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Supplementary information

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Blood pressure reduction and all-cause dementia in people with uncontrolled hypertension: an open-label, blinded-endpoint, cluster-randomized trial

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Supplementary information

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Eligibility Criteria

A total of 326 study villages were selected. On average, each village recruited 104 (ranging from 32 to 145) patients with hypertension from village-wide blood pressure screenings. In this implementation trial, minimal eligibility criteria were applied to include a representative sample of patients.

Eligibility criteria of study villages

- The village has a regular nonphysician community healthcare provider who is willing to participate in the hypertension control project
- The village does not plan to merge with other villages within 3 years
- The village is at least 2 kilometers away from other participating villages
- The village participates in the China New Rural Cooperative Medical Scheme

Eligibility criteria of study participants

- Men or women aged ≥40 years
- Mean untreated systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or mean treated systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥80 mmHg for individuals without a history of clinical cardiovascular diseases; or mean treated/untreated systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥80 mmHg for individuals with a history of clinical coronary heart disease, heart failure, stroke, diabetes, or chronic kidney disease
- Have lived in a participating village for at least 6 months
- No intention to migrate within the next 3 years
- Taking part in the New Rural Cooperative Medical Scheme
- Not pregnant or planning to become pregnant
- No malignant tumors and life expectancy ≥3 years
- Willing to participate and able to sign informed consent

Definitions of Study Outcomes

The primary outcome is all-cause dementia, and the secondary outcomes include cognitive impairment no dementia (CIND), a composite outcome of dementia and CIND, and a composite outcome of dementia and deaths. Mortality will be included as a secondary outcome because cognitive function data are not available for participants who deceased during follow-up.

Study Outcomes

All-cause dementia

The diagnostic criteria for all-cause dementia have been adopted from the Recommendations of the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease.[1] Specifically, a diagnosis of dementia requires the simultaneous presence of four conditions:

1. An expert adjudication panel confirms the presence of significant cognitive impairment.
2. Cognitive or neuropsychiatric symptoms interfere with the ability to function at work or in usual activities.
3. Cognitive and physical function represent a decline from previous levels of functioning and performance.
4. Cognitive impairments are not explained by delirium or major psychiatric disorders.

No attempt to classify dementia subtype will be made.

Cognitive impairment no dementia (CIND)

The diagnostic criteria for CIND have been adopted from the Recommendations of the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease.[2] In this study, the diagnosis of CIND requires meeting the following four conditions:

1. Confirmation of cognitive impairment by an expert adjudication panel.
2. Evidence of concern regarding a decline in cognition from previous levels.
3. Preserved functionality and independence at work or in usual activities
4. Not being demented

Composite outcome of dementia and CIND

Composite outcome of dementia and CIND includes dementia or cognitive impairment no dementia.

All-cause mortality

Composite outcome of dementia and deaths

Adjudication of Dementia and Cognitive Impairment No Dementia

The final diagnosis of all-cause dementia or CIND will be determined by an expert adjudication panel that is blinded to the intervention assignment. Study records, including medical and psychiatric history, neurological examination findings, cognitive and functional assessments, will be used to adjudicate cognitive status. Participants will be categorized into one of three primary groups: no cognitive impairment, CIND, or dementia. Unclassifiable cases will be placed in a 'cannot classify' category and treated as missing data in all analyses.

Each case will be independently reviewed by two adjudicators using standardized diagnostic criteria. If the two reviewers agree on the diagnosis, it will be recorded as the final diagnosis. If the two reviewers disagree, a third and more experienced adjudicator will join the review and discussion. If a consensus cannot be reached through this additional process, the disagreements will be discussed by the entire panel during regularly scheduled meetings. The classification decision is made by a majority vote of the panel members. There will be no attempt to classify dementia subtypes.

Reference

1. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011; 7(3): 263-9.
2. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011; 7(3): 270-9.

