nature medicine

Article

https://doi.org/10.1038/s41591-025-03616-8

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

Received: 6 July 2024

Accepted: 26 February 2025

Published online: 21 April 2025

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Jiang He[1,2,3,4,11] ✉, Chuansheng Zhao[5,11], Shanshan Zhong[5,11], Nanxiang Ouyang[6,11], Guozhe Sun[6,11], Lixia Qiao[6,11], Ruihai Yang[7], Chunxia Zhao[8], Huayan Liu[5], Weiyu Teng[5], Xu Liu[5], Chang Wang[6], Songyue Liu[6], Chung-Shiuan Chen[9], Jeff D. Williamson[10] & Yingxian Sun[6] ✉

Dementia is a leading cause of death and disability worldwide. Here we tested the effectiveness of blood pressure (BP) reduction on the risk of all-cause dementia among 33,995 individuals aged ≥40 years with uncontrolled hypertension in rural China. We randomly assigned 163 villages to a non-physician community healthcare provider-led intervention and 163 villages to usual care. In the intervention group, trained non-physician community healthcare providers initiated and titrated antihypertensive medications according to a simple stepped-care protocol to achieve a systolic BP goal of <130 mm Hg and a diastolic BP goal of <80 mm Hg, with supervision from primary care physicians. Over 48 months, the net reduction in systolic BP was 22.0 mm Hg (95% confidence interval (CI) 20.6 to 23.4; $P < 0.0001$) and that in diastolic BP was 9.3 mm Hg (95% CI 8.7 to 10.0; $P < 0.0001$) in the intervention group compared to usual care. The primary outcome of all-cause dementia was significantly lower in the intervention group than in the usual care group (risk ratio: 0.85; 95% CI 0.76 to 0.95; $P = 0.0035$). Additionally, serious adverse events occurred less frequently in the intervention group (risk ratio: 0.94; 95% CI 0.91 to 0.98; $P = 0.0006$). This cluster-randomized trial indicates that intensive BP reduction is effective in lowering the risk of all-cause dementia in patients with hypertension. ClinicalTrials.gov: NCT03527719.

The number of individuals living with dementia is high and increasing worldwide. It has been estimated that, globally, the number of people who have dementia will rise from 57.4 million in 2019 to 152.8 million by 2050 (ref. 1). The majority of these individuals reside in low- and middle-income countries[2]. Dementia is the fifth leading cause of death globally, accounting for 2.4 million deaths worldwide each year[3]. Furthermore, dementia places substantial financial and emotional burdens on patients, caregivers and society as a whole[4]. In the absence of curative treatments, the primary prevention of dementia through the reduction of risk factors has become a public health priority[4]. Observational epidemiology studies have identified several risk factors for dementia, including hypertension[5].

Hypertension is the leading modifiable risk factor for cardiovascular disease (CVD) and premature deaths worldwide[6,7]. However, the effect of blood pressure (BP) on the risk of dementia is less established[8,9]. Observational cohort studies showed that individuals

A full list of affiliations appears at the end of the paper. ✉e-mail: jiang.he@utsouthwestern.edu; yxsun@cmu.edu.cn

