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An investigation of antihypertensive class, dementia and cognitive decline.

A meta-analysis.

Short title: Meta-analysis of antihypertensive class and incident dementia

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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 optimising cognition. Our objective was to determine whether any particular class of antihypertensive 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 pre-existing 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.

Conclusions

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

Registration

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

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Introduction

Dementia is a major public health problem affecting around 50 million individuals worldwide. A new case is diagnosed every three seconds and prevalence is estimated to rise to 131.5 million cases by 2050. [1] High blood pressure is widely recognized as one of the main modifiable risk factors for dementia. [2-5] Even though blood pressure 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 optimising cognitive outcomes and reducing risk of dementia with some classes e.g. calcium channel blockers, thought to have a pleiotropic neuroprotective effect above and beyond blood pressure lowering. [3,4,6-14] Existing meta-analyses are limited because information is lost with pooling of published results which conflate data across different age groups (mid and late-life), lack data on minimum length of exposure to antihypertensive class, adjust for differing confounders and 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 comprehensive meta-analysis examining antihypertensive class using standardised measures across studies and subsequent meta-analysis. Data from 56866 participants drawn from 27 studies were synthesized to evaluate the relationship between each class of antihypertensive and incident cognitive decline and dementia.

Method

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 beta blocker OR adrenergic beta-antagonist). Details of the search strategy are given in Dryad data repository (https://datadryad.org/review?doi=doi:10.5061/dryad.t9n4n3p) appendix A. Reference lists and lists of studies contained within established study consortia relating to cognitive outcomes were screened for potentially relevant published papers 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 (http://www.ClinicalTrials.gov)

The lead reviewer (RP) 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 two reviewers (RP,JP). 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 minimise the impact of publication bias, a list of potentially eligible studies was also compiled by examining those included in pre-existing 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 two 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, harmonisation and reduction in risk of bias

Exposure to an antihypertensive (AHM) class was present if recorded over a minimum of a twelve-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, Beta 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 standardisation 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 for RCI categorised as reliable. Follow-up cognitive testing was required to be after the minimum one year AHM exposure period and cognitive change was assessed subsequent to or concurrent with this. Cognitive tests were categorised 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 blood pressure and cognitive function may differ in mid and late-life [3-5] data were dichotomised by age into (late-life) >65 years at baseline versus (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 year follow-up, i.e. participants were only seen at intervals of five or more years, these were included in the latter category. The analyses for each study data set 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 AHM (cohort studies).

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

- compared to no treatment (cohort studies)
- compared to placebo (clinical trials).

Since 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 impact of AHM class on cognitive function is thought to be pleiotropic, models examining class were adjusted at study level for baseline systolic blood pressure 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 impact of baseline AHM class on later mortality or dropout was also examined using logistic regression. These analyses were adjusted for baseline systolic blood pressure 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's 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 males and females.

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 obtained from the Science and Medical Human

Research Medical Committee (DERC) Australian National University (reference 2016/500) was granted 23 Sept 2016. Analyses were carried out using SAS v9.3 and StatsDirect v3.0.198.

Role of the funding source

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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 (Dryad data repository (https://datadryad.org/review?doi=doi:10.5061/dryad.t9n4n3p) appendix-fig. 1). Of the 64 studies, five held no relevant data or indicated that data were no longer maintained [16-20], twenty-seven studies [7-9,21-46] contributed data (Dryad data repository (https://datadryad.org/review?doi=doi:10.5061/dryad.t9n4n3p) appendix-table 1) and there were 28 studies that did not participate. Reasons for non-participation included a lack of valid email contact or no response to enquiries and 4 declined to provide data. There were no evident differences in study design, proportion of study type, population nor 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 seven selected cohorts), and six were trials, two [22,36] were clinical trials treated as cohort studies (where the randomised intervention was not an antihypertensive agent and where randomised groups had no significant impact on cognitive outcomes) and four [7-9,39] were RCTs of antihypertensive treatment. Studies represented populations from Europe [7,8,24,27,28,31-38,40,41,42-45], America [21-23,26,29,39,42], Australia [25,30,43] and Asia [8,9,46]. In total there were 43049 participants from cohort studies and 13817 from clinical trials with ≥1 year follow-up and without prevalent dementia at baseline (Dryad data repository (https://datadryad.org/review?doi=doi:10.5061/dryad.t9n4n3p) appendix-table 1). Mean baseline age in the sampled studies ranged from 57.0 (Standard Deviation (SD) ±5.2) years [24] to 93.0 (SD ±2.6) [26] with the mean age of participants in the majority of participating studies [7,21-23,27,29,31,33,26,37,39-43] in the range 70-79 years. Mean baseline Systolic Blood Pressure (SBP) was in the normotensive range (≤140mmHg) for eight studies [21-26,44-46], between 140-159mmHg for thirteen studies [8,27-38,43] and ≥160mmHg for three studies [7,9,39]. For three studies [40-42], baseline blood pressure was not available.

