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Treatment of hypertension reduces cognitive decline in older adults: a systematic review and meta-analysis

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ABSTRACT

Objectives To systematically analyse the effect of pharmacological treatment of hypertension (HTN) on cognitive decline in older adults.

Methods Randomised, placebo-controlled trials with a prespecified quantitative outcome of cognition and a pharmacological intervention for at least 12 months to treat HTN in older adults (>60 years). Our primary outcome was change in cognition with pharmacological treatment of HTN. Standardised mean difference (SMD) was used to analyse different outcomes reported in the selected studies. We searched PubMed CENTRAL and the Cochrane Library from inception to 6 July 2020. Two independent reviewers assessed trial quality and extracted data. Internal and external validity of the studies was assessed.

Results Nine randomised controlled trials with 34 994 participants were included in the final analysis. The net SMD for change in cognition was −0.049 (CI: −0.078 to −0.019) indicating that treatment of HTN decreased cognitive decline. Heterogeneity was low with an I² of 6%.

Discussion Current evidence does not indicate worsening of cognition with treatment of HTN. Treatment of HTN in older adults may reduce cognitive decline. These results have important implications in clinical management of patients at risk for dementia.

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INTRODUCTION

Dementia is a disease of the old with an estimated prevalence of 45 million worldwide.[1] With increasing life expectancy and an upsurge in the ageing population, these numbers are expected to rise and the number of persons with dementia is projected to triple by 2050.[2] Currently, effective pharmacological treatment for dementia is limited. Approximately half of Alzheimer's disease cases are attributable to modifiable risk factors and even a modest 10%–25% reduction in these risk factors could cut the number of adults in the USA with Alzheimer's by nearly 500 000 cases.[3] Thus, non-pharmacological interventions such as aggressive management of hypertension (HTN) are being investigated.

HTN affects an estimated 1.39 billion people worldwide,[4] and up to two-thirds of

Strengths and limitations of this study

► This is a meta-analysis of nine published randomised controlled trials with almost 35 000 participants included in this analysis.
► We converted ORs to standardised mean difference, which enabled us to include studies reporting incident dementia, mild cognitive impairment or cognitive decline on continuous measures.
► To improve the clinical interpretability of the results, we estimated the absolute magnitude of effect of aggressive treatment of hypertension on reducing cognitive decline.
► The included studies were heterogeneous in blood pressure goals, antihypertensives used and acquired blood pressure at the end of the study.
► Since this analysis includes randomised clinical trials, results may not be generalisable to the old and frail patients who may not participate in clinical trials.

people >65 years of age. HTN is an independent risk factor for dementia and Alzheimer's disease.[5–8] Longstanding HTN leads to vascular remodelling, decrease in vascular compliance and increase in pulse pressure,[9] decrease in cerebral blood flow,[10] degenerative changes of the vessel wall[11] and decrease in cerebrovascular reserve.[12] These changes disrupt cerebral autoregulation and lead to increased white matter lesions,[13] microinfarcts, microhaemorrhages and cerebrovascular events,[14] known causes for faster cognitive decline and incident dementia.[15 16]

Despite these associations and other known adverse effects of HTN,[14] blood pressure (BP) remains inadequately controlled in three out of four older adults (>65 years) with HTN.[17 18] Concerns about decreasing cerebral perfusion and thereby worsening cognition with lowering of systemic BP in older adults have limited aggressive HTN management in clinical practice.[19–22] However, studies indicate protective adaptation of the

cerebral vasculature with BP reduction to prevent cerebral hypoperfusion.[23 24]

The objective of this meta-analysis is to systematically analyse the effect of pharmacological treatment of HTN on cognitive decline in older adults. Previous systematic reviews and meta-analyses have reported conflicting and equivocal results on the effect of treating HTN on cognition.[25–28] In the absence of conclusive evidence regarding safety of BP reduction in older persons at risk of dementia, clinical decision-making remains challenging. Since the publication of the last systematic review on treatment of HTN and cognition in 2009,[28] new studies evaluating the effect of treating HTN on cognitive decline and dementia have been published. Here, we present the results of a systematic review and meta-analysis of existing randomised controlled clinical trials on the effect of pharmacological treatment of HTN on cognition in older persons without previous stroke.

