JAMA | Original Investigation

Association of Blood Pressure Lowering With Incident Dementia or Cognitive Impairment
A Systematic Review and Meta-analysis

Diarmaid Hughes, MB, BEng; Conor Judge, MB, BEng; Robert Murphy, MB; Elaine Loughlin, MB; Maria Costello, MB; William Whiteley, PhD; Jackie Bosch, PhD; Martin J. O'Donnell, PhD; Michelle Canavan, PhD

IMPORTANCE The benefit of blood pressure lowering for the prevention of dementia or cognitive impairment is unclear.

OBJECTIVE To determine the association of blood pressure lowering with dementia or cognitive impairment.

DATA SOURCES AND STUDY SELECTION Search of PubMed, EMBASE, and CENTRAL for randomized clinical trials published from database inception through December 31, 2019, that evaluated the association of blood pressure lowering on cognitive outcomes. The control groups consisted of either placebo, alternative antihypertensive agents, or higher blood pressure targets.

DATA EXTRACTION AND SYNTHESIS Data were screened and extracted independently by 2 authors. Random-effects meta-analysis models were used to report pooled treatment effects and CIs.

MAIN OUTCOMES AND MEASURES The primary outcome was dementia or cognitive impairment. The secondary outcomes were cognitive decline and changes in cognitive test scores.

RESULTS Fourteen randomized clinical trials were eligible for inclusion (96 158 participants), of which 12 reported the incidence of dementia (or composite of dementia and cognitive impairment [3 trials]) on follow-up and were included in the primary meta-analysis, 8 reported cognitive decline, and 8 reported changes in cognitive test scores. The mean (SD) age of trial participants was 69 (5.4) years and 40 617 (42.2%) were women. The mean systolic baseline blood pressure was 154 (14.9) mm Hg and the mean diastolic blood pressure was 83.3 (9.9) mm Hg. The mean duration of follow-up was 49.2 months. Blood pressure lowering with antihypertensive agents compared with control was significantly associated with a reduced risk of dementia or cognitive impairment (12 trials; 92 135 participants) (7.0% vs 7.5% of patients over a mean trial follow-up of 4.1 years; odds ratio [OR], 0.93 [95% CI, 0.88-0.98]; absolute risk reduction, 0.39% [95% CI, 0.09%-0.68%]; I^2 = 0.0%) and cognitive decline (8 trials) (20.2% vs 21.1% of participants over a mean trial follow-up of 4.1 years; OR, 0.93 [95% CI, 0.88-0.99]; absolute risk reduction, 0.71% [95% CI, 0.19%-1.2%]; I^2 = 36.1%). Blood pressure lowering was not significantly associated with a change in cognitive test scores.

CONCLUSIONS AND RELEVANCE In this meta-analysis of randomized clinical trials, blood pressure lowering with antihypertensive agents compared with control was significantly associated with a lower risk of incident dementia or cognitive impairment.

Supplemental content

CME Quiz at jamacmelookup.com and CME Questions page 1965

Author Affiliations: HRB Clinical Research Facility, NUI Galway and Saolta University Hospital Group, Galway, Ireland (Hughes, Judge, Murphy, Loughlin, Costello, O'Donnell, Canavan); Translational Medical Device Lab, NUI Galway, Galway, Ireland (Judge); Wellcome Trust-HRB, Irish Clinical Academic Training, Dublin, Ireland (Judge); Centre for Clinical Brain Sciences, The University of Edinburgh, Edinburgh, Scotland (Whiteley); Population Health Research Institute, Hamilton, Canada (Bosch, O'Donnell).

Corresponding Author: Michelle Canavan, PhD, HRB Clinical Research Facility, Galway University Hospital, Newcastle Road, Galway, Ireland, H91YR7 (michelle.canavan@hse.ie).

JAMA. 2020;323(19):1934-1944. doi:10.1001/jama.2020.4249

Hypertension, especially in midlife, is associated with dementia and cognitive impairment later in life.[1-4] Some randomized clinical trials have reported a lower risk of dementia with blood pressure–lowering treatment.[5-7] However, results of some previous meta-analyses of randomized clinical trials that have evaluated the association of antihypertensive therapy with the risk of neurocognitive syndromes, in either primary or secondary prevention populations, have been inconclusive.[8-11] Two clinical trials have been recently published.[12,13] The SPRINT MIND trial[12] reported a lower risk of mild cognitive impairment in individuals randomized to an intensive blood pressure target group. Conversely, the HOPE-3 study[13] reported no significant reduction in the risk of cognitive impairment or dementia with combination antihypertensive therapy compared with placebo. An updated meta-analysis was performed to determine whether blood pressure lowering was associated with a reduced risk of dementia or cognitive impairment.

Key Points

Question Is there an association between blood pressure lowering with antihypertensive therapy and the incidence of dementia or cognitive impairment?

Findings In this meta-analysis that included 12 trials with 92 135 participants for the primary outcome measure, blood pressure lowering with antihypertensive agents, compared with control, was associated with the development of a composite dementia or cognitive impairment outcome in 7.0% vs 7.5% of patients over a mean trial follow-up of 4.1 years, a difference that was statistically significant.

Meaning Lowering blood pressure may be associated with a lower risk of dementia or cognitive impairment.

Methods

We performed a systematic review and meta-analysis, reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[14] The protocol was registered with PROSPERO (registration number CRD42019125088).

Data Sources and Searches

We developed the search strategy, without language restriction, for PubMed, EMBASE, and CENTRAL for articles published from database inception to December 31, 2019. The search terms included *dementia, cognitive decline, cognitive impairment, blood pressure, hypertension, antihypertensive,* and *randomized controlled trials*. The search strategy was peer-reviewed by a second information specialist. The full search strategy is included in the Supplement (eMethods 1). Three reviewers (D.H., C.J., and R.M.) independently screened titles and abstracts. Full texts were sourced for relevant articles. Inclusion criteria were assessed independently, and inconsistencies were resolved by consensus. The reference lists of included trials and other published meta-analyses were also reviewed for relevant articles.

Eligibility Criteria

Trials were considered eligible if they were randomized clinical trials, compared blood pressure lowering with antihypertensive agents with a control, had at least 1 year of follow-up, included more than 1000 participants, and provided information on any of the prespecified outcomes. Control was defined as placebo, alternative antihypertensive agent, or higher blood pressure target (**Table 1**). Trials were required to report at least 1 of the following outcomes: dementia, cognitive impairment, cognitive decline, or change in cognitive test scores (Table 1). Trials that specifically recruited participants with known dementia or cognitive impairment at the start of the trial were excluded.

Data Extraction

Data were extracted independently by 2 authors (D.H. and C.J.) using a standardized data extraction form. Extracted data were entered into a dedicated database and checked independently by 4 authors (R.M., M.C., E.L., and M.C.). We extracted the following data: study characteristics, baseline demographics of participants, description of the intervention, cumulative blood pressure changes, incidence of dementia and cognitive impairment, and cognitive test scores. The cumulative blood pressure change (net change in systolic blood pressure from baseline to longest follow-up between groups) was reported in 10 of the included trials and the difference between the systolic blood pressure of the groups at trial end was reported in the other trials. We reported outcomes at the point of longest follow-up.[15] Majority primary prevention populations were defined as those in which greater than 50% of participants had no history of cardiovascular events. All other populations were considered majority secondary prevention populations.

