[a] Adjusted for sex, age, baseline systolic blood pressure, or presence of hypertension and education. Additional adjustment for ethnic group in the Einstein Aging Study.

classes (table 1 and table e-2, doi.org/10.5061/dryad.t9n4n3p; figure 2 and figure e-3, doi.org/10.5061/dryad.t9n4n3p; full-size forest plots in appendix e-B, doi.org/10.5061/dryad.t9n4n3p). Unadjusted results were similar (table e-3, doi.org/10.5061/dryad.t9n4n3p). Each antihypertensive class was also compared to those receiving any other antihypertensive treatment (cohort studies only). For incident cognitive decline measured using the RCI of the MMSE, results for CCB, ACE-I, ARB, and BB were similarly not statistically significant for ≥1 or ≥5 years follow-up. Exposure to diuretics was associated with a decreased risk of incident cognitive decline in those with ≥5 years of follow-up (OR 0.69; 95% CI 0.51–0.92) but not in those with ≥1 year of follow-up (OR 0.98; 95% CI 0.82–1.18) (table 2 and table e-4, doi.org/10.5061/dryad.t9n4n3p). Unadjusted results were similar (table e-5, doi.org/10.5061/dryad.t9n4n3p).

Data for further analyses per cognitive domain were available for a subset of cohorts and sufficient to allow meta-analyses for the cognitive domains of memory and attention but not for speed of processing or executive function. For memory, BB use was associated with an increased risk of decline in those with ≥1-year follow-up pooled ratio (OR 1.53; 95% CI 1.04–2.27). There were no further statistically significant associations between AHM class and incident decline in memory or attention measures (table e-6, doi.org/10.5061/dryad.t9n4n3p).

Midlife ≤65 years

Fewer data were available in the ≤65 age group. No discernible pattern of results was evident for the differing antihypertensive classes (table e-7, doi.org/10.5061/dryad.t9n4n3p).

Heterogeneity and publication bias

Point estimates varied considerably in direction and magnitude per study (figures 1 and 2 and figures e-2 and e-3, doi.org/10.5061/dryad.t9n4n3p). Heterogeneity in the meta-analyses ranged from 0% to 67.7% (tables 1 and 2 and tables e-2 and e-3, doi.org/10.5061/dryad.t9n4n3p), but publication bias measured by Egger test was only observed for BB compared to the untreated population for dementia in those with ≥1-year follow-up ($p = 0.0471$) and for ACE-I compared to those with other antihypertensive treatment for dementia in those with ≥5 years of follow-up ($p = 0.0362$). Overall, there were no consistent patterns for either dementia or cognitive decline outcomes.