METHODS
We conducted a systematic review and meta-analysis to assess the effect of treatment of HTN on cognition.

Inclusion criteria
Studies were included in the final analysis if they were (1) randomised controlled trials on pharmacological treatment of HTN, (2) in adult participants where the majority of participants were >60 years old, (3) with a pre-specified outcome of cognition and with a measure of cognition such as a standard neuropsychological test (eg, Mini-Mental State Examination (MMSE)), (4) with comparison group with either placebo, no intervention, standard of care or a higher BP goal and (5) with at least 1-year follow-up. The randomisation could be for a BP goal or by medications for HTN. Observational studies and studies specifically assessing treatment of HTN after stroke were excluded. However, studies where stroke was not listed as a specific inclusion criterion (ie, some but not all participants may have a history of stroke) were included.

Changes from PROSPERO protocol
We made some modifications to the published protocol to address unanticipated characteristics of the available studies. These changes were made after our initial review of the identified papers but before extraction of study results.
1. The initial intended target age was people >60 years of age. However, only five studies published prior 2008 met this criterion. Therefore, we modified this selection criterion to allow inclusion of all studies of adults where the median or mean age of participants was ≥60 years.
2. Several studies identified in the search exclusively enrolled patients with stroke or transient ischaemic attack. Since we were not primarily interested in the effect of aggressive BP control on recurrent stroke

(which could affect cognitive function), we excluded these studies. We included studies enrolling some patients with stroke as long as they constituted a minority of patients.

Data sources and searches
We searched PubMed CENTRAL and the Cochrane Library (from inception to 6 July 2020) for relevant studies (online supplemental data A). Search included keywords such as cognition, dementia or cognitive dysfunction, HTN or antihypertensive agents, placebo or control and randomised clinical trial.

Patient and public involvement statement
Individual patients were not recruited for this study or involved in the study in any other way. The study was inspired by questions arising during clinical care of older patients. Dementia is a public health crisis and discovering ways to reduce cognitive decline is important for patients. Considering the high prevalence of HTN in the old, even a small effect of BP reduction on cognitive decline is clinically relevant.

Study selection
Two independent reviewers (AG and SP) reviewed titles and abstracts to select articles for further review. In case of disagreements, the manuscript in question was included with an intention of being more inclusive at this stage. After assessment of inclusion and exclusion criteria, the qualifying studies were selected for the final analysis. Two reviewers independently abstracted data elements from the selected studies. Disagreements between the two reviewers were resolved with mutual discussion and in some cases by involving a third member (GG).

Data extraction and quality assessment
We developed a data extraction form in Microsoft Excel. For internal validity assessment, this form included fields regarding Cochrane risk of bias domains for therapeutic studies. For external validity assessment, we gathered information on about baseline characteristics, inclusion and exclusion criteria, enrolment, study setting, study methods, intervention for treatment of HTN, BP goals, change in BP, achieved BP, difference in BP in the intervention versus control groups, study size, outcomes, effect, primary and secondary outcomes for cognition and study duration. To ensure consistency in data extraction, we piloted the form using studies that were excluded from this analysis. Two reviewers independently extracted the data listed in this form from the selected studies. A third reviewer (GG) spot checked certain studies for data extraction for accuracy.

The primary measure for assessing cognition was different in the selected studies. Continuous measures of cognition were extracted where available. The mean change in the primary measure for cognition, the SD and the number of participants in the intervention and control groups was extracted. In the absence of a continuous measure of cognition, dichotomous measures or ORs were extracted. For the

selected studies, the number of participants in each treatment group and the number experiencing the outcome selected were extracted. When available, results from an intention-to-treat analysis were chosen.

Data synthesis and analysis

To maximise precision, our preferred outcome measure was the difference in the change in a continuous measure of global cognition from baseline. Because we anticipated that change in cognition would be measured on different continuous scales, we used standardised mean differences (SMDs) as our primary effect size measure. For studies reporting the count of events (eg, the number of participants developing dementia) and not continuous cognitive measures, we converted ORs to SMDs using the Hasselblad and Hedges method.[29 30] We calculated 95% CIs of the SMDs as our measure of precision. We used inverse variance, random effects model to calculate a summary measure of effect and I^2 as the measure of heterogeneity.