https://doi.org/10.1038/s41591-025-03616-8

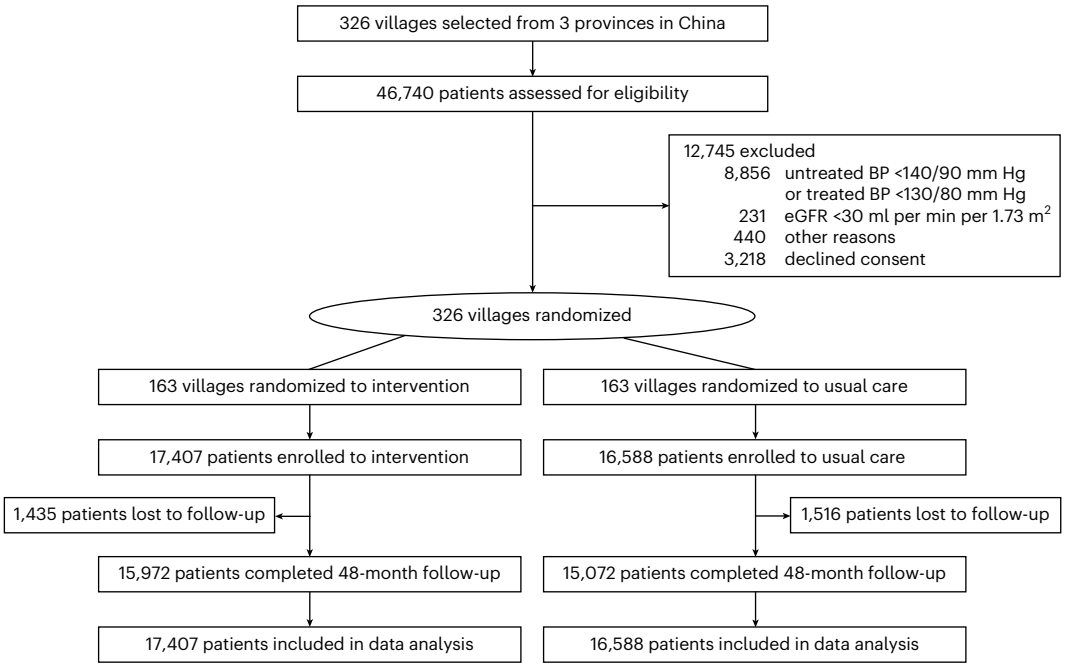


Fig. 1 | Flowchart of recruitment, randomization and follow-up. eGFR, estimated glomerular filtration rate.

with untreated hypertension experienced an increased risk of dementia, whereas those who had received treatment for their hypertension did not experience a significant increase in the risk of dementia compared to healthy controls[8]. A meta-analysis of seven cohort studies with 17,286 participants with a mean baseline age of 74.5 years found a U-shaped relationship between baseline systolic BP (SBP) and dementia risk[9]. Several randomized controlled trials have tested the effect of antihypertensive medications compared to placebo on the risk of dementia in patients with hypertension or a history of stroke[10–12]. These trials reported a non-significant reduction in dementia associated with antihypertensive treatment. However, dementia was only a secondary outcome in these trials. In the SPRINT-MIND trial, intensive hypertension treatment (SBP goal <120 mm Hg) was associated with a non-significant 17% reduction in adjudicated dementia compared to standard treatment (SBP goal <140 mm Hg) in 9,361 patients aged ≥50 years with hypertension and high CVD risk[13]. Recent meta-analyses of randomized controlled trials suggested that antihypertensive treatment was associated with a reduced risk of dementia and mild cognitive impairment[14,15]. However, definitive evidence supporting BP reduction for the primary prevention of dementia in hypertensive patients remains insufficient.

The China Rural Hypertension Control Project Phase-3 (CRHCP-3) aimed to assess the effectiveness of an intensive BP intervention targeting an SBP <130 mm Hg and a diastolic BP (DBP) <80 mm Hg, compared to usual care, in reducing the risk of all-cause dementia among patients with uncontrolled hypertension over a 48-month period. This trial will provide evidence regarding the effectiveness of intensive BP intervention in lowering the risk of dementia in real-world primary care settings within resource-constrained communities.

Results

Patient disposition

From 8 May 2018 to 28 November 2018, a total of 46,740 individuals were assessed for eligibility from 326 villages in rural China. Of these, 33,995 participants (17,407 in 163 intervention villages and 16,588 in 163 usual care villages) were enrolled (Fig. 1). Of these participants, 15,972 (91.8%) in the intervention group and 15,072 (90.9%) in the usual care group were followed up for clinical outcomes at the 48-month visit, which concluded on 26 March 2023. During the follow-up, 1,269 participants in the intervention group and 1,392 in the usual care group died. Additionally, 62 participants in the intervention group and 74 in the usual care group were categorized as 'cannot classify' during the endpoint adjudication process and were treated as missing in the data analysis. A total of 14,541 participants in the intervention group and 13,594 participants in the usual care group had data for the primary outcome.

Baseline characteristics were comparable between the intervention and usual care groups (Table 1). On average, study participants were 62.8 years old in the intervention group and 63.3 years old in the usual care group. In the intervention group, 60.8% of participants were female, compared to 61.6% in the usual care group. The mean 10-year risk for atherosclerotic CVD, calculated using the American College of Cardiology and American Heart Association pooled cohort equations[16], was 14.7% in the intervention group and 14.5% in the usual care group.