Outcomes

The primary outcome of this meta-analysis was dementia or cognitive impairment. For our primary analysis, we used a hierarchical approach in which we included trials that reported incident dementia, or a composite of dementia or cognitive impairment (if dementia alone was not reported), on follow-up. We chose this approach to maximize the number of clinical trials included in our primary analysis, while also giving priority to the most clinically relevant neurocognitive outcome reported in trials. In addition, cognitive impairment and dementia represent a continuum of the same neurocognitive syndrome, and we expected blood pressure lowering using antihypertensives to have a consistent association with both. The definition of dementia was criterion referenced in 7 of the included trials (based on *International Classification of Diseases* criteria, the *Diagnostic and Statistical Manual of Mental Disorders* criteria, or criteria from an adjudicated panel), clinically based in 2 trials, and included in a composite in the remainder of the trials (Table 1).

The secondary outcomes were cognitive decline and mean change in cognitive test scores. The definition of cognitive decline varied among trials, and we used a definition of cognitive decline when the cognitive score decreased by an absolute value within the study period (eg, 3 points in the

Table 1. Characteristics of Included Studies in an Analysis of the Association of Blood Pressure Lowering With Incident Dementia or Cognitive Impairment

Trial	No. of participants	Trial design	Study population	Prevention population	Intervention group	Control group	Follow-up, mo	Testing	Mean or median baseline cognitive score (SD or IQR)		Primary outcome (dementia or cognitive impairment) criteria	Secondary outcome (cognitive decline) criteria	Secondary outcome (cognitive score)
									Intervention	Control			
Dementia (criterion-referenced definition)													
SHEP,[22] 1994	4736	Randomized, double-blind, placebo control	Age, >60 y; SBP of 160-219 mm Hg and DBP <90 mm Hg	Majority primary	Diuretic with or without β-blocker	Placebo	60	Short-Care instrument[a]	0.37 (0.65)	0.38 (0.69)	Adjudicated panel	Not reported	Not reported
PROGRESS,[23] 2003	6105	Randomized, double-blind, placebo control	Stroke/transient ischemic attack in preceding 5 y	Secondary	ACE inhibitor with or without diuretic	Placebo	46.8	MMSE[b]	29 (27-30)	29 (27-30)	*DSM-IV* criteria	Decrease in MMSE score ≥3	Change in MMSE score
Syst-Eur,[5] 2002	2902	Open-label extended follow-up of randomized trial	Age, >60 y; SBP of 160-219 mm Hg and DBP <95 mm Hg	Majority primary	CCB with or without ACE inhibitor and/or diuretic	Placebo	46.8	MMSE[b]	29 (27-30)	29 (27-30)	*DSM-III-R* criteria	Not reported	Change in MMSE score
SCOPE,[24] 2003	4937	Randomized, double-blind, placebo control	Age, 70-89 y; SBP of 160-179 mm Hg and/or DBP of 90-99 mm Hg	Majority primary	ARB with or without second antihypertensive drug	Placebo	44.6	MMSE[b]	28.5 (1.6)	28.5 (1.5)	*ICD-10* criteria	Decrease in MMSE score ≥4	Change in MMSE score
HYVET-COG,[6] 2008	3336	Randomized, double-blind, placebo control	Age, >80 y; sitting SBP of 160-200 mm Hg and DBP <110 mm Hg	Majority primary	Diuretic with or without ACE inhibitor	Placebo	26.4	MMSE[b]	26 (15-30)	26 (15-30)	*DSM-IV* criteria	Decrease in MMSE score ≥3 or MMSE score ≤24	Change in MMSE score
ADVANCE,[24] 2009	11 140	Randomized, double-blind, placebo control (2×2 factorial design)	Age, ≥55 y; diagnosis of type 2 diabetes at age ≥30 y with history/risk factor for CVD	Majority primary	ACE inhibitor and diuretic	Placebo	51.6	MMSE[b]	29 (28-30)	29 (28-30)	*DSM-IV* criteria	Not reported	Not reported
SPRINT MIND,[12] 2019	8563	Randomized, open-label	Age, ≥50 y; SBP between 130 and 180 mm Hg	Majority primary	SBP target <120 mm Hg	SBP target <140 mm Hg	61.3	MoCA[c]	23 (20-26)	23 (20-25)	Adjudicated panel	MCI defined by adjudicated panel criterion	Not reported
								DSCT[d]	51 (41-60)	51 (41-61)			
								LMF II[e]	8 (6-11)	8 (6-11)			
Dementia (clinical-based definition)													
PROFESS,[26] 2008	17 270	Randomized, double-blind, placebo control (2×2 factorial design)	Ischemic stroke in past 90 d	Secondary	ARB	Placebo	30	MMSE[b]	28 (26-30)	28 (26-30)	Investigator reported	Decrease in MMSE score ≥3 and MMSE score ≤24	Not reported
HOPE-3,[13] 2019	1626	Randomized, double-blind, placebo control (2×2 factorial design)	Age, ≥70 y; CVD risk	Majority primary	ARB and diuretic	Placebo	68.4	Modified 12-item MoCA	10.8 (1.7)	10.7 (1.8)	Investigator reported	Decrease of modified MoCA score ≥2 points, TMT Part B score ≥10%, and DSST score ≥5 points	Change in modified MOCA score
								TMT Part B[f]	150.6 (90.7)	152.8 (87.3)			
								DSST[g]	32.8 (18.3)	32.6 (18.3)			

(*continued*)

Table 1. Characteristics of Included Studies in an Analysis of the Association of Blood Pressure Lowering With Incident Dementia or Cognitive Impairment (continued)

Trial	No. of participants	Trial design	Study population	Prevention population	Intervention group	Control group	Follow-up, mo	Testing	Mean or median baseline cognitive score (SD or IQR)		Primary outcome (dementia or cognitive impairment) criteria	Secondary outcome (cognitive decline) criteria	Secondary outcome (cognitive score)
									Intervention	Control			
Dementia and cognitive impairment (composite)													
TRANSCEND,[7] 2011	5383	Randomized, double-blind, placebo control	ACE inhibitor intolerant; CVD/stroke or diabetes	Majority secondary	ARB	Placebo	56	MMSE[b]	29 (27-30)	29 (27-30)	Investigator reported, specialist confirmed, or MMSE score ≤23	Decrease in MMSE score ≥3	Not reported
ONTARGET,[7] 2011	23 469	Randomized, double-blind, placebo control	CVD/stroke or diabetes	Majority secondary	ACE inhibitor and/or ARB	ACE inhibitor	56	MMSE[b]	29 (27-30)	29 (27-30)	Investigator reported, specialist confirmed, or MMSE score ≤23	Decrease in MMSE score ≥3	Not reported
SPS3,[27] 2014	2668	Randomized, open-label (2×2 factorial design)	Lacunar stroke within 6 mo (confirmed on magnetic resonance imaging)	Secondary	SBP target <130 mm Hg	SBP target 130-149 mm Hg	36	CASI z score[h]	−0.63 (1.47)	-0.56 (1.39)	MCI by cognitive score	MCI based on cognitive score	Change in CASI z score
Change in cognitive score only													
MRC-Diuretic,[18] 1996	2584	Randomized, single-blind	Age, 65-74 y; SBP of 160-209 mm Hg and DBP <115 mm Hg	Majority primary	Diuretic or β-blocker	Placebo	54	PALT[i]	17.0 (16.9-17.1)	17.0 (16.9-17.1)	Not reported	Not reported	Change in TMT score
								TMT[f]	59.9 (57.7-62.1)	61 (59.3-62.8)			
MRC-BB,[18] 1996	2584	Randomized, single-blind	Age, 65-74 y; SBP of 160-209 mm Hg and DBP <115 mm Hg	Majority primary	Diuretic or β-blocker	Placebo	54	PALT[i]	17.0 (16.8-17.1)	17.0 (16.9-17.1)	None reported	None reported	Change in TMT score
								TMT[f]	59.5 (57.7-62.0)	61 (59.3-62.8)			
ACCORD-MIND,[28] 2014	1439	Randomized, open-label (2×2 factorial design)	Age, ≥55 y; SBP of 130-180 mm Hg; type 2 diabetes	Majority primary	SBP target <120 mm Hg	SBP target <140 mm Hg	40	DSST[g]	52.28 (15.7)	52.28 (15.7)	Not reported	Not reported	Change in MMSE score
								MMSE[b]	27.25 (26-29)	28 (26-29)			

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; CVD, cardiovascular disease; DBP, diastolic blood pressure; *DSM, Diagnostic and Statistical Manual of Mental Disorders*; *ICD, International Classification of Diseases*; IQR, interquartile range; MCI, mild cognitive impairment; SBP, systolic blood pressure.