We performed a cumulative meta-analysis according to the date of publication to detect overall estimate changes over time. We performed exploratory random effects meta-regression to examine the impact of moderator variables for change in systolic BP (SBP), baseline SBP, year of publication, participant age, duration of follow-up, prevalence of diabetes mellitus and proportion of women in the study on the relationship between cognition and treatment of HTN. We assessed publication bias by inspecting a funnel plot of SE by effect size and with Egger's regression test.[31] We calculated the absolute effect of treatment of HTN on cognition and number needed to treat (NNT) from studies reporting ORs or dichotomous outcomes.

Sensitivity analysis

For sensitivity analysis, we assessed the impact of individual studies on the summary effect by performing a one-study-removed analysis. To determine whether the results of our analysis were affected by the choice of effect size measure (continuous vs binary), we separately meta-analysed studies selecting a continuous measure of cognition (where we converted a raw mean difference to an SMD) from those selecting a binary measure of cognition (where we converted an OR to an SMD). We also did a fixed effect meta-analysis. Additionally, to determine if modifications to the analysis plan influenced the results, we meta-analysed studies that only met our original protocol's age criteria (no patients ≤60 years old).

Analysis was done using Comprehensive Meta-Analysis V.3[32] and Microsoft Excel.

RESULTS

We identified 2072 records of interest with our search strategy (figure 1) and reviewed 1863 abstracts after removing duplicate records. Of these, 28 full-text articles from 14 independent trials were selected for further review. Final analysis included nine studies.[33–41] The

reasons for exclusion of remaining 19 studies are listed in online supplemental data B. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the selection of included studies is presented in figure 1. We included three studies with participants >55 years old[37 39 40] and a study with participants >50 years old,[41] as they also included participants >60 years old as outlined in our inclusion criteria.

Assessment of bias in included studies
Internal validity

All included studies had adequate sequence generation except the Systolic Hypertension in the Elderly Program (SHEP),[33] where the method of sequence generation was unclear. Allocation concealment was unclear in Medical Research Council (MRC) treatment trial of HTN by Prince et al[34] and the study by Pantoni et al.[37] Characteristics of prognostic importance were substantially similar between treatment groups in all studies except SHEP,[33] where the data presented were inadequate to assess balance in baseline characteristics (figure 2 and online supplemental data table 1). The study by Pantoni et al[37] was described as double blinded; however, it was unclear if the outcome assessor was also blinded. MRC,[34] Memory in Diabetes (MIND) substudy of the Action to Control Cardiovascular Risk in Diabetes (ACCORD)[40] and the Systolic Blood Pressure Intervention Trial (SPRINT) MIND[41] were open label studies. All studies had a predefined cognitive outcome and specific tests included in the protocol for assessment of cognition. Attrition was low in all studies.

External validity

Table 1 shows important characteristics of the included studies. All included studies[33–41] were multicentre studies, including both men and women. Mean follow-up was up to 5 years.

Participants

The participants in SHEP,[33] MRC,[34] Systolic Hypertension in Europe,[35] the Study on Cognition and Prognosis in the Elderly (SCOPE),[36] study by Pantoni et al[37] and the SPRINT[41] had similar ages, whereas participants in the Hypertension in the Very Elderly Trial[38] were older, and those in TRANSCEND (Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease)[39] and the ACCORD-MIND[40] were younger. All selected studies except the one by Pantoni et al[37] either excluded or had a small proportion of participants with known dementia. Insulin use or a history of diabetes was an exclusion criterion for most studies except TRANSCEND,[39] where 36% participants had diabetes, and ACCORD,[40] where all participants had diabetes.