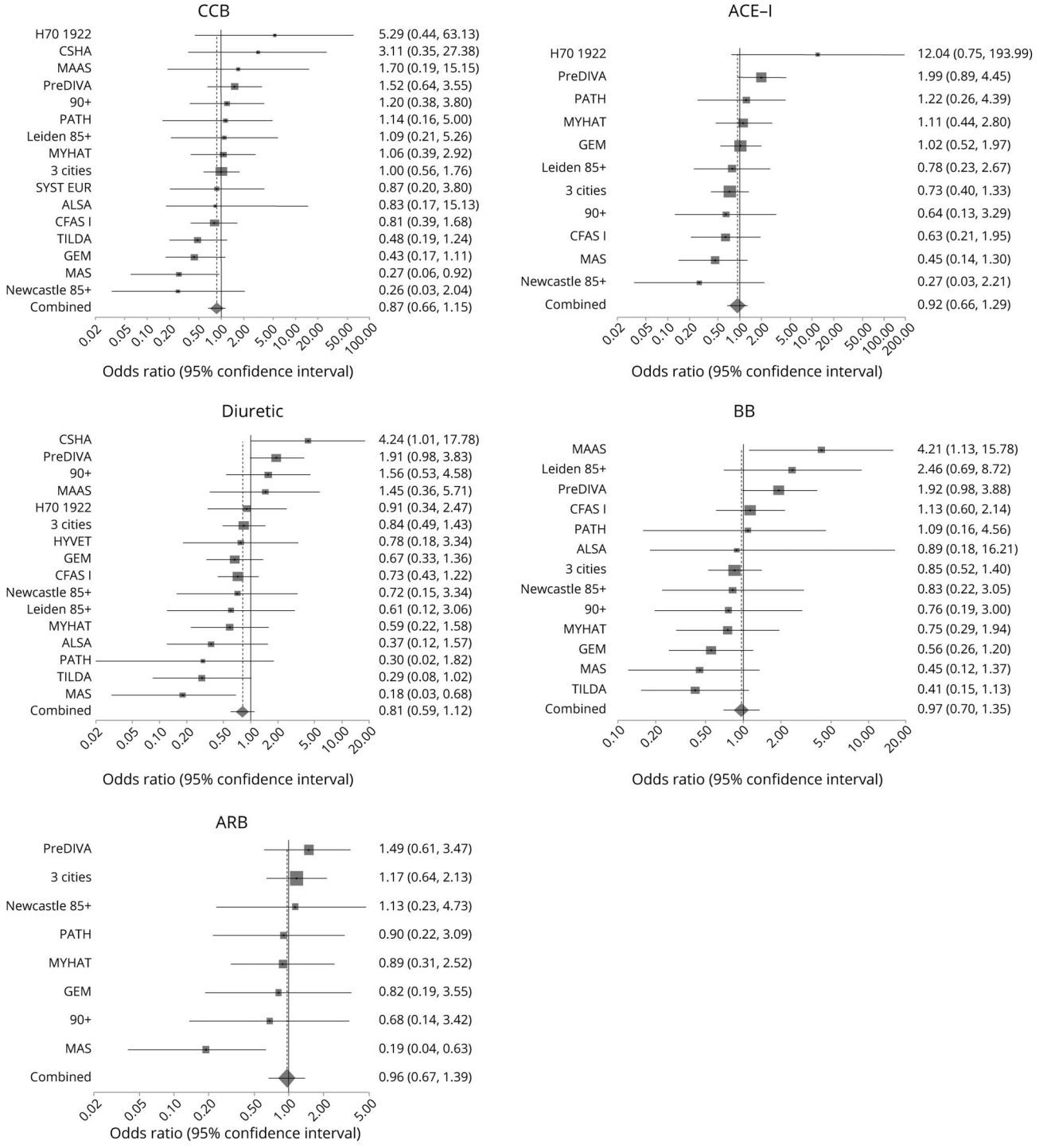
Mortality and attrition by antihypertensive class

Additional analyses were performed to assess whether there was an association between baseline AHM class and risk of death or dropout. OR for the outcomes death and dropout (combined) for the different AHM classes adjusted for age, sex, education, and baseline SBP or, where this was unavailable, for presence of hypertension at baseline, were as follows: diuretics, OR 0.95 (95% CI 0.79–1.13); BB, OR 0.98 (95% CI 0.86–1.12); CCB, OR 0.93 (95% CI 0.76–1.13); ACE-I, OR 1.04 (95% CI 0.94–1.16); and ARB, OR 0.79 (95% CI 0.63–1.00). For some studies, data were available for either dropout or death but not both. Results did not change when the analyses were rerun excluding these studies.

Secondary analyses: Antihypertensive treatment compared to placebo or no treatment

Secondary analysis was carried out to examine the relationship between any AHM use (a minimum of 12 months

Figure 2 Forest plots showing odds ratios for risk of developing cognitive decline by exposure to each antihypertensive class compared to no treatment in participants aged over 65 years with ≥5 years follow-up



[a]Adjusted for sex, age, baseline systolic blood pressure, and education. [b]Cognitive decline classified using the reliable change index and a deterioration in the cognitive screening test, the Mini-Mental State Examination. ACE-I = angiotensin-converting enzyme inhibitor; ALSA = Australian Longitudinal Study of Aging; ARB = angiotensin receptor blocker; BB = β-blocker; CCB = calcium channel blocker; CFAS = Cognitive Function and Ageing Studies; CSHA = Canadian Study of Health and Ageing; GEM = Ginkgo Evaluation and Memory trial; HYVET = Hypertension in the Very Elderly Trial; MAAS = Maastricht Ageing Study; MAS = Sydney Memory and Ageing Study; MYHAT = Monongahela Valley Independent Elders Survey; PATH = Personality and Total Health study; PreDIVA = Prevention of Dementia by Intensive Vascular Care; *Syst-Eur* = Systolic Hypertension in Europe; TILDA = Irish Longitudinal Study on Ageing.

exposure) as compared to no treatment (cohorts) and to placebo (trials) for both incident dementia and cognitive decline.