[a] Short-Care Instrument assesses global cognitive impairment using a diagnostic scale, with a cutoff score of 0.88 for dementia; higher scores indicate worse cognitive function. The mean score in SHEP of 0.37 denotes normal cognitive function.

[b] Mini-Mental State Examination (MMSE) assesses global cognitive function. Scores range from 0 to 30, with higher scores indicating better cognitive function; a score greater than 26 represents normal cognitive function. For trials that reported MMSE score, mean score of 28.34 denotes normal cognitive function.

[c] Montreal Cognitive Assessment (MoCA) assesses global cognitive function. Scores range from 0 to 30, with higher scores indicating better cognitive function; a score of at least 26 indicates normal cognitive function. The mean score in SPRINT MIND of 23 denotes mild cognitive impairment.

[d] Digit Symbol Coding Test (DSCT) assesses processing speed. Scores range from 0 to 135, with higher scores indicating better cognitive function. The mean score in SPRINT MIND of 51 denotes mild cognitive impairment.

[e] Logical Memory form II (LMF II) assesses long-term narrative memory. Scores range from 0 to 14, with higher scores indicating better cognitive function. The mean score in SPRINT MIND of 8 denotes mild cognitive impairment.

[f] Trail Making Test (TMT) assesses rote memory and executive function. The maximum time for each part is 300 seconds, with slower times denoting worse cognitive function. The mean times of 60.4 in MRC and 151.7 in HOPE-3 denote normal cognitive function.

[g] Digit Symbol Substitution Test (DSST) assesses working memory. Scores range from 0 to 133, with higher scores indicating better cognitive function. For trials that reported DSST score, a mean score of 42.5 denotes normal cognitive function.

[h] Cognitive Abilities Screening Instrument (CASI) z score assesses global cognitive function by reporting SD above or below population means. The mean score in SPS3 of −0.6 denotes normal cognitive function.

[i] Paired Associate Learning Test (PALT) assesses semantic memory. Scores range from 3 to 93, with higher scores indicating worse cognitive function. The mean score of 17 in MRC denotes normal cognitive function.

Mini-Mental State Examination [MMSE] score), alone or combined with below a cut point in cognitive score. All included studies reported a cognitive test score.

Risk of Bias Assessment

We used the Cochrane risk of bias tool[16] to assess methodological quality of eligible trials. Trials were assessed on random sequence generation, allocation concealment, blinding of participants and health care personnel, blinded outcome assessment, completeness of outcome data, evidence of selective reporting, and other biases. Risk of bias assessments were performed independently by 2 reviewers (D.H. and R.M.), and disagreements were resolved by a third reviewer (C.J.). If 2 of the domains were rated as high, the study was considered to be at high risk of bias. A risk-of-bias summary table was created in Review Manager, version 5.3. Additional details are included in the Supplement (eTable 1, eFigure 1, and eFigure 2).

Data Synthesis and Analysis

A descriptive analysis of each individual trial is provided in Table 1. Baseline, follow-up, and mean difference in blood pressure for each trial are reported in **Table 2**. For dichotomous outcomes (dementia, cognitive impairment, and cognitive decline), odds ratios (ORs) and 95% CIs were estimated for each trial. Weighted pooled treatment effects were calculated using restricted maximum likelihood estimation to fit a random-effects meta-analysis model. For continuous outcomes (eg, MMSE score), the mean change from baseline to follow-up was analyzed. If this was not reported, the mean between-group difference reported at follow-up was used. Standard errors were calculated by converting 95% CIs using the following formula: SD = $\sqrt{N}$ × (upper bound of the CI − lower bound of the CI)/3.92.[17] The difference in MMSE score change between the intervention and control group was calculated when the difference was not reported in the trial. A pooled mean difference and 95% CI was calculated using a random-effects meta-analysis. A positive mean difference implies that the intervention, compared with the control, had a smaller magnitude of decrease in MMSE score between baseline and follow-up (ie, reduced cognitive decline on testing). For additional cognitive test scores, we calculated a pooled mean standardized difference (Cohen *d*) using a random-effects meta-analysis model. The variability across studies due to heterogeneity was investigated using forest plots and I^2 statistics. Publication bias was assessed using a funnel plot (eFigure 3 in the Supplement). Two trials had 2 investigational treatment groups with a common control group.[7,18] To prevent double counting and a unit-of-analysis error, we split the common control group into 2 equal-sized groups.[17]

A priori subgroup sensitivity analyses that assessed pooled estimates for trials that reported cumulative blood pressure change that was above and below the median cumulative blood pressure change and trials that reported years of follow-up above and below the median number of years of follow-up were performed. We tested for an interaction between subgroup relative risks by dividing the difference in log relative risk by its standard error.[19] We completed meta-regression analyses to evaluate the association of select variables with treatment effect estimates, including baseline mean systolic blood pressure, years of follow-up, or cumulative systolic blood pressure change. In post hoc analyses, absolute risk reductions (ARRs) and 95% CIs were calculated for each study, the Mantel-Haenszel method was used to obtain a pooled estimate of the risk difference, and bootstrapping was used to estimate the ARRs for trials that reported dementia only. In addition, a sensitivity analysis that included only studies at low risk of bias was performed and the fragility index was calculated for the primary outcome. Statistical analyses were performed using the Metafor package[20] in R statistical software, version 3.5.3. Comparisons were 2-tailed using a threshold of $P \leq .05$ for significance for all analyses except for subgroup interactions, in which we used a threshold of $P \leq .10$ for significance.[21]

Results

The systematic search of articles published before December 31, 2019, identified 1543 results. After title and abstract screening, 163 articles were considered potentially relevant. Fourteen studies, available as 22 articles, were included after full-text review (eFigure 4 in the Supplement). Twelve studies reported the incidence of dementia (n = 9) or composite of dementia or cognitive impairment (n = 3) on follow-up and were included in the primary meta-analysis.[5-7,12,13,22-27] Two studies were used for secondary outcomes only.[18,28]

Study Characteristics

In total, 96 158 participants were enrolled, comprising 394 558 participant-years of follow-up. The mean (SD) age of trial participants was 69 (5.4) years and 40 617 participants (42.2%) were women. The mean baseline systolic blood pressure among participants was 154 (14.9) mm Hg and the mean baseline diastolic blood pressure was 83.3 (9.9) mm Hg. The mean (range) duration of follow-up was 49.24 (26.4-68.4) months. The publication year ranged from 1994 to 2019 (Table 1). Nine trials were of a majority primary prevention population,[5,6,12,13,18,22,24,25,28] 3 trials were of a poststroke secondary prevention population,[23,26,27] and 2 trials were of participants with cardiovascular disease.[7] Ten trials were placebo controlled,[5-7,13,18,22-26] 3 trials compared different blood pressure targets,[12,27,28] and 1 compared 2 antihypertensive agents alone or in combination (resulting in 2 comparisons).[7]

Risk of Bias

Risk of bias was assessed in all 14 trials (eTable 1, eFigure 1, and eFigure 2 in the Supplement). The overall risk of bias was deemed low in 11 trials, unclear in 1 trial, and high in 2 trials. The majority of trials (n = 11) were double-blind randomized clinical trials with prespecified outcomes and 1 was single-blinded.[18] Two trials were open label,[12,27] while 1 trial had a double-blind phase followed by open-label observational follow-up.[5] Randomization sequence was adequately generated in 13 studies and 13 adequately concealed allocation. Reporting bias was noted in 1 trial.[27] There was no evidence of publication bias for the primary outcome (Egger test, −0.53; $P = .61$).