Twenty-four studies [7-9,21-23,25-31,33-55] contributed data on those aged >65 years at baseline, and nine [7,8,24,25,28,32,39,44-46] had some data on those aged ≤65 years at baseline. Twenty-four studies [7-9,21-31,33-38,40,41,43,44-46] reported results for cognitive decline from the most commonly used screening test, the Mini-Mental State Examination (MMSE) and seventeen [7-9,22,26-29,31,33,34,36,37,39,41,42] reported results for incident dementia. Diagnosis of dementia was based on the Diagnostic Statistical Manual (DSM) version III-R or IV (n=15)[7-9,22,24,26-29,31,33,34,36,37,39,41,42], the Clinical Dementia Rating scale (CDR) ≥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 impact of antihypertensive class compared to no antihypertensive treatment or placebo for incident dementia. After adjustment for age, sex, baseline systolic blood pressure 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 or ≥1 year follow-up (for ≥5 year follow up please see Table 1 and Fig. 1, and for ≥1 year follow up Dryad data repository (https://datadryad.org/review?doi=doi:10.5061/dryad.t9n4n3p) appendix-table 2, and Dryad data repository (https://datadryad.org/review?doi=doi:10.5061/dryad.t9n4n3p) appendix-fig. 2, for full-size forest plots see the online supplement Dryad data repository (https://datadryad.org/review?doi=doi:10.5061/dryad.t9n4n3p) appendix B). 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 year follow-up OR=0.84 (95% CI 0.55:1.29). Unadjusted results showed a similar association (Dryad data repository (https://datadryad.org/review?doi=doi:10.5061/dryad.t9n4n3p) appendix-table 3)

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 or ≥1 year follow-up (Tables 2 and Dryad data repository (https://datadryad.org/review?doi=doi:10.5061/dryad.t9n4n3p) appendix-table 4).

Late-life >65 years, incident cognitive decline

We evaluated the impact 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 or ≥1 year follow-up for any drug classes. (Table 1 and Dryad data repository (https://datadryad.org/review?doi=doi:10.5061/dryad.t9n4n3p) appendix-table 2, Fig. 2 and Supplementary Dryad data repository (https://datadryad.org/review?doi=doi:10.5061/dryad.t9n4n3p) appendix-fig. 3, full-size forest plots in the online supplement Dryad data repository (https://datadryad.org/review?doi=doi:10.5061/dryad.t9n4n3p) appendix B). Unadjusted results were similar (Dryad data repository (https://datadryad.org/review?doi=doi:10.5061/dryad.t9n4n3p) appendix-table 3). 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 year follow-up. Exposure to diuretics was associated with a decreased risk of incident cognitive decline in those with ≥5 year follow-up OR=0.69 (95% CI 0.51:0.92) but not in those with ≥1 year follow-up OR=0.98 (0.82:1.18) (Table 2, Dryad data repository (https://datadryad.org/review?doi=doi:10.5061/dryad.t9n4n3p) appendix-table 4). Unadjusted results were similar (Dryad data repository (https://datadryad.org/review?doi=doi:10.5061/dryad.t9n4n3p) appendix-table 5).

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 (Dryad data repository (https://datadryad.org/review?doi=doi:10.5061/dryad.t9n4n3p) appendix-table 6).