Intervention

The pharmacological therapies and attained BP varied across the studies. BP goals were different in the selected studies with higher BP goal (SBP <160 mm Hg or 150 mm Hg) in older studies,[33–36 38] and lower BP goals (SBP <120 mm Hg) in more recent studies.[40 41] Some studies did not
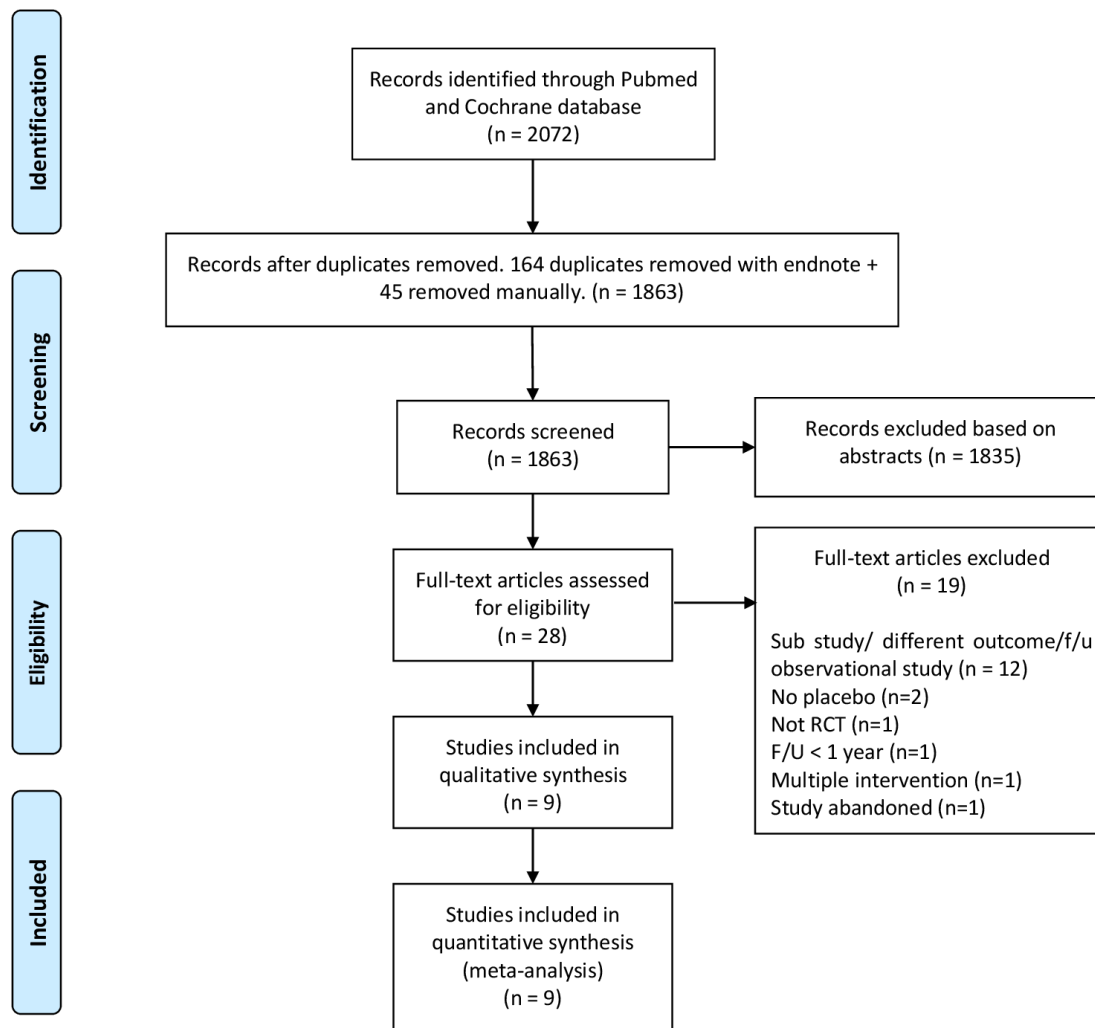
Figure 1 A Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram.

specify a BP goal.[37 39] The study by Pantoni et al[37] did not show any change in SBP compared with baseline.