Table 2. Participant Characteristics of Studies Included in an Analysis of the Association of Blood Pressure Lowering With Incident Dementia or Cognitive Impairment

Trial	Country	Mean or median age at entry (SD or IQR), y	Female participants, No. (%)	Intervention group, mean (SD or IQR), mm Hg			Control group, mean (SD or IQR), mm Hg			Difference in BP difference
				Baseline BP	Follow-up BP	Difference in BP	Baseline BP	Follow-up BP	Difference BP	
Dementia (criterion-referenced definition)										
SHEP,[22] 1994	US	72 (6.7)	2700 (57)	Systolic: 170.5 (9.5); diastolic: 76.7 (9.6)	Systolic: 144.0 (19.3); diastolic: 67.7 (10.2)	Not reported	Systolic: 170.1 (9.2); diastolic: 76.4 (9.8)	Systolic: 155.1 (20.9); diastolic: 71.1 (12.8)	Not reported	Systolic: −11.1; diastolic: −3.4
PROGRESS,[23] 2003	Asia, Australasia, United Kingdom, and Europe	64 (10)	1831 (30)	Systolic: 147 (19); diastolic: 86 (11)	Not reported	Not reported	Systolic: 147 (19); diastolic: 86 (11)	Not reported	Not reported	Systolic: −9; diastolic: −4
Syst-Eur,[5] 2002	Europe	68 (60-92)	1918 (66)	Systolic: 173.8 (9.9); diastolic: 85.5 (5.8)	Systolic: 149.1 (9.7); diastolic: 79.4 (6.1)	Systolic: 23 (16); diastolic: 7 (8)	Systolic: 173.9 (10.1); diastolic: 85.5 (5.9)	Systolic: 156.1 (12); diastolic: 82.5 (6)	Systolic: 13 (17); diastolic: 2 (8)	Systolic: −7; diastolic: −3.2
SCOPE,[24] 2003	Europe, United Kingdom, US	76.4	3177 (65)	Systolic: 166 (8.9); diastolic: 90.3 (6.6)	Systolic: 145.2 (16.1); diastolic: 79.9 (8.7)	Not reported	Systolic: 166.5 (9.0); diastolic: 90.4 (6.6)	Systolic: 148.5 (16.8); diastolic: 81.6 (8.8)	Not reported	Systolic: −3.2; diastolic: −1.6
HYVET-COG,[6] 2008	Europe, China, Tunisia, Southeast Asia, and Australia	83.5 (3.1)	2017 (61)	Systolic: 173.0 (8.4); diastolic: 90.8 (8.5)	Systolic: 143.4; diastolic: 77.7	Systolic: 29.6 (15.3); diastolic: 13.1 (9.6)	Systolic: 173.0 (8.6); diastolic: 90.8 (8.5)	Systolic: 155.4; diastolic: 83.6	Systolic: 14.6 (18.5); diastolic: 7.2 (10.5)	Systolic: −15; diastolic: −5.9
ADVANCE,[24] 2009	Asia, Australasia, Europe, and North America	67 (6)	4735 (43)	Systolic: 145; diastolic: 81	Systolic: 136; diastolic: 73	Not reported	Systolic: 145; diastolic: 81	Systolic: 140; diastolic: 73	Not reported	Systolic: −5.6; diastolic: −2.2
SPRINT MIND,[12] 2019	US	67.9 (9.4)	3332 (35.5)	Systolic: 139.7 (15.8); diastolic: 78.2 (11.9)	Systolic: 121.6 (120.8-122.3); diastolic: not reported	Not reported	Systolic: 139.7 (15.4); diastolic: 78.0 (12.0)	Systolic: 134.8 (134.1-135.6); diastolic: not reported	Not reported	Systolic: −13.3; diastolic: not reported
Dementia (clinical-based definition)										
PRoFESS,[26] 2008	35 countries worldwide	66.1 (8.6)	7310 (36)	Systolic: 144 (17); diastolic: 84 (11)	Systolic: 135.7; diastolic: not reported	Systolic: 8.3; diastolic: not reported	Systolic: 144 (17); diastolic: 84 (11)	Systolic: 141.1; diastolic: not reported	Systolic: 2.9; diastolic: not reported	Systolic: −5.4; diastolic: not reported
HOPE-3,[13] 2019	21 countries worldwide	74 (3.5)	963 (59.2)	Systolic: 139.7 (15.0); diastolic: 79.4 (9.6)	Not reported	Not reported	Systolic: 139.7 (15.0; diastolic: 79.4 (9.6)	Not reported	Not reported	Systolic: −6; diastolic: Not reported
Dementia and cognitive impairment (composite)										
TRANSCEND,[7] 2011	40 countries worldwide	67 (7.3)	2547 (43)	Systolic: 140.7 (16.8); diastolic: 81.8 (10.1)	Not reported	Not reported	Systolic: 141.3 (16.4); diastolic: 82.0 (10.2)	Not reported	Not reported	Systolic: −4; diastolic: −2.2
ONTARGET (dual treatment),[7] 2011	40 countries worldwide	66 (7.2)	6831 (27)	Systolic: 141.9 (17.6); diastolic: 82.1 (10.4)	Not reported	Not reported	Systolic: 141.8 (17.4); diastolic: 82.1 (10.4)	Not reported	Not reported	Systolic: −2.4; diastolic: −1.4
ONTARGET (ARB treatment),[7] 2011				Systolic: 141.7 (17.2); diastolic: 82.1 (10.4)	Not reported	Not reported	Systolic: 141.8 (17.5); diastolic: 82.1 (10.5)	Not reported	Not reported	Systolic: −0.9; diastolic: −0.6
SPS3,[27] 2014	North America, Latin America, and Spain	63 (11)	1088 (37)	Systolic: 144 (19); diastolic: 79 (11)	Systolic: 127 (2.97); diastolic: Not reported	Not reported	Systolic: 142 (19); diastolic: 78 (10)	Systolic: 137 (3.4); diastolic: Not reported	Not reported	Systolic: −11; diastolic: not reported

(continued)

Table 2. Participant Characteristics of Studies Included in an Analysis of the Association of Blood Pressure Lowering With Incident Dementia or Cognitive Impairment (continued)

Trial	Country	Mean or median age at entry (SD or IQR), y	Female participants, No. (%)	Intervention group, mean (SD or IQR), mm Hg			Control group, mean (SD or IQR), mm Hg			Difference in BP difference
				Baseline BP	Follow-up BP	Difference in BP	Baseline BP	Follow-up BP	Difference BP	
Change in cognitive score only										
MRC-Diuretic,[18] 1996	United Kingdom	70	1498 (58)	Systolic: 184.9 (183.9-185.9); diastolic: 90.3 (89.4-91.2)	Not reported	Not reported	Systolic: 183.5 (182.8-184.2); diastolic: 90.5 (89.9-91.2)	Not reported	Not reported	Systolic: −17.1; diastolic: not reported
MRC-BB,[18] 1996				Systolic: 184.2 (183.2-185.2); diastolic: 90.7 (89.9-91.6)	Not reported	Not reported	Systolic: 183.5 (182.8-184.2); diastolic: 90.5 (89.9-91.2)	Not reported	Not reported	Systolic: −14.5; diastolic: not reported
ACCORD-MIND,[28] 2014	North America	62 (5.8)	670 (46.6)	Systolic: 138.8 (17.0); diastolic: 76.0 (10.4)	Systolic: 119 (14.7); diastolic: 64 (10.1)	Not reported	Systolic: 139.2 (15.7); diastolic: 76.3 (10.3)	Systolic: 133.2 (14.8); diastolic: 70.2 (9.9)	Not reported	Systolic: −13.8; diastolic: −5.9

Abbreviations: ARB, angiotensin II receptor blocker; BP, blood pressure; IQR, interquartile range.