In those aged >65 years, analysis of the cohort studies found no significant associations between AHM use and incident dementia or cognitive decline (MMSE RCI) in those with

≥1-year or ≥5-year follow-ups, adjusted for age, sex, education, and baseline SBP or presence of hypertension. Further analyses in a subset of 10 cohorts adjusting only for age, sex, and education to avoid overadjustment for BP did not change conclusions. In RCTs, there were no statistically significant associations between AHM use in RCT populations with ≥1-year follow-up and either incident dementia or cognitive decline (table e-8, doi.org/10.5061/dryad.t9n4n3p). However with ≥5 years of follow-up, AHM use was associated with a 35% lower risk of developing dementia in the fully adjusted pooled ratio (OR 0.65; 95% CI 0.51–0.82), but the association was not statistically significant with the risk of incident cognitive decline (OR 0.44; 95% CI 0.15–1.25).

In those aged ≤65 years, 2 cohort studies were available to compare antihypertensive treatment with no treatment or placebo and could be combined for the outcome of dementia in those with ≥5 years of follow-up (pooled OR 0.79; 95% CI, 0.43–1.48). Four cohorts were similarly pooled for the outcome of incident cognitive decline in those with ≥5 years of follow-up (pooled OR 1.00; 95% CI 0.60–1.67) and 2 cohorts for cognitive decline in those with ≥1 year of follow-up (pooled OR 1.15; 95% CI 0.81–1.64). There were 2 RCTs with data available for cognitive decline in those with ≥1 year of follow-up (pooled OR 0.91; 95% CI 0.57–6.42). There were no data to examine dementia outcomes in those with ≥1 year of follow-up.

Results for AHM treatment compared to no treatment were different for RCTs and cohort studies, and the RCTs reported the highest baseline SBP. It is possible that RCTs, despite the placebo effect, have had comparator untreated populations at higher risk than untreated populations in the cohort studies. Where data were available, the cohort studies in general reported only small to moderate differences between mean baseline BP in their treated and untreated populations. This suggests the possibility of some degree of successful BP control over time in the treated group, at least in some of the cohorts.

Sensitivity analyses

There were no clear patterns in findings or significant relationships by study type for those that were not trials of antihypertensives or when the OR of the participating study samples were plotted against decade of recruitment or percentage of female participants (appendix e-C, doi.org/10.5061/dryad.t9n4n3p). Furthermore, rerunning the treated and untreated comparison by sex in those >65 years showed no differences for men and women (table e-9, doi.org/10.5061/dryad.t9n4n3p).

Discussion

In this standardized comprehensive analysis examining the associations between AHM class and incident dementia or cognitive decline, we found no consistent pattern of evidence to support the benefit of one AHM class over another. In those aged >65 years, use of diuretics was associated with a reduced risk, but this was not consistent across cognitive outcomes (dementia, cognitive decline), comparator group (no treatment or treatment with other antihypertensives), or length of follow-up (≥1 or ≥5 years). To be specific: (1) diuretic use compared to no AHM or placebo was not associated with a reduced risk of cognitive decline and was only associated with a reduced risk of dementia in those with ≥1 but not ≥5 years of follow-up; and (2) diuretic use compared to other AHM was not associated with a reduced risk of dementia and was only associated with a reduced risk of cognitive decline (MMSE) in those with ≥5 but not ≥1 year of follow-up. Use of BB compared to no AHM was associated with an increased risk of decline in memory in a subset of 7 cohorts with available data in those with ≥1 year of follow-up only and showed no relationship with incident dementia or general cognitive decline. Secondary analyses found AHM to be associated with a reduced risk of dementia and cognitive decline compared to placebo in hypertensive clinical trial populations with ≥5 years of follow-up. No association was observed in cohort studies.