BP reduction

SBP decreased from 157.0 (s.d. 18.0) at baseline to 127.6 (12.8) mm Hg at 48 months, while DBP decreased from 87.9 (10.9) to 72.6 (8.3) mm Hg in the intervention group. During the same period, SBP decreased from 155.4 (17.4) to 147.7 (20.2) mm Hg, and DBP decreased from 87.2 (10.7) to 81.0 (11.3) mm Hg in the usual care group (Fig. 2). Over 48 months, the net group difference in BP reduction was −22.0 mm Hg (95% CI −23.4 to −20.6, $P < 0.0001$) for systolic and −9.3 mm Hg (95% CI −10.0 to −8.7, $P < 0.0001$) for diastolic. A total of 67.7% of participants in the intervention group and 15.0% in the usual care group achieved an SBP <130 mm Hg and a DBP <80 mm Hg at 48 months (Table 2).

On average, patients in the intervention group took 3.0 antihypertensive medications (95% CI 3.0 to 3.1), while patients in the usual care group took 1.2 medications (95% CI 1.1 to 1.2) at the 48-month follow-up visit ($P < 0.0001$ for group difference; Table 2). The proportions of participants taking angiotensin-converting enzyme inhibitors ((ACEI) 50.3% versus 6.3%), calcium channel blockers ((CCB) 86.8% versus 53.3%) and diuretics (63.8% versus 10.8%) were significantly higher in the intervention group compared to the usual care group ($P < 0.0001$ for all comparisons). By contrast, the use of angiotensin-II receptor blockers ((ARB) 30.1% versus 32.3%) was similar between the two groups

($P = 0.19$). These trends in antihypertensive medication use were consistent throughout the 48 months of intervention (Supplementary Table 1). Self-reported adherence to medication was 88.0% (95% CI 86.8% to 89.2%) in the intervention group and 66.4% (95% CI 64.3% to 68.6%) in the usual care group at 48 months (Table 2).

Primary outcomes

At the 48-month follow-up visit, the primary outcome of adjudicated all-cause dementia was confirmed in 668 participants (4.59%) in the intervention group and 734 participants (5.40%) in the usual care group (Table 3). The risk ratio (RR) of all-cause dementia associated with the intervention was 0.85 (95% CI 0.76 to 0.95, $P = 0.0035$).

Secondary outcomes

The secondary outcome of adjudicated cognitive impairment no dementia (CIND) was confirmed in 2,506 participants (17.2%) in the intervention group and 2,808 participants (20.7%) in the usual care group (Table 3). The RR of CIND associated with the intervention was 0.84 (95% CI 0.80 to 0.87, $P < 0.0001$). The RR for the composite outcome of dementia or CIND was 0.84 (95% CI 0.81 to 0.87, $P < 0.0001$). Likewise, the RR for the composite outcome of dementia or death was 0.86 (95% CI 0.81 to 0.92, $P < 0.0001$). Causes of death are provided in Supplementary Information (Supplementary Table 2).

Safety

During the 4-year follow-up, serious adverse events occurred in 6,201 participants (35.7%) in the intervention group and 6,329 participants (38.2%) in the usual care group, with the RR of 0.94 (95% CI 0.91 to 0.98; $P = 0.0006$; Table 3). Serious adverse events included 1,269 deaths and 4,932 hospitalizations in the intervention group, as well as 1,392 deaths and 4,937 hospitalizations in the usual care group, all adjudicated as non-study-related events by blinded-study physicians. There was no difference between the two randomization groups in terms of injurious falls requiring medical care, symptomatic hypotension confirmed at a village doctor visit or syncope needing medical care.

Sensitivity analysis

In a sensitivity analysis adjusted for age, sex, education, history of cigarette smoking, history of major CVD, use of antihypertensive medication, body mass index, SBP, low-density lipoprotein (LDL) cholesterol and fasting plasma glucose at baseline, the risk reduction for the primary and secondary outcomes associated with the intervention remained significant (Table 3). Additionally, in the multiple imputation analysis using the Markov Chain Monte Carlo method assuming missing at random, the RR of all-cause dementia associated with the intervention was 0.85 (95% CI 0.77 to 0.92; $P < 0.0001$) (Supplementary Table 3). Likewise, in the multiple imputation analysis using the pattern-mixture method assuming missing not at random, the RR was 0.86 (95% CI 0.78 to 0.95; $P < 0.0001$) (Supplementary Table 4). Furthermore, the risk reduction for the primary outcome of all-cause dementia was consistent across subgroups of age, sex, education, history of cigarette smoking, body mass index, SBP, fasting plasma glucose and the 10-year risk of developing atherosclerotic CVD at baseline (Fig. 3a). The risk reduction for the main secondary outcome of CIND was also consistent across subgroups, except for the subgroup of 10-year risk of atherosclerotic CVD. The RR was 0.75 (95% CI 0.70 to 0.80) in individuals with a risk <23.2% and 0.94 (95% CI 0.89 to 0.99) in individuals with a risk ≥23.2% ($P < 0.0001$ for subgroup interaction, Fig. 3b).