Blood Pressure Lowering and Dementia or Cognitive Impairment

Twelve trials reported dementia or cognitive impairment on follow-up (92 135 participants).[5-7,12,13,22-27] Dementia or cognitive impairment was diagnosed in 2992 participants in the intervention group and 2558 participants in the control group. Blood pressure lowering with antihypertensive agents compared with control was significantly associated with a reduction in dementia or cognitive impairment (7.0% vs 7.5% over a mean trial follow-up of 4.1 years; OR, 0.93 [95% CI, 0.88-0.98]; ARR, 0.39% [95% CI, 0.09%-0.68%]) (**Figure 1**). Heterogeneity was low (I^2 = 0.0%). A sensitivity analysis that divided trials by cumulative blood pressure change above and below the median cumulative blood pressure change did not reveal a significant difference between subgroups (*P* value for interaction = .13) (**Figure 2**; eFigure 5 in the Supplement). A sensitivity analysis that divided trials by baseline blood pressure above and below the median baseline blood pressure did not reveal a significant difference between subgroups (*P* value for interaction = .36) (Figure 2; eFigure 6 in the Supplement). Meta-regression analysis showed no significant association of select variables with treatment effect estimates, including age, baseline systolic blood pressure, years of follow-up, and cumulative systolic blood pressure change (eFigure 7 in the Supplement).

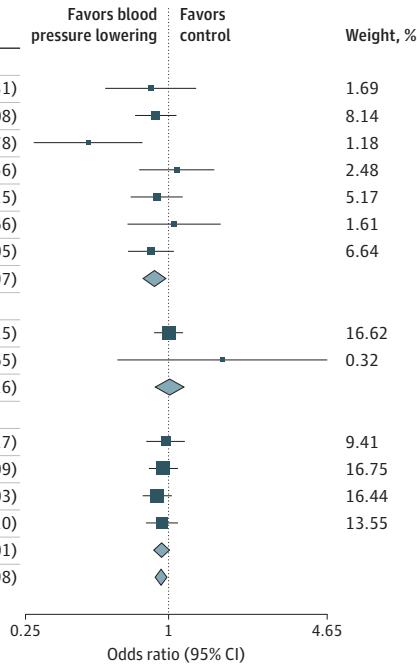
In post hoc analyses, for trials that employed a criterion-referenced definition for diagnosis of dementia (7 trials; 41 719 participants), blood pressure lowering was significantly associated with a reduction in dementia (OR, 0.87 [95% CI, 0.78-0.97]; ARR, 0.20% [95% CI, 0.05%-0.70%]). A sensitivity analysis that only included studies at low risk of bias did not materially alter the findings (OR, 0.94 [95% CI, 0.877-0.997]) (eFigure 8 in the Supplement). The fragility index for a meta-analysis of the primary outcome was 9.[29]

Blood Pressure Lowering and Cognitive Decline

Eight trials reported cognitive decline on follow-up (67 476 participants).[6,7,12,13,23,24,26] Cognitive decline was reported in 5513 participants in the intervention group and 4468 participants in the control group. Blood pressure lowering with antihypertensive agents compared with control was significantly associated with a reduction in cognitive decline (20.2% vs 21.1% over a mean trial follow-up of 4.1 years; OR, 0.93 [95% CI, 0.88-0.99]; ARR, 0.71% [95% CI, 0.19%-1.2%]) (**Figure 3**). Heterogeneity was low to moderate (I^2 = 36.1%). Sensitivity analysis by cumulative change in blood pressure (above and below median) showed a significant association for cumulative blood pressure change above the median (OR, 0.89 [95% CI, 0.82-0.96]), but there was no statistically significant association for cumulative blood pressure change below the median (OR, 0.98 [95% CI, 0.92-1.05]) (*P* value for interaction = .07) (Figure 2; eFigure 9 in the Supplement). Sensitivity analysis by baseline blood pressure above and below the median reported no significant subgroup interaction (*P* value for interaction = .74) (Figure 2; eFigure 10 in Supplement). Meta-regression analysis showed no significant association of

Figure 1. Association of Blood Pressure Lowering With Dementia or Cognitive Impairment

Study	Participants with dementia or cognitive impairment/total No.		Absolute risk reduction (95% CI), %	Odds ratio (95% CI)	Weight, %
	Blood pressure lowering group	Control group			
Dementia (criterion-referenced)					
SHEP,[22] 1994	37/2365	44/2371	0.29 (-0.45 to 1.03)	0.84 (0.54 to 1.31)	1.69
PROGRESS,[23] 2003	193/3051	217/3054	0.78 (-0.48 to 2.04)	0.88 (0.72 to 1.08)	8.14
Syst-Eur,[5] 2002	21/1485	43/1417	1.62 (0.54 to 2.70)	0.46 (0.27 to 0.78)	1.18
SCOPE,[24] 2003	62/2477	57/2460	-0.19 (-1.04 to 0.67)	1.08 (0.75 to 1.56)	2.48
HYVET-COG,[6] 2008	126/1687	137/1649	0.84 (-0.99 to 2.67)	0.89 (0.69 to 1.15)	5.17
ADVANCE,[25] 2009	39/5569	37/5571	-0.04 (-0.34 to 0.27)	1.05 (0.67 to 1.66)	1.61
SPRINT MIND,[12] 2019	149/4278	176/4285	0.62 (-0.18 to 1.43)	0.84 (0.67 to 1.05)	6.64
Random-effects model for subgroup (Q_6 = 7.92; P = .24; I^2 = 0.0%)				0.87 (0.78 to 0.97)	
Dementia (clinical-based)					
PRoFESS,[26] 2008	408/8624	409/8646	0.00 (-0.63 to 0.63)	1.00 (0.87 to 1.15)	16.62
HOPE-3,[13] 2019	10/811	6/815	-0.50 (-1.46 to 0.46)	1.68 (0.61 to 4.65)	0.32
Random-effects model for subgroup (Q_1 = 0.99; P = .32; I^2 = 0.0%)				1.01 (0.88 to 1.16)	
Dementia and mild cognitive impairment (composite)					
TRANSCEND,[7] 2011[a]	239/2694	245/2689	0.24 (-1.29 to 1.77)	0.97 (0.81 to 1.17)	9.41
ON TARGET (Dual),[7] 2011[a]	618/7807	326/3932.5	0.37 (-0.68 to 1.42)	0.95 (0.83 to 1.09)	16.75
ON TARGET (ARB),[7] 2011[a]	584/7797	326/3932.5	0.80 (-0.24 to 1.84)	0.90 (0.78 to 1.03)	16.44
SPS3,[27] 2014[a]	506/1323	535/1345	1.53 (-2.17 to 5.23)	0.94 (0.80 to 1.10)	13.55
Random-effects model for subgroup (Q_3 = 0.57; P = .90; I^2 = 0.0%)				0.93 (0.87 to 1.01)	
Test for overall effect: z = -2.50; P = .01			0.39 (0.09 to 0.68)	0.93 (0.88 to 0.98)	
Heterogeneity: τ^2 = 0.00; χ^2 = 12.14; P = .43; I^2 = 0.0%					

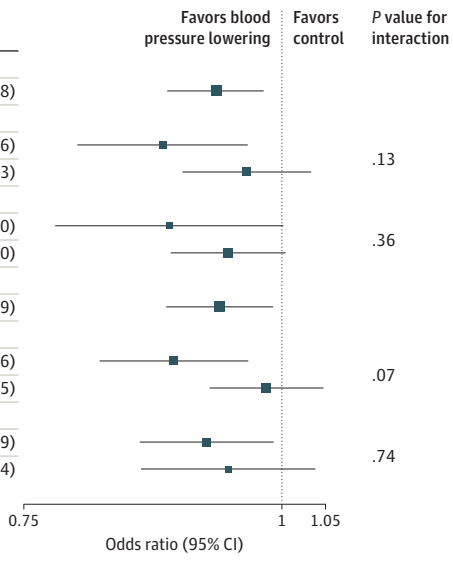


The squares and bars represent the mean values and 95% CIs of the effect sizes and the area of the squares reflects the weight of the studies. Diamonds represent the combined effects and the vertical dotted line represents the line of no association.