Supplementary Table 1. Classes of Antihypertensive Medications Used During the 48 Months of Follow Up*

Antihypertensive medication classes	Intervention				Usual care			
	12 months (n=13,726)	24 months (n=14,586)	36 months (n=15,738)	48 months (n=14,198)	12 months (n=10,028)	24 months (n=11,215)	36 months (n=12,256)	48 months (n=10,827)
Angiotensin II receptor blockers	3,271 (23.4%)	4,323 (28.8%)	5,246 (32.8%)	4,260 (30.1%)	2,477 (24.9%)	2,812 (25.1%)	3,542 (28.7%)	3,465 (32.3%)
Angiotensin-converting-enzyme inhibitors	3,517 (25.1%)	5,682 (39.3%)	7,865 (50.5%)	7,113 (50.3%)	1,779 (16.7%)	1,094 (9.7%)	969 (7.7%)	685 (6.3%)
Calcium channel blockers	8,230 (59.9%)	11,022 (75.5%)	14,028 (89.2%)	12,320 (86.8%)	4,686 (47.4%)	5,838 (52.0%)	6,437 (52.6%)	5,766 (53.3%)
Diuretics	3,754 (27.0%)	8,207 (56.4%)	10,441 (66.1%)	9,086 (63.8%)	1,000 (9.7%)	1,213 (10.4%)	1,275 (10.1%)	1,224 (10.8%)
Beta blockers	386 (2.8%)	355 (2.4%)	204 (1.3%)	132 (0.9%)	244 (2.5%)	193 (1.8%)	219 (1.8%)	205 (1.9%)
Others	513 (3.8%)	102 (0.7%)	96 (0.6%)	352 (2.5%)	1,407 (14.1%)	1,250 (11.0%)	1,260 (10.5%)	1,048 (9.5%)

Data are numbers (percentages). The sums of proportions are over 100% due to participants who took multiple antihypertensive medications.

* Medication use among participants who reported taking antihypertensive medications during the past 2 weeks.

† For single pill combinations, each component was counted as an antihypertensive medication separately.

Supplementary Table 2. Causes of Death

Cause of death	Intervention	Usual care	Overall
All cause	**1,269**	**1,392**	**2,661**
Cardiovascular disease death	**674**	**832**	**1,506**
Coronary heart disease death	261	301	562
Stroke death	373	493	866
Heart failure death	40	38	78
Non-cardiovascular disease death	**533**	**480**	**1,013**
Cancer	291	289	580
Accident/injury/suicide/homicide	73	50	123
Pulmonary disease	42	34	76
Kidney disease	13	10	23
Aortic dissection	5	6	11
Coronavirus disease 2019 (COVID-19)*	45	41	86
Others	64	50	114
Unclassifiable	**62**	**80**	**142**

* Four cases were confirmed by a positive real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test for COVID-19. All others did not have RT-PCR test.

Supplementary Table 3. Risk Ratios for Blood Pressure-Lowering Interventions on Clinical Outcomes: A Multiple Imputation Analysis using Markov Chain Monte Carlo method

Study outcomes	Unadjusted risk ratio (95% CI)*	*P* value	Multiple-adjusted risk ratio (95% CI)†	*P* value
Primary outcome				
All-cause dementia	0.85 (0.77, 0.92)	<0.0001	0.88 (0.81, 0.95)	<0.0001
Secondary outcomes				
Cognitive impairment no dementia	0.85 (0.81, 0.88)	<0.0001	0.86 (0.83, 0.90)	<0.0001
Composite outcome of dementia and cognitive impairment no dementia	0.85 (0.82, 0.88)	<0.0001	0.87 (0.84, 0.90)	<0.0001
Death from all causes	0.87 (0.81, 0.94)	<0.0001	0.88 (0.82, 0.95)	<0.0001
Composite outcome of dementia and deaths	0.86 (0.81, 0.91)	<0.0001	0.88 (0.83, 0.93)	<0.0001

* Accounted for cluster effects of villages and stratified by town, county, and province.

† Accounted for cluster effects of villages and stratified by town, county, and province. Additionally, adjusted for age, sex, education, cigarette smoking, history of major cardiovascular disease, use of antihypertensive medication, body mass index, systolic blood pressure, low-density lipoprotein cholesterol, and fasting plasma glucose at baseline.