Post hoc analysis

The average Mini-Mental State Examination (MMSE) score was significantly higher in the intervention group, while the Functional Activities Questionnaire (FAQ) score and the Quick Dementia Rating System (QDRS) score were significantly lower compared to the usual care group at 48-month follow-up visit (Supplementary Table 5). In a post hoc subgroup analysis, the RR for dementia did not significantly differ among subgroups based on conventional age categories (≥75, 65–74 and <65 years), history of antihypertensive medication use or history of stroke (Supplementary Table 6). Additionally, we conducted a meta-analysis that included four previously published randomized trials alongside the CRHCP-3 trial, which found that antihypertensive treatment was associated with a 15% reduction in dementia events (RR 0.85, 95% CI 0.78 to 0.92, $P < 0.0001$; Supplementary Table 7).

The intraclass correlation coefficient (ICC) was 0.0072 (95% CI 0.0043 to 0.0101) for all-cause dementia and 0.0040 (95% CI 0.0016 to 0.0064) for CIND (Supplementary Table 8).

Table 1 | Baseline characteristics of the study participants

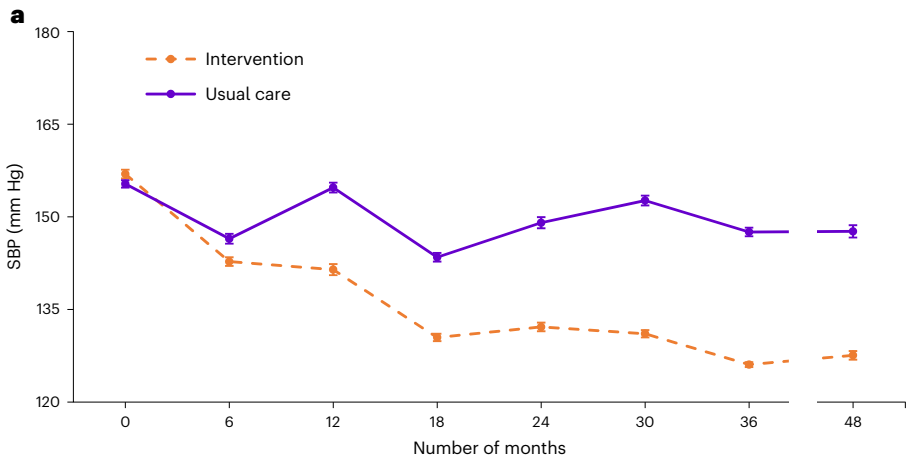
Characteristics	Intervention (*n*=17,407)	Usual care (*n*=16,588)
Mean age, years	62.8 (9.3)	63.3 (9.2)
Female sex	10,603 (60.8%)	10,222 (61.6%)
Less than primary school	3,617 (21.6%)	3,848 (23.8%)
Currently smokes	3,690 (21.4%)	3,609 (22.0%)
Drinking alcohol weekly	2,793 (16.2%)	2,687 (16.4%)
Physical activity ≥5 times per week[a]	8,496 (49.3%)	8,233 (50.0%)
Median duration of hypertension, years	8.0 (5.0–10.5)	8.0 (5.0–11.0)
Use of antihypertensive medications	10,574 (60.4%)	8,990 (54.3%)
Mean antihypertensive medications, number per patient	0.8 (1.1)	0.7 (1.0)
History of major CVD[b]	3,713 (21.2%)	3,377 (20.4%)
History of diabetes	1,585 (9.1%)	1,426 (8.6%)
History of chronic kidney disease	108 (0.6%)	91 (0.5%)
Mean body mass index, kg per m^2	26.0 (3.9)	25.8 (3.9)
Mean SBP, mm Hg	157.0 (18.0)	155.4 (17.4)
Mean DBP, mm Hg	87.9 (10.9)	87.2 (10.7)
Mean total cholesterol, mg per dl	195.2 (38.8)	194.4 (39.0)
Mean LDL cholesterol, mg per dl	105.4 (31.8)	104.7 (31.6)
Mean high-density lipoprotein cholesterol, mg per dl	55.7 (13.7)	55.6 (13.3)
Mean plasma glucose, mg per dl	111.3 (37.0)	110.9 (35.7)
Mean uric acid, mg per dl	5.1 (1.5)	5.1 (1.4)
Mean estimated glomerular filtration rate, ml per min per 1.73 m^2[c]	95.8 (13.0)	95.5 (12.8)
Mean 10-year risk for atherosclerotic CVD, %[d]	14.7 (11.9)	14.5 (11.6)