[a] Composite of dementia and cognitive impairment.

Figure 2. Association of Blood Pressure Lowering With Dementia or Cognitive Impairment/Decline by Cumulative Systolic Blood Pressure Change and Baseline Systolic Blood Pressure

Subgroup	No. of events/total No.		Absolute risk reduction (95% CI), %	Odds ratio (95% CI)	*P* value for interaction
	Blood pressure lowering group	Control group			
Blood pressure lowering and dementia or cognitive impairment					
Overall	2992/49968	2558/42167	0.39 (0.09 to 0.68)	0.93 (0.88 to 0.98)	
Cumulative systolic blood pressure change					
Above median	1032/14189	1152/14121	0.81 (0.20 to 1.40)	0.88 (0.80 to 0.96)	.13
Below median	1960/35779	1406/28046	0.19 (-0.20 to 0.54)	0.96 (0.90 to 1.03)	
Baseline systolic blood pressure					
Above median	478/16634	535/16522	0.37 (0.01 to 0.74)	0.88 (0.78 to 1.00)	.36
Below median	2514/33334	2023/25645	0.39 (-0.03 to 0.82)	0.94 (0.88 to 1.00)	
Blood pressure lowering and cognitive decline					
Overall	5513/37504	4468/29972	0. 71 (0.19 to 1.20)	0.93 (0.88 to 0.99)	
Cumulative systolic blood pressure change					
Above median	2427/17358	2617/17321	1.10 (0.50 to 1.80)	0.89 (0.82 to 0.96)	.07
Below median	3086/20146	1851/12651	0.21 (-0.60 to 1.00)	0.98 (0.92 to 1.05)	
Baseline systolic blood pressure					
Above median	1669/14746	1777/14681	0.82 (0.10 to 1.50)	0.92 (0.85 to 0.99)	.74
Below median	3844/22758	2691/15291	0.62 (-0.10 to 1.40)	0.94 (0.85 to 1.04)	

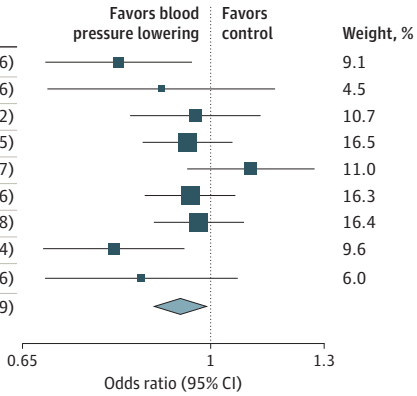


The squares and bars represent the mean values and 95% CIs of the effect sizes and the area of the squares reflects the weight of the studies. The vertical dotted line represents the line of no association.

select variables with treatment effect estimates, including age, baseline systolic blood pressure, years of follow-up, and cumulative systolic blood pressure change (eFigure 11 in Supplement).

Figure 3. Association of Blood Pressure Lowering and Cognitive Decline

Study	Participants with dementia or cognitive impairment/total No.		Absolute risk reduction (95% CI), %	Odds ratio (95% CI)
	Blood pressure lowering group	Control group		
PROGRESS,[23] 2003	276/3051	334/3054	1.89 (0.39 to 3.39)	0.81 (0.68 to 0.96)
SCOPE,[24] 2003	113/2477	125/2460	0.52 (-0.68 to 1.71)	0.89 (0.69 to 1.16)
HYVET-COG,[6] 2008	485/1687	486/1649	0.72 (-2.36 to 3.81)	0.97 (0.83 to 1.12)
PRoFESS,[26] 2008	795/7531	832/7518	0.51 (-0.48 to 1.50)	0.95 (0.86 to 1.05)
TRANSCEND,[7] 2011[a]	454/2642	412/2589	-1.27 (-3.28 to 0.74)	1.10 (0.95 to 1.27)
ON TARGET (Dual),[7] 2011	1240/7461	657/3801	0.67 (-0.80 to 2.13)	0.95 (0.86 to 1.06)
ON TARGET (ARB),[7] 2011	1279/7566	657/3801	0.38 (-1.09 to 1.85)	0.97 (0.88 to 1.08)
SPRINT MIND,[12] 2019	287/4278	353/4285	1.53 (0.42 to 2.64)	0.80 (0.68 to 0.94)
HOPE-3,[13] 2019	584/811	612/815	3.08 (-1.20 to 7.37)	0.85 (0.68 to 1.06)
Test for overall effect: $z = -2.28$; $P = .02$ Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 12.60$; $P = .13$; $I^2 = 36.1\%$			0.71 (0.19 to 1.2)	0.93 (0.88 to 0.99)



The squares and bars represent the mean values and 95% CIs of the effect sizes and the area of the squares reflects the weight of the studies. The diamond represents the combined effect and the vertical dotted line represents the line of no association.

Blood Pressure Lowering and Change in Cognitive Score

Eight trials reported a change in cognitive score as an outcome.[5,6,13,18,23,24,27,28] For the meta-analyses, change in MMSE score in 5 trials,[5,6,23,24,28] change in Trail Making Test score in 2 trials,[13,18] and change in Cognitive Abilities Screening Instrument z score in 1 trial[27] were used. Three studies reported baseline cognitive scores but not follow-up scores, and these data were insufficient to include in the meta-analysis.[7,26] Blood pressure lowering with antihypertensive agents compared with control was not significantly associated with a difference in the standardized mean cognitive score (standardized mean difference, 0.25 [95% CI, −0.10 to 0.61]; *P* value for heterogeneity < .01; I^2 = 99.5%; Q = 853.24) (eFigure 12 in the Supplement). For trials that reported change in MMSE score, blood pressure lowering with antihypertensive agents compared with control was not significantly associated with a difference in mean MMSE score (mean difference, 0.44 [95% CI, −0.22 to 1.10]; I^2 = 98.5%; Q = 143.17) (eFigure 13 in Supplement).

Discussion

This meta-analysis, which included 12 trials with 92 135 participants for the primary outcome analysis, found that blood pressure lowering with antihypertensive agents compared with control was significantly associated with a lower risk of dementia or cognitive impairment. This study builds on previous meta-analyses that have examined the association of blood pressure lowering and dementia and includes the largest number of randomized clinical trials to date. A 2013 pooled analysis that combined randomized clinical trials and observational studies reported a similar risk reduction with treatment of hypertension to the current analysis, but no significant association in an analysis of trials alone.[10] A meta-analysis by van Middelar et al[30] reported a similar, but nonsignificant, magnitude of association of blood pressure lowering, and included 2 trials that evaluated multicomponent lifestyle interventions rather than blood pressure lowering alone. Both these meta-analyses, and Cochrane reviews, were published before the SPRINT MIND and HOPE-3 trials.[9,10,30] The most recent meta-analysis, by Peters et al,[11] which included the SPRINT MIND trial, reported an association of blood pressure lowering with reduced risk of dementia (OR, 0.93 [95% CI, 0.86-1.00]) and included fewer trials than the current meta-analysis (8 trials) due to different selection criteria. In an analysis confined to trials that reported a between-group blood pressure difference of greater than 10 mm Hg (4 trials), Peters et al[11] reported an OR of 0.88 (95% CI, 0.78-0.98), but did not report a *P* value for interaction. The approach taken in the current meta-analysis resulted in the inclusion of a larger number of clinical trials and a more extensive panel of reported outcome measures (eg, cognitive decline and mean change of cognitive test scores) and in the completion of a meta-regression for preselected variables. Although the increased number of clinical trials resulted in a statistically significant summary estimate, the upper bound of the CI was close to 1.0, which should prompt some caution in interpreting the findings as definitive evidence of an association of blood pressure lowering with dementia or cognitive impairment.