Midlife ≤65 years

Fewer data were available in the ≤65 age group. No discernible pattern of results was evident for the differing antihypertensive classes (Dryad data repository (https://datadryad.org/review?doi=doi:10.5061/dryad.t9n4n3p) appendix-table 7).

Heterogeneity and publication bias

Point estimates varied considerably in direction and magnitude per study (Figs. 1 and 2; Dryad data repository (https://datadryad.org/review?doi=doi:10.5061/dryad.t9n4n3p) appendix-figs. 2 and 3). Heterogeneity in the meta-analyses ranged from 0 to 67.7% (Tables 1-2, Dryad data repository (https://datadryad.org/review?doi=doi:10.5061/dryad.t9n4n3p) appendix-tables 2-3), but publication bias measured by Egger's 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 year 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 systolic blood pressure or, where this was unavailable, for presence of hypertension at baseline, were: 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 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 or ≥5 year follow-ups, adjusted for age, sex, education and baseline systolic blood pressure or presence of hypertension. Further analyses in a subset of 10 cohorts adjusting only for age, sex and education to avoid over-adjustment for blood pressure 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. (Dryad data repository (https://datadryad.org/review?doi=doi:10.5061/dryad.t9n4n3p) appendix-table 8). However with ≥5 year 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 two 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 year 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 year follow-up, pooled OR=1.00 (95% CI 0.60:1.67) and two cohorts for cognitive decline in those with ≥1 year follow-up, pooled OR=1.15 (95% CI 0.81:1.64). There were two RCTs with data available for cognitive decline in those with ≥1 year 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 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 blood pressure in their treated and untreated populations. This suggests the possibility of some degree of successful blood pressure 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 nor when the OR of the participating study samples were plotted against decade of recruitment or percentage of female participants (Online supplement Dryad data repository (https://datadryad.org/review?doi=doi:10.5061/dryad.t9n4n3p) appendix C). Furthermore, rerunning the treated and untreated comparison by sex in those >65 years showed no differences for men and women (Dryad data repository (https://datadryad.org/review?doi=doi:10.5061/dryad.t9n4n3p) appendix-table 9).

Discussion

In this standardised 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, i) 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 year follow-up; and ii) 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 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 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; to examine the impact of antihypertensive drug class on cognitive outcomes using reanalysed individual person data standardised across and assembled from individual studies. Similarly it is the first, to our knowledge, that uses standardised 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 favour of diuretics [12], ARB [13,14], ACE-I [13,14], CCB [11] and BB [48] without the evidence coalescing consistently in favour 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 year 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 blood pressure 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). Additionally, 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 standardisation of cognitive decline. Unlike prior work; strengths of this study include i) minimising the risk of publication bias by deriving data from systematic literature searches and pre-existing consortia, ii) combining data from a large number of participants across a wide geographical range of studies, maximising the inclusion of relevant data, iii) standardisation of exposure to antihypertensive classes (minimum exposure one year), iv) separation of data into exposure in mid and late life age groups (>65,≤65 years), v) requirement of a minimum follow-up/lag period (≥1 and ≥5 year) i.e. excluding those who were followed for less than 12 months etc.:, vi) standardisation of cognitive decline across varied time periods and taking account of variation within each sample, vii) standardisation of statistical methods and available co-variates, viii) use of both unadjusted and adjusted results, ix) comparison of each class against no treatment and against other antihypertensive treatment, and, x) a low level of heterogeneity in the analyses.

Limitations include a potential differential drop out or survivor bias in normotensives or controlled hypertensives, 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 is maximised in a combined study such as ours. Pragmatic use of the reliable change index and standardised 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 between blood pressure, treatment, ageing and cognition using a life-course approach; 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 still been no clinical trial designed primarily to test the impact of blood pressure lowering on cognitive function. This too remains a crucial gap in the evidence base.

In conclusion, our findings show some support for the message that lowering blood pressure may lower dementia risk whilst also supporting clinical freedom in the selection of antihypertensive regimens to achieve blood pressure goals.

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Participating studies details as required by each study are below.