Supplementary Table 4. Risk Ratios for Blood Pressure-Lowering Interventions on Clinical Outcomes: A Multiple Imputation Analysis using pattern-mixture method

Study outcomes	Unadjusted risk ratio (95% CI)*	*P* value	Multiple-adjusted risk ratio (95% CI)†	*P* value
Primary outcome				
All-cause dementia	0.86 (0.78, 0.95)	<0.0001	0.89 (0.80, 0.98)	<0.0001
Secondary outcomes				
Cognitive impairment no dementia	0.85 (0.81, 0.89)	<0.0001	0.86 (0.83, 0.90)	<0.0001
Composite outcome of dementia and cognitive impairment no dementia	0.85 (0.82, 0.89)	<0.0001	0.87 (0.84, 0.91)	<0.0001
Death from all causes	0.87 (0.80, 0.94)	<0.0001	0.88 (0.82, 0.94)	<0.0001
Composite outcome of dementia and deaths	0.87 (0.81, 0.92)	<0.0001	0.89 (0.84, 0.94)	<0.0001

* Accounted for cluster effects of villages and stratified by town, county, and province.

† Accounted for cluster effects of villages and stratified by town, county, and province. Additionally, adjusted for age, sex, education, cigarette smoking, history of major cardiovascular disease, use of antihypertensive medication, body mass index, systolic blood pressure, low-density lipoprotein cholesterol, and fasting plasma glucose at baseline.

Supplementary Table 5. Average MMSE, FAQ, and QDRS Scores at the 48-Month Follow-Up Visit

	Intervention (n = 14,541)	**Usual care (n = 13,594)**	**P-value for group difference**
Mini-Mental State Examination*			
Mean (SD)	22.8 (5.8)	22.3 (5.8)	0.002
Media (IQR)	24.0 (20.0 – 27.0)	23.5 (19.0 – 27.0)	0.12
Functional Activities Questionnaire†			
Mean (SD)	2.4 (5.5)	2.6 (5.7)	0.039
Media (IQR)	0 (0 – 2)	0 (0 – 2)	0.98
Quick Dementia Rating System‡			
Mean (SD)	2.1 (3.9)	2.4 (4.0)	0.03
Media (IQR)	1.0 (0 – 2.5)	1.0 (0 – 2.5)	0.12

SD = standard deviation; IQR = interquartile range

* The Mini-Mental State Examination (MMSE) scores range from 0 to 30, with a lower score indicating poorer cognitive function. The optimal cut-off points for dementia screening were as follows: 16/17 for illiterate individuals (sensitivity 87.6% and specificity 80.8%), 19/20 for those with 1–6 years of education (sensitivity 93.6% and specificity 92.7%), and 23/24 for individuals with 7 or more years of education (sensitivity 94.3% and specificity 94.3%) in China (J Alzheimers Dis. 2016;53:487-96).

† The Functional Activities Questionnaire (FAQ) scores range from 0 to 30. The recommended cut-point of 9 (dependent on 3 or more activities) indicates impaired function and possible cognitive impairment (J Gerontol. 1982;37:323-329).

‡ The Quick Dementia Rating System (QDRS) scores range from 0 to 30. QDRS scores differentiate dementia stages with the following cut-points: normal 0-1, mild cognitive impairment 2-5, mild dementia 6-12, moderate dementia 13-20, and severe dementia 20-30 (Alzheimers Dement (Amst). 2015;1:249-259).

Supplementary Table 6. Post-Hoc Subgroup Analyses of Adjudicated All-Cause Dementia

Subgroups	Intervention		Usual care		Risk ratio (95% CI)	P-value for interaction
	No. of events/ No. of participants	Cumulative prevalence, %	No. of events/ No. of participants	Cumulative prevalence, %		
Age, years						
≥75	188/ 1,192	15.77	203/ 1,220	16.64	0.95 (0.78, 1.14)	
65-74	316/ 4,918	6.43	347/ 4,740	7.32	0.88 (0.74, 1.05)	0.32
<65	164/ 8,431	1.95	184/ 7,634	2.41	0.81 (0.64, 1.02)	
Antihypertensive treatment at baseline						
Treated	371/ 8,920	4.16	376/ 7,411	5.07	0.82 (0.71, 0.96)	
Untreated	297/ 5,621	5.28	358/ 6,183	5.79	0.92 (0.77, 1.10)	0.33
History of stroke						
Stroke	311/ 3,087	10.07	360/ 2,974	12.10	0.83 (0.72, 0.97)	0.63
Non-stroke	357/11,454	3.12	374/10,620	3.52	0.89 (0.77, 1.04)	