Although observational studies report hypertension to be an important risk factor for dementia,[1,3,4,31] the benefit of blood pressure lowering on dementia or cognitive impairment in clinical trials is modest (OR, 0.93 [95% CI, 0.88-0.98]) and lower than the risk reduction for stroke.[5,6,18,22-24] The causes of neurocognitive syndromes are more heterogenous than stroke, including Alzheimer disease and other causes, and the population-attributable fraction of hypertension for dementia is lower than that reported for stroke based on indirect comparison of studies.[32,33] In addition, the association of hypertension with neurocognitive syndromes, mediated through chronic covert vascular damage (ischemia, microhemorrhage, or atrophy[34]), appears to have an extended time lag between cause and clinical consequence, although dementia may be a complication of acute stroke. Observational studies relating blood pressure to

neurocognitive outcomes have often required extended follow-up (eg, >10 y). Therefore, large sample sizes, with extended follow-up, are required to identify an effect of antihypertensive treatment on neurocognitive outcomes. These considerations may explain why many individual randomized clinical trials have failed to demonstrate a treatment effect.

Epidemiologic studies have reported a stronger association of hypertension in midlife with neurocognitive outcomes in late-life than hypertension in late-life, during which a null or inverse association has been reported in some studies.[35,36] These findings have led some investigators to speculate that populations included in some blood pressure trials may have been in an older age group that may not benefit from blood pressure lowering to prevent cognitive outcomes. Findings from the current meta-regression analyses would not fully support this contention because baseline age was not a determinate of treatment effect and the mean age of participants in included trials was 69 years at baseline.

These findings have the potential to inform public health strategies to reduce the burden of dementia globally. Effective screening for and management of hypertension is essential for reducing premature dependence from dementia. Although the lower risk associated with blood pressure treatment is modest for an individual, the effect at a population level, given the incidence of dementia in an aging population, may be considerable. Rates of blood pressure control are low, even in high-income countries, but especially in middle- and low-income countries, which carry the largest burden of dementia.[37] The World Health Organization's global action plan on the public health response to dementia recommends management of hypertension in midlife to reduce the risk of dementia, a recommendation supported by the results of the current study.[38]

Although there was a significant reduction of clinically important neurocognitive syndromes, there was no significant difference in mean change in cognitive testing, contrasting from the clinical outcomes. This finding supports the need for large, simple trials with clinically important outcomes to evaluate preventative interventions in populations.[39] None of the included clinical trials reported dementia as their primary outcome measure in the original trial. When dementia was reported, it was as a secondary outcome with differences in outcome definition. In post hoc analyses confined to include clinical trials that reported criterion-referenced dementia, the association of blood pressure lowering and dementia was most evident (Figure 1).

Limitations

This study has several limitations. First, there are inherent challenges in performing and interpreting a meta-analysis with heterogenous populations, interventions, and definitions of the outcomes of dementia, cognitive impairment, and cognitive decline. Second, the low incidence of dementia in all clinical trials, despite the large number of participants, reduced power to detect differences in treatment effect and limited exploration of subgroups or meta-regression. Third, underdetection of dementia in clinical trials due to preferential loss to follow-up of participants with dementia and the potential effect of survival bias (participants with blood pressure reductions are more likely to be alive) are unmeasured sources of potential error. Fourth, we are unable to identify the optimal blood pressure range for dementia prevention.

Conclusions

In this meta-analysis of randomized clinical trials, blood pressure lowering with antihypertensive agents compared with control was significantly associated with a lower risk of incident dementia or cognitive impairment.

ARTICLE INFORMATION

Accepted for Publication: March 13, 2020.

Author Contributions: Drs Hughes and Judge had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis as co–first authors.
Concept and design: Hughes, Judge, Murphy, Loughlin, O'Donnell, Canavan.
Acquisition, analysis, or interpretation of data: Hughes, Judge, Murphy, Costello, Whiteley, Bosch, O'Donnell, Canavan.
Drafting of the manuscript: Hughes, Judge, Murphy, Loughlin, Costello, O'Donnell, Canavan.
Critical revision of the manuscript for important intellectual content: Hughes, Judge, Murphy, Whiteley, Bosch, O'Donnell, Canavan.
Statistical analysis: Hughes, Judge, Costello, Canavan.
Obtained funding: Judge.
Administrative, technical, or material support: Murphy, Loughlin, Canavan.
Supervision: Murphy, Loughlin, O'Donnell, Canavan.

Conflict of Interest Disclosures: Dr Judge reported receiving grants from the Wellcome Trust and the Health Research Board during the conduct of the study. Dr Whiteley reported receiving grants from the Chief Scientist Office outside the submitted work. Dr Bosch reported receiving personal fees from Bayer AG outside the submitted work. No other disclosures were reported.

Funding/Support: Dr Judge was supported by the Irish Clinical Academic Training Programme, the Wellcome Trust, the Health Research Board (grant number 203930/B/16/Z), the Health Service Executive, National Doctors Training and Planning, and the Health and Social Care Research and Development Division Northern Ireland. Dr O'Donnell was supported by the European Research Council (COSIP grant 640580).

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: John Ferguson, PhD (HRB Clinical Research Facility, Galway), contributed to the updated analysis (bootstrapping method for applying relative risk reduction to baseline risk of dementia). He did not receive compensation for his contribution.

REFERENCES

1. Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology*. 2005;64(2):277-281. doi:10.1212/01.WNL.0000149519.47454.F2

2. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *Lancet Neurol*. 2014;13(8):788-794. doi:10.1016/S1474-4422(14)70136-X

3. Launer LJ, Ross GW, Petrovitch H, et al. Midlife blood pressure and dementia: the Honolulu-Asia aging study. *Neurobiol Aging*. 2000;21(1):49-55. doi:10.1016/S0197-4580(00)00096-8

4. Skoog I, Lernfelt B, Landahl S, et al. 15-Year longitudinal study of blood pressure and dementia. *Lancet*. 1996;347(9009):1141-1145. doi:10.1016/S0140-6736(96)90608-X

5. Forette F, Seux M-L, Staessen JA, et al; Systolic Hypertension in Europe Investigators. The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study. *Arch Intern Med*. 2002;162(18):2046-2052. doi:10.1001/archinte.162.18.2046

6. Peters R, Beckett N, Forette F, et al; HYVET investigators. Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. *Lancet Neurol*. 2008;7(8):683-689. doi:10.1016/S1474-4422(08)70143-1

7. Anderson C, Teo K, Gao P, et al; ONTARGET and TRANSCEND Investigators. Renin-angiotensin system blockade and cognitive function in patients at high risk of cardiovascular disease: analysis of data from the ONTARGET and TRANSCEND studies. *Lancet Neurol*. 2011;10(1):43-53. doi:10.1016/S1474-4422(10)70250-7

8. Zonneveld TP, Richard E, Vergouwen MD, et al. Blood pressure-lowering treatment for preventing recurrent stroke, major vascular events, and dementia in patients with a history of stroke or transient ischaemic attack. *Cochrane Database Syst Rev*. 2018;7:CD007858. doi:10.1002/14651858.CD007858.pub2