3 Cities study	The Three-City Study is conducted under a partnership agreement between 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 3C 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.” The 3C study supports are listed on the study website (www.threecity-study.com). Thanks are due to the study team and participants of the 3 Cities study.
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*Figure 1 Forest plots showing odds ratios for risk of developing dementia by exposure to each antihypertensive class compared to no treatment in those with ≥5 year follow-up in those aged over 65**

Figure 2 Forest plots showing the odds ratios for risk of developing cognitive decline by exposure to each antihypertensive class compared to no treatment in those with ≥5 year follow-up 65†*

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

	Antihypertensive class				
	CCB	ACE-I	ARB	Diuretic	BB
Risk of developing dementia (Pooled OR 95% CI)*	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)
Number 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 Mini-Mental State Exam (MMSE) (Pooled OR 95% CI)*	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)
Number 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

**Adjusted for sex, age, baseline systolic blood pressure and education. Additional adjustment for ethnic group in the Einstein Aging Study (EAS)*

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

	Antihypertensive class				
	CCB	ACE-I	ARB	Diuretic	BB
Risk of developing dementia (Pooled OR 95% CI)*	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)
Number 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 Mini-Mental State Exam (MMSE) (Pooled OR 95% CI)*	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)
Number 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

*Adjusted for sex, age, baseline systolic blood pressure or presence of hypertension and education. Additional adjustment for ethnic group in the Einstein Aging Study (EAS)

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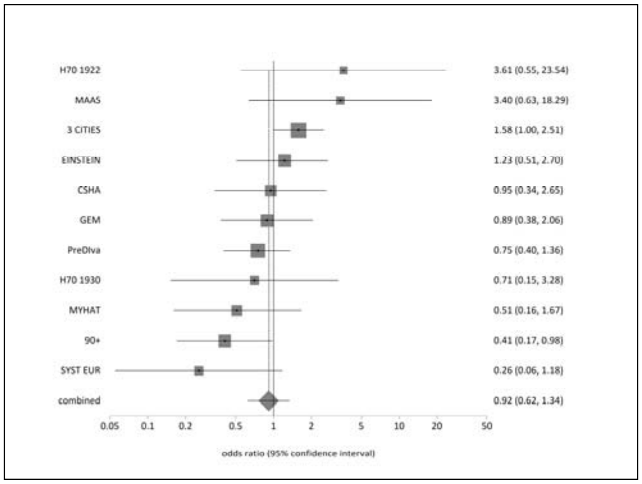
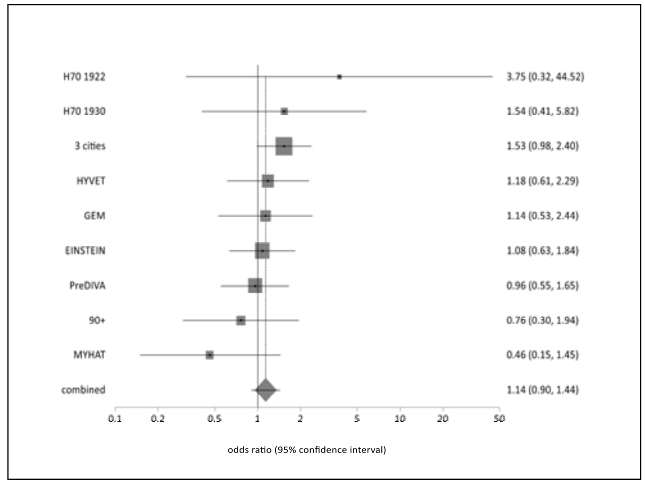
*Figure 1 Forest plots showing odds ratios for risk of developing dementia by exposure to each antihypertensive class compared to no treatment in those with ≥5 year follow-up in those aged over 65**

CCB



ACE-I



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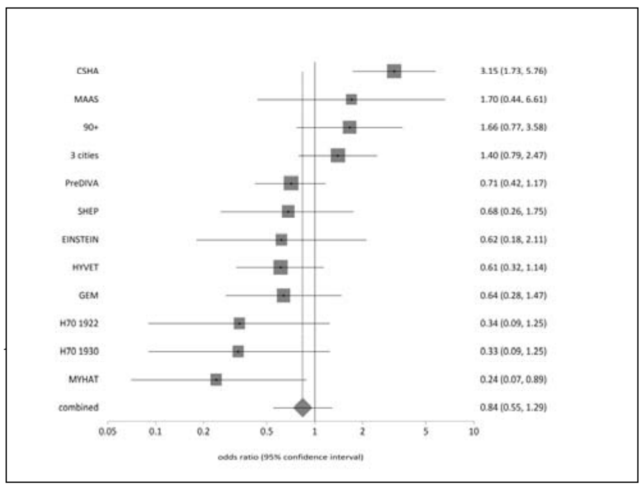