Evidence in context

To our knowledge, this study is the first of its kind examining the effect of antihypertensive drug class on cognitive outcomes using reanalyzed individual data standardized across and assembled from individual studies. Similarly, it is the first, to our knowledge, that uses standardized measures of cognitive decline; looks separately at midlife and late life; requires a minimum exposure to antihypertensive treatment; and examines both short- and longer-term follow-up as recommended for the robust evaluation of incident dementia.[10]

The association between diuretics and reduced risk of cognitive decline or dementia is promising. However, given the variation in results from the individual studies and the lack of any consistently clear finding across cognitive outcomes, these results should be interpreted with caution. Furthermore, as one of the earlier classes of drug, diuretics may have been used more frequently as first-line treatment. As such, they may disproportionately represent those more recently diagnosed with hypertension or those with lower severity or chronicity of hypertension, which may have been associated with relatively lower disk of cognitive decline and dementia. The absence of a clear benefit of one antihypertensive class over another is congruent with the cardiovascular literature[47] and the mixed nature of the current evidence base. For example, the cognitive function literature has reported on different combinations of singular and multiple antihypertensive classes and found varyingly in favor of diuretics,[12] ARB,[13,14] ACE-I,[13,14] CCB,[11] and BB[48] without the evidence coalescing consistently in favor of one particular class.

Regarding AHM as a group, our meta-analyses that compared treated and untreated groups reported a significant result only in the RCT data of those with ≥5 years of follow-up. This is congruent with, but larger than, the reductions seen in the existing literature.[9] One explanation for the lack of a finding in cohort studies could be the comparison of a higher-risk already-treated group with a lower-risk untreated

normotensive comparator group. That is not to imply that further reduction in BP would not result in a lowering of risk, as has recently been suggested in the Systolic Blood Pressure Intervention Trial–Memory and Cognition in Decreased Hypertension (SPRINT-MIND),[49] although of course close monitoring would be needed to avoid excessive lowering and potential harm. It is also possible that there are differences in the decision-making of participants when choosing to enter intervention studies compared with non-intervention-based cohort studies, leading to representation of different population groups, neither of which may be representative of the general population. There were, moreover, relatively few studies with data from the midlife age group or with domain-specific neuropsychological outcomes (which are arguably more robust than the MMSE). In addition, a recent study has suggested that genetic risk may influence the relationship between AHM, specifically ACE-I, and cognitive outcomes[50] and should therefore be taken into account, but these data were unavailable for our analyses.

Strengths and limitations

Prior systematic reviews, observational studies, and clinical trials reporting on antihypertensive class and cognition have risked bias due to inclusion of participants without requirement for any minimum follow-up or minimum exposure to a particular class, without separation of participants from mid and late-life, and often without standardization of cognitive decline. Unlike prior work, strengths of this study include (1) minimizing the risk of publication bias by deriving data from systematic literature searches and preexisting consortia; (2) combining data from a large number of participants across a wide geographical range of studies, maximizing the inclusion of relevant data; (3) standardization of exposure to antihypertensive classes (minimum exposure 1 year); (4) separation of data into exposure in mid and late-life age groups (>65, ≤65 years); (5) requirement of a minimum follow-up/lag period (≥1 and ≥5 years), i.e., excluding those who were followed for less than 12 months; (6) standardization of cognitive decline across varied time periods and taking account of variation within each sample; (7) standardization of statistical methods and available covariates; (8) use of both unadjusted and adjusted results; (9) comparison of each class against no treatment and against other antihypertensive treatment; and (10) a low level of heterogeneity in the analyses.

Limitations include a potential differential dropout or survivor bias in normotensive or controlled hypertensive participants; nevertheless, there was no association between baseline AHM class and subsequent dropout or death, suggesting no particular bias by class for inclusion in these longitudinal analyses. There was a lack of data available on individual drug or drug subclass and dose, reasons for prescription choice, and, as is common to all such observational studies and most clinical trials, an unavoidable overlap between classes, where participants are prescribed additional classes as needed to control their BP. However, if pleiotropic effects were present by class, they might be expected to be shown regardless. Furthermore, there is no strong evidence as yet to suspect that any pleiotropic effect by class would manifest only in a subpopulation, and our results show no obvious pattern by age, sex, or decade of study recruitment. Further limitations include the inevitable use of a general cognitive screening instrument, the MMSE, which although allowing us comparability across studies is far from the sophisticated neuropsychological testing that would ideally be used to measure cognitive change. The classification or diagnosis of cognitive decline and dementia during a disease process with insidious onset and progression is also inevitably open to bias in any study and particularly where data are maximized in a combined study such as ours. Pragmatic use of the RCI and standardized dementia diagnoses for binary outcomes without taking time to event into account is the most robust option but may lose some of the subtleties available within individual cohorts.