Data are mean (s.d.), *n* (%) or median (interquartile range) unless otherwise stated. Proportions, means and medians were calculated by accounting for cluster effects of villages and stratifying by town, county and province. To convert cholesterol from mg per dl to mmol per l multiply by 0.0259. To convert glucose from mg per dl to mmol per l multiply by 0.0555. To convert uric acid from mg per dl to mmol per l multiply by 0.0595. [a]Moderate or heavy physical activity ≥30 min per time. [b]Major CVD includes myocardial infarction, stroke and heart failure. [c]Estimated glomerular filtration rate was calculated based on the 2021 Chronic Kidney Disease Epidemiology Collaboration creatinine equations. [d]Atherosclerotic CVD risk was calculated based on the American College of Cardiology and American Heart Association pooled cohort equations.

Discussion

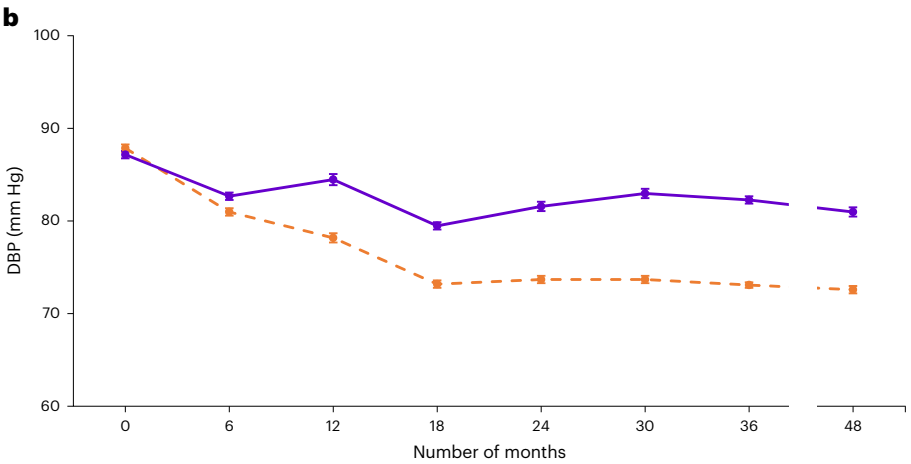
Our study is one of the first large-scale randomized controlled effectiveness trials to demonstrate a significant reduction in all-cause dementia associated with lowering BP. In the CRHCP-3 trial, SBP was reduced by 22.0 mm Hg and DBP by 9.3 mm Hg in the intervention group compared to the usual care group over 4 years of intervention. This reduction in BP was associated with a 15% lower risk of all-cause dementia and a 16% lower risk of CIND. After adjusting for important risk factors for

https://doi.org/10.1038/s41591-025-03616-8



Mean SBP (mm Hg)

Usual care	155.4	146.5	154.8	143.5	149.1	152.7	147.6	147.7
Intervention	157.0	142.8	141.5	130.5	132.2	131.1	126.1	127.6



Mean DBP (mm Hg)

Usual care	87.2	82.7	84.5	79.5	81.6	83.0	82.3	81.0
Intervention	87.9	81.0	78.2	73.2	73.7	73.7	73.1	72.6

Number of participants with data

Usual care	16,588	13,831	12,943	14,500	14,335	14,088	15,004	13,634
Intervention	17,407	14,781	14,563	15,414	15,310	15,085	15,941	14,683

Fig. 2 | SBP and DBP in the intervention and usual care groups over the 48 months of follow-up. a, Mean SBP. **b**, Mean DBP. Error bars represent 95% CI.

dementia, these associations remained significant. Furthermore, the effectiveness of BP reduction on the risk of dementia was consistent across subgroups based on age, sex, education, history of cigarette smoking, body mass index, SBP, fasting plasma glucose and 10-year atherosclerotic CVD risk at baseline. Adverse events were comparable between the two groups, and serious adverse events were significantly lower in the intervention group. The CRHCP-3 trial provides strong evidence for the effectiveness of antihypertensive treatment in reducing the risk of dementia in patients with hypertension.