Outcome measures

We used continuous measures of cognition where possible such as MMSE,[36 37] Short-Comprehensive Assessment and Referral Evaluation (CARE) cognitive impairment,[33] paired associate learning test score[34] and Digit Symbol Substitution Test.[40] We used cognitive decline,[38 39] incident dementia[35] or adjudicated mild cognitive impairment[41] in others where a continuous measure was not available for analysis.

We judged the risk of bias to be low to moderate in the studies. All nine studies were included in the quantitative synthesis.

Effect sizes

Figure 3 lists the effect sizes and accompanying forest plot for differences in the change in cognition (SMDs with 95% CI) for the included studies. The pooled SMD for change in cognition was −0.049 (95% CI: −0.078 to −0.019) indicating a positive effect on cognition with treatment of HTN. I^2 was 6% indicating low heterogeneity. The fixed effect meta-analysis was very similar (SMD −0.048, 95% CI: −0.077 to −0.020) to the random effects given the low heterogeneity.

Pooled results from studies with a continuous measure of cognition[33 34 37 40] (SMD −0.045, 95% CI: −0.087 to −0.004) were substantially similar to those with a binary measure of cognition[35 36 38 39 41] (SMD −0.056, 95% CI: −0.112 to 0) (online supplemental data figure 1). P value for interaction was 0.76.

Cumulative meta-analysis for detection of temporal trends indicated significant point estimates at all but two time points (1996 and 1998) (online supplemental data figure 2). Random effects meta-analysis with one study removed at a time did not substantially change the summary effect (not shown). A meta-analysis restricted to studies enrolling patients over 60 years of age alone also demonstrated substantially similar results (SMD −0.047, 95% CI: −0.084 to −0.009). Random effects meta-regression for change in SBP, baseline SBP, year of publication, participant age, duration of follow-up, prevalence of diabetes mellitus and proportion of women in the study did not change the effect on cognition (online supplemental data table 2).

The funnel plot used to assess publication bias is shown in online supplemental data figure 3. Egger's regression

Figure 2 Risk of bias assessment: green indicates low risk of bias; yellow indicates medium risk of bias and red indicates high risk of bias.

test demonstrated no significant association between SE and effect size (p=0.54). However, inspection of the plot suggested asymmetry. Thus, we adjusted for potential publication bias with a trim and fill procedure.[42] The estimated effect size was not substantially changed by this adjustment (SMD −0.047, 95% CI: −0.081 to −0.014).

DISCUSSION

Our analysis of the current evidence from randomised trials indicates that pharmacological treatment of HTN in older adults without prior stroke modestly reduces cognitive decline (figure 2). Contrary to previous fears, treatment of HTN did not worsen cognitive decline. The reduction in cognitive decline with treatment of HTN was consistent with variable SBP goals, although the study with the largest effect had a more aggressive SBP goal of 120 mm Hg.[41] The benefit of reducing cognitive decline was also consistent over time from 1994 to 2020 when the studies included in this meta-analysis were published. The benefit of treatment of HTN on cognition persisted after adjusting for the impact of moderator variables of vascular dementia and diabetes in the random effects meta-regression (online supplemental data table 2).

Previous reviews and meta-analysis found equivocal results.[28 43 44] A Cochrane review by McGuinness *et al*[28]

included four studies and did not report a benefit in cognition with treatment of HTN. New studies[39–41] with lower SBP goals[40 41] have been published since. More recent reviews indicated benefit of treatment of HTN in prospective cohort studies,[43 45] but not in randomised controlled trials.[43] No harm in cognition or rates of incident dementia were observed with lowering BP. Our analysis shows a small beneficial effect on cognition, perhaps due to increased precision due to inclusion of a larger number of studies. We converted ORs to SMD, which enabled us to include studies reporting incident dementia, mild cognitive impairment or cognitive decline on continuous measures. A recently published review[44] showed a lower risk of incident dementia or cognitive impairment similar to our study. However, both studies included different populations; with a goal to assess primary prevention with treatment of HTN, and to decrease heterogeneity, we did not include studies specifically assessing treatment of HTN in persons with previous stroke.