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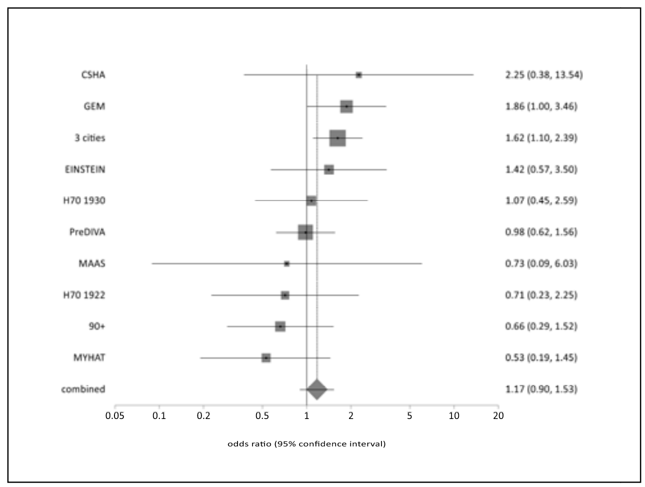

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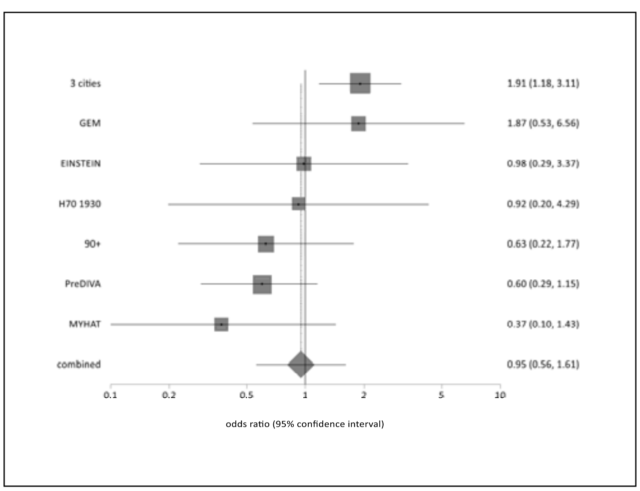
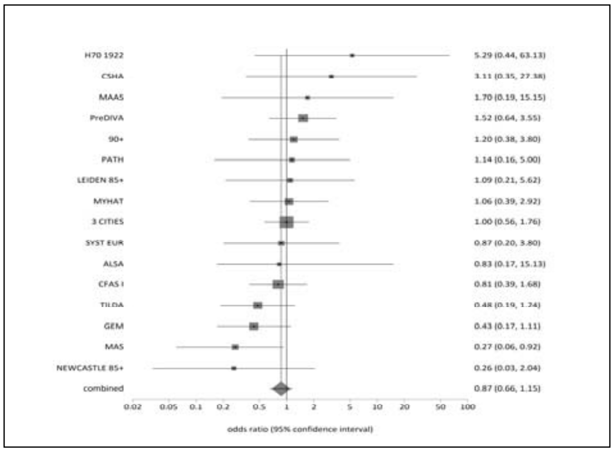


* Adjusted for sex, age, baseline systolic blood pressure and education. Additional adjustment for ethnic group in the Einstein Aging Study (EAS). Calcium Channel Blocker CCB, Angiotensin Converting Enzyme Inhibitor ACE-I, Angiotensin Receptor Blocker ARB, Beta Blocker BB

Figure 2 Forest plots showing the odds ratios for risk of developing cognitive decline by exposure to each antihypertensive class compared to no treatment in those with ≥5 year follow-up 65†*