Future perspectives

Outstanding questions remain and future research should investigate whether the results would differ had we been able to take fuller account of the changing relationships among BP, treatment, aging, and cognition using a life-course approach and had had access to further data from those younger than ≤65 years or examined those with existing cognitive impairment. It is also unclear whether there are selected drugs or subclasses that have particular protective or detrimental effects on cognition and the current studies were not equipped with sufficient detail to examine this. Future clinical trials could investigate this in detail using careful single drug comparisons and comprehensive neuropsychological testing. Furthermore, despite the positive results we found from the clinical trial samples we included, there has been no clinical trial designed primarily to test the effect of BP-lowering on cognitive function. This remains a crucial gap in the evidence base.

Our findings show some support for the message that lowering BP may lower dementia risk while also supporting clinical freedom in the selection of antihypertensive regimens to achieve BP goals.

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R.P., S.Y., and K.J.A. conceived of and designed the research. Individual authors are responsible for the design and delivery of the constituent studies. R.P. and authors from the individual studies performed the analyses; data aggregation was by R.P.

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Publication history

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Sevil Yasar, PhD	Johns Hopkins University	Author	Conceived and designed the study, finalized study design and delivery, contributed to the design or analysis for contributing study, commented on the manuscript
Craig S. Anderson, PhD	The George Institute for Global Health, Faculty of Medicine, UNSW, Australia	Author	Contributed to the design or analysis for contributing study, commented on the manuscript
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Riitta Antikainen, PhD	University of Oulu, Finland	Author	Contributed to the design or analysis for contributing study, commented on the manuscript
Hisatomi Arima, PhD	Department of Preventive Medicine and Public Health, Fukuoka University, Japan	Author	Contributed to the design or analysis for contributing study, commented on the manuscript
Nigel Beckett, MD	Guys and St Thomas' NHS Foundation Trust, UK	Author	Contributed to the design or analysis for contributing study, commented on the manuscript
Joanne C. Beer, PhD	University of Pittsburgh	Author	Contributed to the design or analysis for contributing study, commented on the manuscript
Anne Suzanne Bertens, MD	Leiden University Medical Centre, the Netherlands	Author	Contributed to the design or analysis for contributing study, commented on the manuscript
Andrew Booth, PhD	University of Sheffield, UK	Author	Contributed to the design or analysis for contributing study, commented on the manuscript
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Appendix 1 *(continued)*

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Carol Brayne, MD	University of Cambridge, UK	Author	Contributed to the design or analysis for contributing study, commented on the manuscript
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Appendix 1 *(continued)*

Author	Location	Role	Contributions
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Continued

Appendix 1 *(continued)*

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Iris Rawtaer, MMed	National University of Singapore	Author	Contributed to the design or analysis for contributing study, commented on the manuscript
Edo Richard, PhD	Department of Neurology, Academic Medical Center, Amsterdam, and Department of Neurology, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, the Netherlands	Author	Contributed to the design or analysis for contributing study, commented on the manuscript
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Appendix 1 *(continued)*

Author	Location	Role	Contributions
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Appendix 1 *(continued)*

Author	Location	Role	Contributions
Jane Warwick, PhD	University of Warwick, UK	Author	Contributed to the design or analysis for contributing study, commented on the manuscript
Kaarin J. Anstey, PhD	Neuroscience Research Australia and University of New South Wales, Australia	Author	Finalized study design and delivery, contributed to the design or analysis for contributing study, commented on the manuscript

Appendix 2 Participating studies

Participating studies	Participating studies details
The Three-City Study	The Three-City Study is conducted under a partnership agreement among the Institut National de la Santé et de la Recherche Médicale (INSERM), the Institut de Santé Publique et Développement of the Bordeaux Segalen 2 University, and Sanofi-Aventis. The Fondation pour la Recherche Médicale funded the preparation and initiation of the study. The Three-City Study is also supported by the Caisse Nationale Maladie des Travailleurs Salariés, Direction Générale de la Santé, Mutuelle Générale de l'Education Nationale, Institut de la Longévité, Regional Governments of Aquitaine and Bourgogne, Fondation de France, and Ministry of Research–INSERM Programme "Cohortes et collections de données biologiques." This work was carried out with the financial support of the "ANR—Agence Nationale de la Recherche—The French National Research Agency" under the "Programme National de Recherche en Alimentation et Nutrition Humaine," project "COGINUT ANR-06-PNRA-005." Three-City Study supports are listed on the study website (www.three-city-study.com). The authors thank the study team and participants of the Three-City Study.
90+ Study	Supported by US funding awards R01 AG21055 and R01 AG042444. The authors thank the study team and participants of the 90+ Study.
Australian Longitudinal Study of Aging (ALSA)	The authors thank the study team and participants of the ALSA and Shaun Lehmann for help with drug coding.
Canadian Study of Health and Ageing (CSHA)	The CSHA was funded by the Seniors' Independence Research Program through the National Health Research and Development Program, project 6606-3954-MC (S). Additional funding was provided by Pfizer Canada Incorporated through the Medical Research Council/Pharmaceutical Manufacturers Association of Canada Health Activity Program, National Health Research and Development Program project 6603-1417-302(R). The study was coordinated through the University of Ottawa and Health Canada's Division of Aging and Seniors. The authors thank the study team and participants of the CSHA.