Supplementary Table 7. Meta-Analysis of Randomised Controlled Trials of Antihypertensive Treatment on Dementia

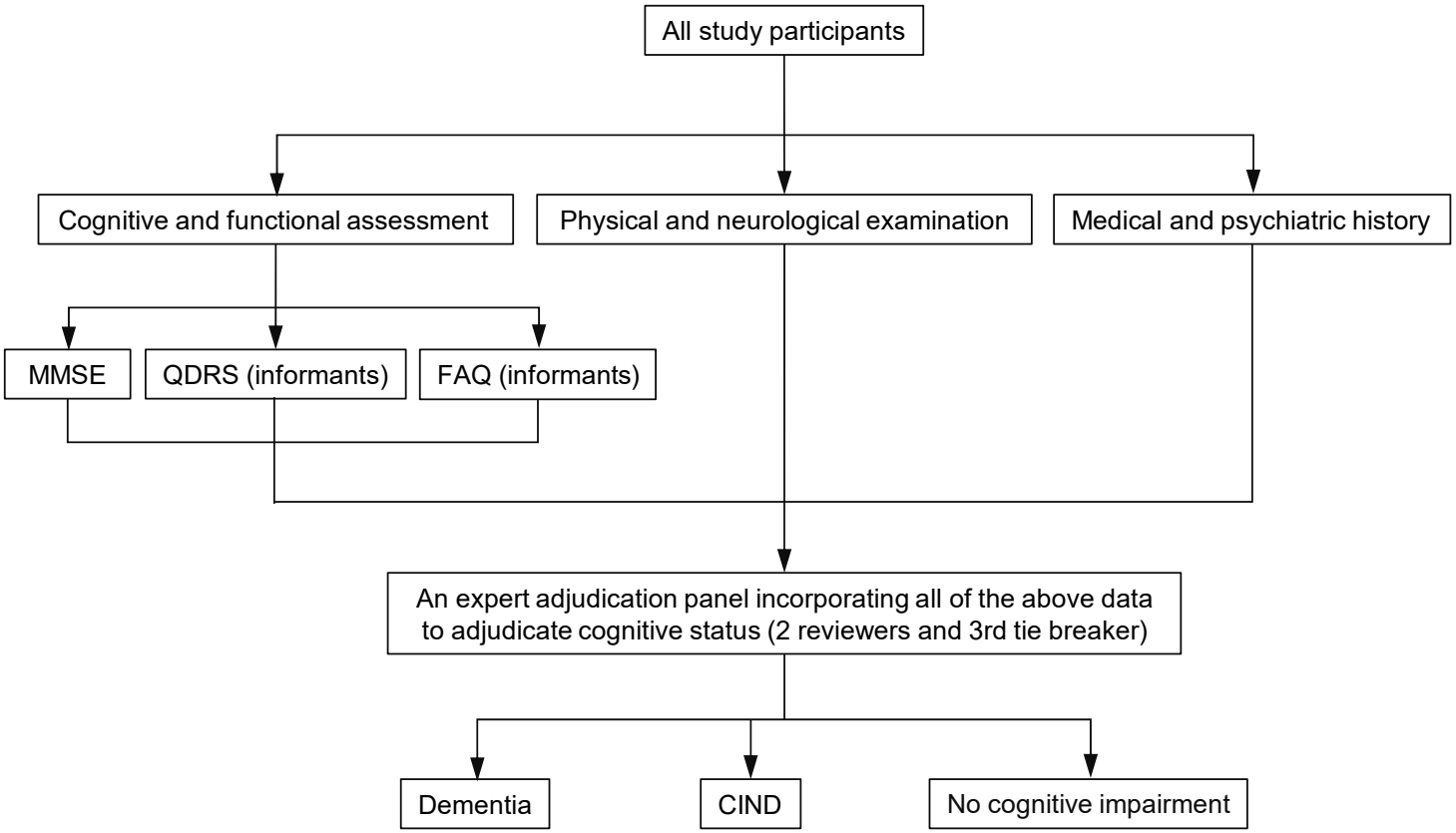
Trials	Study participants	Intervention	Control	Duration of follow-up, years	No. of events/No. of participants		Risk ratio (95% CI)	p-value
					Intervention	Control		
Syst-Eur[1]	Aged ≥60 yrs, SBP 160-219 mmHg and DBP <95 mmHg	Nitrendipine with or without enalapril or hydrochlorothiazide	Placebo	2.0	11/1,238	21/1,180	0.50 (0.24 to 1.03)	0.06
PROGRESS[2]	Prior stroke or transient ischemic attack	Perindopril with or without indapamide	Placebo	3.9	193/3,051	217/3,054	0.89 (0.74 to 1.07)	0.22
HYVET[3]	Aged ≥80 yrs, SBP 160-200 mmHg and DBP <110 mmHg	Indapamide with or without perindopril	Placebo	2.2	126/1,687	137/1,649	0.86 (0.67 to 1.09)	0.21
SPRINT-MIND[4]	Aged ≥50 yrs, hypertension and high CVD risk	SBP target <120 mmHg	SBP target <140 mmHg	5.1	149/4,278	176/4,285	0.83 (0.67 to 1.04)	0.10
CRHCP	Aged ≥40 yrs, hypertension	SBP target <130 and DBP target <80 mmHg	Usual care	4.0	668/15,972	734/15,072	0.85 (0.76 to 0.95)	0.0035
Overall							**0.85 (0.78 to 0.92)**	**<0.0001**