The effect size of −0.049 (CI: −0.078 to −0.019) is small, but clinically important. Dementia affects approximately 45 million people worldwide, decreases self-esteem and quality of life, and increases healthcare costs and mortality. Current pharmacological management of dementia improves symptoms but does not address the aetiology or affect long term outcome. An intervention that addresses the aetiology of cognitive impairment and reduces cognitive decline will be of a large epidemiological significance. To improve the clinical interpretability of the results, we estimated the absolute magnitude of effect of aggressive treatment of HTN on reducing cognitive decline. We converted the pooled SMDs to an OR. Assuming linearity of effect and using the absolute rates of developing mild cognitive impairment or dementia in the control group from SPRINT-MIND,[41] we estimated 16 mild cognitive impairment/probable dementia events would be prevented in 1000 patients followed for 10 years. This corresponded to an absolute risk reduction of 1.6% and an NNT of 63.

This systematic review has some limitations. First, the included studies had heterogeneity in BP goals and acquired BP at the end of the study. This was in part due to the change in HTN management guidelines which have reduced the BP goal over time. Second, the antihypertensives used in the included studies were different. We were unable to evaluate the effect size with different antihypertensives as the number of studies with a single class of antihypertensives was small. Third, included studies used different measures for assessing cognition. We used an SMD to circumvent this limitation. Fourth, the results of the meta-analysis are based on published randomized controlled trials (RCTs). As explanatory, non-pragmatic RCTs may not include the very old and frail patients; these results may not be generalisable to patients not adequately represented in these RCTs.

Despite these limitations, and the small effect size of reducing cognitive decline, this meta-analysis provides

Table 1 Characteristics of the nine studies included in the analysis

Author, Year (trial name) Number of participants	Methods	Duration	Main outcome	Primary measure of cognition assessed	BP goal of intervention	Intention-to-treat analysis	Intervention	Participants				
								Age (years)	Gender	% with DM	Baseline SBP	Achieved SBP
Applegate et al 1994 (SHEP)[33] N=4736	Multicentre double-blind placebo controlled stepped-care treatment programme in 16 academic clinical trial clinics.	5 years (mean)	Incidence of fatal and nonfatal stroke	Change in mean Short-CARE score	SBP <160 mm Hg or 20 mm Hg below baseline	Yes	Treatment: step 1: chlorthalidone 12.5–25 mg. Step 2: atenolol 25–50 mg/reserpine 0.05–0.10 mg. Control: placebo.	72±6.7	57% women	Not reported	SBP 170.3±9.4 mm Hg	Treatment group: SBP ~26 mm Hg lower than at baseline
Prince et al 1996 (MRC)[34] N=2584	Multicentre single-blind placebo-controlled trial in 226 general practices from the MRC's general practice research framework	4.5 years (mean)	Reduction of strokes, coronary events and deaths from all causes	Change in PALT	SBP <150 mm Hg if mean SBP after run in period was <180 mm Hg, and SBP <160 mm Hg if mean SBP after run in period was ≥180 mm Hg	Yes	β blocker: atenolol 50 mg/day. Diuretic: hydrochlorothiazide 25 mg+amiloride 2–5 mg/day. Control: placebo	β blocker: 70.3±0.2. Diuretic: 70.4±0.2. Control: 70.3±0.15	58% women	None (excluded)	β blocker: 184.2 mm Hg (95% CI: 183.2 to 185.2). Diuretic: 184.9 mm Hg (95% CI: 183.9 to 185.9). Control: 183.5 mm Hg (95% CI: 182.8 to 184.2)	β blocker: SBP decreased by 30.9 mm Hg (95% CI: 29.5 to 32.2). Diuretic: SBP decreased by 33.5 mm Hg (95% CI: 32.2 to 34.9). Control: SBP decreased by 16.4 mm Hg (95% CI: 15.4 to 17.4)
Forette et al 1998 (Syst-Eur)[35] N=2418	Multicentre double-blind placebo-controlled trial at 106 centres in 19 European countries	2 years (median)	Reduction in cardiovascular complications	Incident dementia (MMSE)	Reduce SBP by at least 20 mm Hg to reach a value <150 mm Hg	Yes	Treatment: nitrendipine (10–40 mg/day)±enalapril (5–20 mg/day) and/ or hydrochlorothiazide (12.5–25 mg/day) Control: placebo	Treatment: 69.9±6.5 Control: 69.9±6.2	Treatment: 66.4% women. Control: 65% women	Unclear	Treatment group: 173.5±10.1 mm Hg. Control: 173.4±10.1 mm Hg	Treatment: SBP decreased by 21.7±16.2 mm Hg. Control: SBP decreased by 13.4±16.2 mm Hg
Lithell et al 2003 (SCOPE)[36] N=4964	Multicentre multinational double-blind trial at 527 centres in 15 countries	3.72 years (mean)	Reduction in cardiovascular events, cognitive decline and dementia	Change in MMSE score	SBP <160 mm Hg or decrease >10 mm Hg from baseline. DBP <85 mm Hg	yes	Treatment: candesartan 8–16 mg/day. Control: placebo +open-label antihypertensive therapy	Treatment: 76.4. Control: 76.4 (SD not provided)	Treatment: 64.8% women. Control: 64.2% women	Treatment: 12.5. Control: 11.6	Treatment: 166±8.9 mm Hg. Control: 166.5±9 mm Hg	Treatment: 145.2±16.1 mm Hg. Control: 148.5±16.8 mm Hg
Pantoni et al 2005[37] N=230	Multicentre double-blind trial	1 year	Efficacy and safety in subcortical vascular dementia	Change in MMSE score	None specified	Yes	Treatment: nimodipine 90 mg/day. Control: placebo	75.3±6.0	40% women	None (excluded)	Treatment: 144 mm Hg. Control: 145 mm Hg (SD not provided)	Treatment: 143 mm Hg. Control: 144 mm Hg (SD not provided)
Peters et al 2008 (HYVET-cog)[38] N=3336	Multicentre double-blind trial in Europe, China, Tunisia, southeast Asia and Australia	2.2 years (mean)	Reduction of fatal and non-fatal strokes	Change in MMSE score	SBP <150 mm Hg and DBP <80 mm Hg.	Yes	Treatment: slow release indapamide 1.5 mg±perindopril 2–4 mg. Control: placebo	Treatment: 83.5±3.1 Control: 83.5±3.1	Treatment: 61% women. Control: 60% women	Unclear	Treatment: 173.1±8.5 mm Hg. Control: 172.9±8.5 mm Hg	Treatment: SBP decreased by 29.6±15.3 mm Hg. Control: SBP decreased by 14.6±18.5 Hg