9. McGuinness B, Todd S, Passmore P, Bullock R. Blood pressure lowering in patients without prior cerebrovascular disease for prevention of cognitive impairment and dementia. *Cochrane Database Syst Rev*. 2009;(4):CD004034. doi:10.1002/14651858.CD004034.pub3

10. Levi Marpillat N, Macquin-Mavier I, Tropeano A-I, Bachoud-Levi A-C, Maison P. Antihypertensive classes, cognitive decline and incidence of dementia: a network meta-analysis. *J Hypertens*. 2013;31(6):1073-1082. doi:10.1097/HJH.0b013e3283603f53

11. Peters R, Warwick J, Anstey KJ, Anderson CS. Blood pressure and dementia: What the SPRINT-MIND trial adds and what we still need to know. *Neurology*. 2019;92(21):1017-1018. doi:10.1212/WNL.0000000000007543

12. Williamson JD, Pajewski NM, Auchus AP, Bryan RN, Chelune G, Cheung AK, et al; SPRINT MIND Investigators for the SPRINT Research Group. Effect of intensive vs standard blood pressure control on probable dementia: a randomized clinical trial. *JAMA*. 2019;321(6):553-561. doi:10.1001/jama.2018.21442

13. Bosch J, O'Donnell M, Swaminathan B, et al; HOPE-3 Investigators. Effects of blood pressure and lipid lowering on cognition: Results from the HOPE-3 study. *Neurology*. 2019;92(13):e1435-e1446. doi:10.1212/WNL.0000000000007174

14. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151(4):264-269. doi:10.7326/0003-4819-151-4-200908180-00135

15. Tendal B, Nuesch E, Higgins JPT, Juni P, Gotzsche PC. Multiplicity of data in trial reports and the reliability of meta-analyses: empirical study. *BMJ*. 2011;343:d4829. doi:10.1136/bmj.d4829

16. Higgins JPT, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928. doi:10.1136/bmj.d5928

17. *Cochrane Handbook for Systematic Reviews of Interventions: Version 5.1.0*. Cochrane Collaboration; 2011.

18. Prince MJ, Bird AS, Blizard RA, Mann AH. Is the cognitive function of older patients affected by antihypertensive treatment? results from 54 months of the Medical Research Council's trial of hypertension in older adults. *BMJ*. 1996;312(7034):801-805. doi:10.1136/bmj.312.7034.801

19. Altman DG, Bland JM. Interaction revisited: the difference between two estimates. *BMJ*. 2003;326(7382):219-219. doi:10.1136/bmj.326.7382.219

20. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw*. 2010;36(3). doi:10.18637/jss.v036.i03

21. Sun X, Briel M, Walter SD, Guyatt GH. Is a subgroup effect believable? updating criteria to evaluate the credibility of subgroup analyses. *BMJ*. 2010;340:c117. doi:10.1136/bmj.c117

22. Applegate WB, Pressel S, Wittes J, et al. Impact of the treatment of isolated systolic hypertension on behavioral variables: results from the systolic hypertension in the elderly program. *Arch Intern Med*. 1994;154(19):2154-2160.

23. Tzourio C, Anderson C, Chapman N, et al; PROGRESS Collaborative Group. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. *Arch Intern Med*. 2003;163(9):1069-1075. doi:10.1001/archinte.163.9.1069

24. Lithell H, Hansson L, Skoog I, et al; SCOPE Study Group. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. *J Hypertens*. 2003;21(5):875-886. doi:10.1097/00004872-200305000-00011

25. De Galan BE, Zoungas S, Chalmers J, et al; ADVANCE Collaborative Group. Cognitive function and risks of cardiovascular disease and hypoglycaemia in patients with type 2 diabetes: the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial. *Diabetologia*. 2009;52(11):2328-2336. doi:10.1007/s00125-009-1484-7

26. Diener H-C, Sacco RL, Yusuf S, et al; Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) study group. Effects of aspirin plus extended-release dipyridamole versus clopidogrel and telmisartan on disability and cognitive function after recurrent stroke in patients with ischaemic stroke in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial: a double-blind, active and placebo-controlled study. *Lancet Neurol*. 2008;7(10):875-884. doi:10.1016/S1474-4422(08)70198-4

27. Pearce LA, McClure LA, Anderson DC, et al; SPS3 Investigators. Effects of long-term blood pressure lowering and dual antiplatelet treatment on cognitive function in patients with recent lacunar stroke: a secondary analysis from the SPS3 randomised trial. *Lancet Neurol*. 2014;13(12):1177-1185. doi:10.1016/S1474-4422(14)70224-8

28. Williamson JD, Launer LJ, Bryan RN, et al; Action to Control Cardiovascular Risk in Diabetes Memory in Diabetes Investigators. Cognitive function and brain structure in persons with type 2 diabetes mellitus after intensive lowering of blood pressure and lipid levels: a randomized clinical trial. *JAMA Intern Med*. 2014;174(3):324-333. doi:10.1001/jamainternmed.2013.13656

29. Atal I, Porcher R, Boutron I, Ravaud P. The statistical significance of meta-analyses is frequently fragile: definition of a fragility index for meta-analyses. *J Clin Epidemiol*. 2019;111:32-40. doi:10.1016/j.jclinepi.2019.03.012

30. van Middelaar T, van Vught LA, van Gool WA, et al. Blood pressure-lowering interventions to prevent dementia: a systematic review and meta-analysis. *J Hypertens*. 2018;36(9):1780-1787. doi:10.1097/HJH.0000000000001829

31. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *Lancet Neurol*. 2014;13(8):788-794. doi:10.1016/S1474-4422(14)70136-X

32. Mukadam N, Sommerlad A, Huntley J, Livingston G. Population attributable fractions for risk factors for dementia in low-income and middle-income countries: an analysis using cross-sectional survey data. *Lancet Glob Health*. 2019;7(5):e596-e603. doi:10.1016/S2214-109X(19)30074-9

33. Park TH, Ko Y, Lee SJ, et al. Identifying target risk factors using population attributable risks of ischemic stroke by age and sex. *J Stroke*. 2015;17(3):302-311. doi:10.5853/jos.2015.17.3.302

34. Nasrallah IM, Pajewski NM, Auchus AP, Chelune G, Cheung AK, et al; SPRINT MIND Investigators for the SPRINT Research Group. Association of intensive vs standard blood pressure control with cerebral white matter lesions. *JAMA*. 2019;322(6):524-534. doi:10.1001/jama.2019.10551

35. Abell JG, Kivimäki M, Dugravot A, et al. Association between systolic blood pressure and dementia in the Whitehall II cohort study: role of age, duration, and threshold used to define hypertension. *Eur Heart J*. 2018;39(33):3119-3125. doi:10.1093/eurheartj/ehy288

36. Posner HB, Tang M-X, Luchsinger J, Lantigua R, Stern Y, Mayeux R. The relationship of hypertension in the elderly to AD, vascular dementia, and cognitive function. *Neurology*. 2002;58(8):1175-1181. doi:10.1212/WNL.58.8.1175

37. Mills KT, Bundy JD, Kelly TN, et al. Global disparities of hypertension prevalence and control: a systematic analysis of population-based studies from 90 countries. *Circulation*. 2016;134(6):441-450. doi:10.1161/CIRCULATIONAHA.115.018912

38. WHO global plan on dementia. Alzheimer's Disease International website. Accessed May 26, 2019. https://www.alz.co.uk/dementia-plans/global-plan

39. Whiteley WN, Anand S, Bangdiwala SI, et al. Are large simple trials for dementia prevention possible? *Age Ageing*. 2020;49(2):154-160. doi:10.1093/ageing/afz152