Syst-Eur = Systolic Hypertension in Europe; PROGRESS = Perindopril Protection Against Recurrent Stroke Study; HYVET = Hypertension in the Very Elderly; SPRINT MIND = Systolic Blood Pressure Intervention Trial - Memory and Cognition in Decreased Hypertension; SBP = systolic blood pressure; DBP = diastolic blood pressure; CVD = cardiovascular disease.

1. Forette F, Seux ML, Staessen JA, et al. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. *Lancet* 1998; 352(9137): 1347-51.
2. Tzourio C, Anderson C, Chapman N, Woodward M, Neal B, MacMahon S, Chalmers J. 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): 1069-75.
3. Peters R, Beckett N, Forette F, et al. 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): 683-9.
4. Williamson JD, Pajewski NM, Auchus AP, et al. Effect of Intensive vs Standard Blood Pressure Control on Probable Dementia: A Randomized Clinical Trial. *JAMA* 2019; 321(6): 553-61.

Supplementary Table 8. Intraclass Correlation Coefficients (95% CIs) of Primary and Secondary Outcomes During 48-Month Follow-Up

	Overall	Intervention	Usual care
Dementia	0.0072 (0.0043, 0.0101)	0.0061 (0.0023, 0.0098)	0.0076 (0.0033, 0.0119)
Cognitive impairment no dementia	0.0040 (0.0016, 0.0064)	0.0015 (0.0000, 0.0043)	0.0026 (0.0000, 0.0058)
Composite outcome of dementia and cognitive impairment no dementia	0.0108 (0.0074, 0.0142)	0.0063 (0.0025, 0.0100)	0.0104 (0.0055, 0.0152)
All-cause mortality	0.0056 (0.0032, 0.0079)	0.0061 (0.0027, 0.0094)	0.0044 (0.0013, 0.0075)
Change in systolic blood pressure	0.2831 (0.2530, 0.3178)	0.0701 (0.0559, 0.0892)	0.0953 (0.0769, 0.1197)
Change in diastolic blood pressure	0.2068 (0.1824, 0.2356)	0.0601 (0.0475, 0.0770)	0.0676 (0.0536, 0.0863)



Supplementary Table 1. Flowchart of Dementia Diagnosis

MMSE = Mini-Mental State Examination; QDRS = Quick Dementia Rating System; FAQ = Functional Activities Questionnaire; CIND = Cognitive Impairment No Dementia