Continued

Table 1 Continued

Author, Year (trial name) Number of participants	Methods	Duration	Main outcome	Primary measure of cognition assessed	BP goal of intervention	Intention-to-treat analysis	Intervention	Participants				
								Age (years)	Gender	% with DM	Baseline SBP	Achieved SBP
Anderson et al 2011 (TRANSCEND)[39] N=5926	Multicentre double-blind trial in 733 centres in 40 countries	4.7 years (median)	Reduction of cardiovascular events	Cognitive decline (MMSE)	None specified	Yes	Treatment: telmisartan 80 mg/day. Control: placebo	66.9±7.3	43% women	36	Treatment: 140.7±16.8 mm Hg. Control: 141.3±16.4 mm Hg	Mean SBP was 4.0 mm Hg lower in the telmisartan than in the placebo
Williamson et al 2014 (ACCORD MIND)[40] N=1439	Multicentre open label double 2×2 factorial trial in North America	3.3 years	Reduction of cardiovascular morbidity and mortality	Change in DSST score	SBP <120 mm Hg (intensive treatment) and SBP <140 mm Hg (standard treatment)	Yes	Intensive treatment: SBP goal <120 mm Hg. Standard treatment SBP <140 mm Hg	Intensive treatment: 62.3±5.7 Standard treatment: 62.5±6.1	Intensive treatment: 44.7% women Standard treatment: 45.5% women	100	Intensive treatment: 138.8±17.0 mm Hg. Standard treatment: 139.2±15.7 mm Hg	Intensive treatment: 119.0±14.7. Standard treatment: 133.2±14.8
Williamson et al 2019 (SPRINT MIND)[41] N=9361	Multicentre clinical trial in 102 sites in the USA and Puerto Rico	5.11 years (median)	Reduction of clinical events	Adjudicated mild cognitive impairment and dementia	SBP <120 mm Hg (intensive treatment) and SBP <140 mm Hg (standard treatment)	Yes	Intensive treatment: SBP goal <120 mm Hg. Standard treatment: SBP <140 mm Hg	67.9±9.4	35.6% women	None (excluded)	Intensive treatment: 139.7±15.8 mm Hg. Standard treatment: 139.7±15.4 mm Hg	Intensive treatment: 121.6 mm Hg (95% CI: 120.8 mm Hg to 122.3 mm Hg). Standard treatment: 134.8 mm Hg (95% CI: 134.1 to 135.6)