Appendix 2 *(continued)*

Participating studies	Participating studies details
Cognitive Function and Ageing Studies (CFAS I, CFAS II)	CFAS I: The Medical Research Council (MRC) CFAS is supported by major awards from the MRC, research grant G9901400, and the UK Department of Health. The authors thank the local GPs and their staff for support and assistance, the interviewers, and the residents of East Cambridgeshire, Liverpool, Ynys Mon, Dwyfor, Newcastle upon Tyne, Nottingham, and Oxford for their continuing participation in the study. CFAS II is supported by the MRC, research grant G0601022, the National Institute for Health Research (NIHR) comprehensive clinical research networks (CLRN) in West Anglia and Trent, and the Dementias and Neurodegenerative Disease Research Network (DeNDRoN) in Newcastle. CFAS is a member of the collaboration for leadership in applied health research and care for the east of England (CLAHRC EoE), the Cambridge Biomedical Research Centre infrastructures, Nottingham City and Nottinghamshire County NHS primary care trusts, and the UK NIHR Biomedical Research Centre for Ageing and Age-related Disease award to the Newcastle-Upon-Tyne hospital foundation trust. The authors thank the participants, their families, the general practitioners and their staff, and the primary care trusts for their cooperation and support, and the CFAS II fieldwork interviewers at Cambridge, Nottingham, and Newcastle.
Einstein Aging Study (EAS)	The EAS is supported by NIH/NIA 2 P01 AG 03949. The authors thank the study team and participants of the EAS.
Ginkgo Evaluation and Memory Trial (GEM)	The authors thank the study team and participants of the GEM.
Gothenburg H70 Birth Cohort Studies	The authors thank the study team and participants of the 1922 and 1930 cohorts. Funded by the Swedish Research Council (2015-02830, 2013-8717), Swedish Research Council for Health, Working Life and Welfare (2008-1229, 2012-1138, 2010-0870, 2013-2300, 2013-2496, 2013-0475, 2006-1506), Konung Gustaf V:s och Drottning Victorias Frimurarestiftelse, Hjärnfonden, Sahlgrenska University Hospital (ALF), The Alzheimer's Association Stephanie B. Overstreet Scholars (IIRG-00-2159), Eivind och Elsa K:son Sylvans stiftelse, and Swedish Alzheimer Foundation.
Hypertension in the Very Elderly Trial	See full acknowledgements and funding sources as cited in reference 51.
Invecchiamento Cerebrale in Abbiategrasso study (InveCe.Ab)	The authors thank the study team and participants of the InveCe.Ab study and "Federazione Alzheimer Italia," Milan, for partially funding the study.
Irish Longitudinal Study on Ageing (TILDA)	The authors thank the study team and participants of TILDA. Researchers interested in using TILDA data may access the data for free from the following sites: Irish Social Science Data Archive (ISSDA) at University College Dublin (ucd.ie/issda/data/tilda/); and Interuniversity Consortium for Political and Social Research (ICPSR) at the University of Michigan (icpsr.umich.edu/icpsrweb/ICPSR/studies/34315). TILDA is supported by the Irish Government, The Atlantic Philanthropies, and Irish Life plc.