CCB



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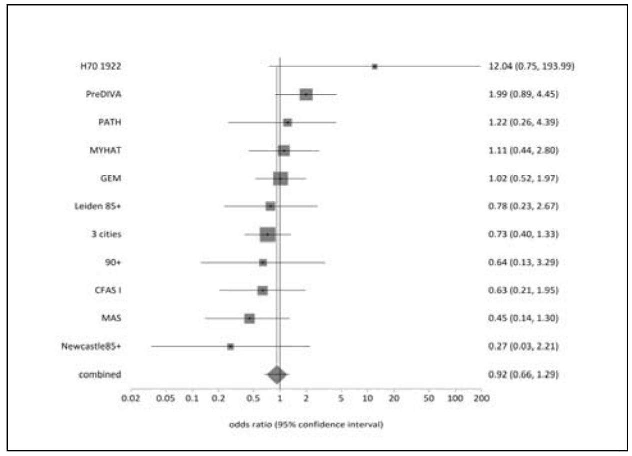

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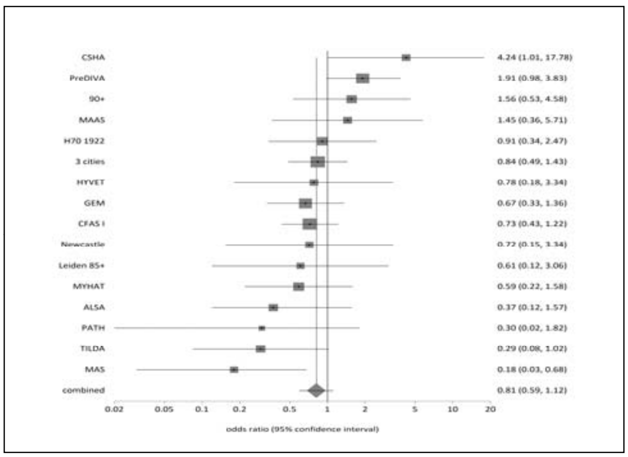

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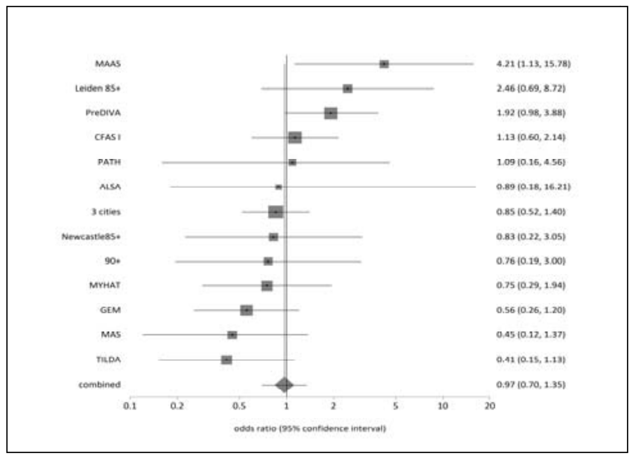

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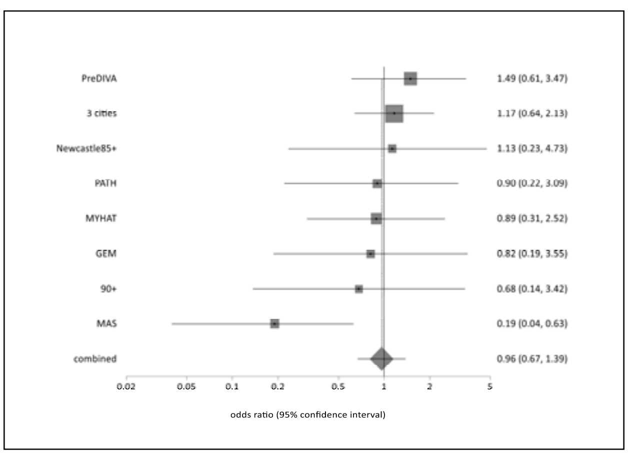

†Cognitive decline classified using the reliable change index and a deterioration in the cognitive screening test, the Mini Mental State Exam (MMSE).

*Adjusted for sex, age, baseline systolic blood pressure and education.