ACCORD, Action to Control Cardiovascular Risk in Diabetes; BP, blood pressure; CARE, Comprehensive Assessment and Referral Evaluation; DBP, diastolic blood pressure; DM, diabetes mellitus; DSST, Digit Symbol Substitution Test; HYVET-cog, Hypertension in the Very Elderly Trial cognitive function assessment; MIND, Memory in Diabetes; MMSE, Mini-Mental State Examination; MRC, Medical Research Council; PALT, Paired Associate Learning Test; SBP, systolic blood pressure; SCOPE, Study on Cognition and Prognosis in the Elderly; SHEP, Systolic Hypertension in the Elderly Program; SPRINT, Systolic Blood Pressure Intervention Trial; Syst-Eur, Systolic Hypertension in Europe; TRANSCEND, Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease.
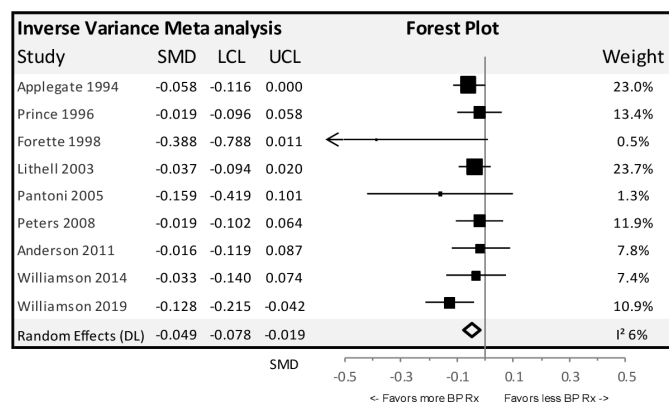
Figure 3 Forest plot with the effect on cognition (SMD with 95% CI). BP, blood pressure; LCL, lower control limit; SMD, standardised mean difference; UCL, upper control limit.

important and clinically relevant information to guide HTN management. BP lowering decreases cardiovascular events and mortality. Despite these data, concern for worsening of cognition with BP lowering prevented clinicians from aggressive HTN management. This meta-analysis of published randomised controlled trials alleviates the concerns of adverse effects of treatment of HTN on cognitive decline.

The effect size of reducing cognitive decline was small. The benefit of HTN management may be currently underestimated due to the measure of cognition used in several studies. It is possible that lowering of BP affects certain domains of cognition more than the others and measurement of global cognition dissipated this effect. For example in SCOPE,[36] the main study did not show any difference in MMSE scores, incident dementia or cognitive decline (defined by reduction in MMSE score by ≥4 points from baseline between the active treatment and control groups), but a substudy of SCOPE[46] showed an improvement in attention and episodic memory with treatment of HTN. Further studies with more extensive neuropsychological tests may be needed to prove this hypothesis.

In conclusion, treatment of HTN may be associated with a reduction in cognitive decline over time. Data from published RCTs show that treatment of HTN does not worsen cognition as previously feared. Although the effect of HTN treatment on reduction of cognitive decline is small, considering the high prevalence of dementia, the impact of dementia on quality of life and mortality, and the lack of promising pharmacological therapies, treating HTN to reduce cognitive decline may be a clinically relevant and effective intervention to reduce cognitive decline and dementia.

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