Continued

Appendix 2 *(continued)*

Participating studies	Participating studies details
Kuopio Ischaemic Heart Disease Risk Factor Study	The authors thank the staff of the Kuopio Research Institute of Exercise Medicine and the Research Institute of Public Health and University of Eastern Finland, Kuopio, for the data collection in the study.
Leiden 85+ Study	The Leiden 85+ Study is partly funded by the Dutch Ministry of Health, Welfare, and Sports. The authors thank Anton J.M. de Craen (deceased) for his work for the Leiden 85+ Study.
Maastricht Ageing Study (MAAS)	The authors thank the study team and participants of the MAAS.
Monongahela-Youghiogheny Healthy Aging Team (MYHAT)	MYHAT was funded by research grant R01 AG023651 from the National Institute on Aging, US Department of Health and Human Services. The authors thank Dr. Tianxiu Wang for performing the analyses and the study team and participants of MYHAT.
Newcastle 85+ Study	The Newcastle 85+ Study was funded by the Medical Research Council, Biotechnology and Biological Sciences Research Council, the Dunhill Medical Trust, Newcastle University, and the North of England Commissioning Support Unit (formerly NHS North of Tyne). The research was also supported by the National Institute for Health Research, Newcastle Biomedical Research Centre, based at Newcastle upon Tyne Hospitals. The authors thank the North of England Commissioning Support Unit and the local general practitioners and their staff for operational support; the research, management, and clerical team; and the study participants and their families and carers.
Oulu Cohort Ageing Study	The authors thank the participants of the Oulu Cohort Ageing Study.
Personality and Total Health Study (PATH)	The PATH Through Life Project is being undertaken by the Centre for Research on Ageing, Health and Well-being at the Australian National University. The authors thank the study participants, PATH interviewers, and PATH chief investigators. The PATH Through Life Study was funded by National Health and Medical Research Council grants: PATH wave 1: NHMRC program grants 229936 and 179839; PATH wave 2: NHMRC program grant 179805; PATH wave 3: NHMRC project grant 418039; PATH wave 4: NHMRC project grant 1002160.
Prevention of Dementia by Intensive Vascular Care (PreDIVA)	The PreDIVA trial was supported by the Dutch Ministry of Health, Welfare and Sports (50-50110-98-020), the Innovatiefonds Zorgverzekeraars (innovation fund of collaborative health insurances, 05-234), and ZonMw (The Netherlands Organisation for Health Research and Development, 62000015). The authors thank participants of the preDIVA study; practice nurses who delivered the intervention; general practitioners involved in care for the participants; Suzanne A. Ligthart, MD, PhD, Lisa S.M. Eurelings, MD, PhD, Jan W. van Dalen, MSc, Carin E. Miedema, and Marieke P. Hoevenaar-Blom, PhD; and Fay Spyropoulou for help with Anatomical Therapeutic Chemical coding.
The Perindopril Protection against Recurrent Stroke Study (PROGRESS)	The authors thank the study team and participants of PROGRESS.

Appendix 2 *(continued)*

Participating studies	Participating studies details
Singapore Longitudinal Ageing Study (SLAS)	The study was supported by research grants from the Agency for Science Technology and Research (A*STAR) Biomedical Research Council (BMRC) (grants 03/1/21/17/214, 08/1/21/19/567) and the National Medical Research Council (grant NMRC/1108/2007). The authors thank the study team, in particular Evie Goh, Gao Qi, and Soh Chang Yuan, and participants of SLAS. The authors thank the following voluntary welfare organizations for their support: Geylang East Home for the Aged, Presbyterian Community Services, St Luke's Eldercare Services, Thye Hua Kwan Moral Society (Moral Neighbourhood Links), Yuhua Neighbourhood Link, Henderson Senior Citizens' Home, NTUC Eldercare Co-op Ltd., Thong Kheng Seniors Activity Centre (Queenstown Centre), and Redhill Moral Seniors Activity Centre.
Sydney Memory and Ageing Study (MAS)	The authors thank the study team and participants of MAS.
Systolic Hypertension in Europe Trial (SYST-EUR)	See full acknowledgements and funding sources as cited in reference 7.
Systolic Hypertension in the Elderly Project (SHEP)	This article was prepared using SHEP Research Materials obtained from the NHLBI Biologic Specimen and Data Repository Information Coordinating Center and does not necessarily reflect the opinions or views of SHEP or NHLBI.
Victoria Longitudinal Study	The authors thank Stuart MacDonald and the VLS team and participants for their contributions and acknowledge funding from the NIH (National Institute on Aging): R01 AG008235 to R.A. Dixon (PI).

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