Strengths and limitations

The CRHCP-3 study is one of the largest randomized effectiveness trials conducted in real-world primary care settings within resource-constrained communities. The BP intervention program was carried out by non-physician community healthcare providers (NPCHPs), achieving and maintaining a substantial reduction in BP in the intervention group compared to the usual care group over 48 months of follow-up. Every effort was made to reduce selection bias by concealing randomization allocation until recruitment and baseline data collection were completed, and by recruiting all eligible patients with hypertension from the participating villages[17,18]. Also, the study staff responsible for collecting clinical, cognitive and functional data, as well as outcome adjudication committee members who made final diagnoses of all-cause dementia or CIND, were blinded to randomization assignments. Furthermore, an intention-to-treat analysis was conducted. The CRHCP-3 trial was sufficiently powered in terms of sample size, intervention duration and BP separation to provide an unbiased assessment of the effectiveness of antihypertensive treatment on dementia outcomes.

There are some limitations to this study. First, cognitive function was not assessed at the baseline examination. Although patients with clinical dementia or other conditions who were not able to consent were excluded at baseline, participants with mild dementia or cognitive impairment could not be excluded without a comprehensive neuropsychological evaluation. Nevertheless, in this large randomized controlled trial, baseline characteristics, including major risk factors for dementia, were comparable between the randomized groups. Furthermore, even after adjusting for these dementia risk factors, the

https://doi.org/10.1038/s41591-025-03616-8

Table 2 | BP control and use of antihypertensive medications during 48-month follow-up in intervention and control groups

	Mean or proportion (95% CI)		Unadjusted net difference (95% CI)[a]	*P* value	Multiple-adjusted net difference (95% CI)[b]	*P* value
	Intervention	Usual care				
Mean BP at 48 months, mm Hg						
Systolic	127.6 (126.9, 128.3)	147.7 (146.8, 148.7)	−20.1 (−21.3, −19.0)	<0.0001	−20.5 (−21.7, −19.4)	<0.0001
Diastolic	72.6 (72.3, 73.0)	81.0 (80.4, 81.5)	−8.4 (−9.0, −7.7)	<0.0001	−8.7 (−9.3, −8.2)	<0.0001
Mean change in BP from baseline to 48 months, mm Hg						
Systolic	−29.2 (−30.1, −28.3)	−7.2 (−8.3, −6.1)	−22.0 (−23.4, −20.6)	<0.0001	−20.5 (−21.7, −19.4)	<0.0001
Diastolic	−15.4 (−15.9, −15.0)	−6.1 (−6.6, −5.6)	−9.3 (−10.0, −8.7)	<0.0001	−8.7 (−9.3, −8.2)	<0.0001
Proportion of participants with controlled BP at 48 months						
BP <130 over 80 mm Hg	67.7% (65.8, 69.6)	15.0% (13.7, 16.4)	52.7% (50.4, 55.0)	<0.0001	52.7% (50.4, 55.0)	<0.0001
BP <140 over 90 mm Hg	85.7% (84.0, 87.3)	35.7% (33.8, 37.6)	50.0% (47.5, 52.5)	<0.0001	49.6% (47.0, 52.1)	<0.0001
Mean antihypertensive medications at 48 months, number per patient	3.0 (3.0, 3.1)	1.2 (1.1, 1.2)	1.9 (1.8, 1.9)	<0.0001	1.8 (1.8, 1.9)	<0.0001
Proportion of antihypertensive medication classes at 48 months						
ACEI	50.3% (47.4, 53.2)	6.3% (5.5, 7.0)	44.0% (41.0, 47.1)	<0.0001	43.9% (40.9, 46.9)	<0.0001
ARB	30.1% (27.5, 32.7)	32.3% (30.3, 34.4)	−2.2% (−5.5, 1.1)	0.19	−1.2% (−4.5, 2.1)	0.47
CCB	86.8% (85.8, 87.9)	53.3% (51.1, 55.4)	33.6% (31.2, 36.0)	<0.0001	33.6% (31.3, 36.0)	<0.0001
Diuretics	63.8% (61.7, 65.9)	10.8% (9.6, 12.1)	53.0% (50.5, 55.4)	<0.0001	52.8% (50.4, 55.2)	<0.0001
Proportion of high adherence to antihypertensive medication at 48 months	88.0% (86.8, 89.2)	66.4% (64.3, 68.6)	21.6% (19.1, 24.0)	<0.0001	16.1% (14.0, 18.1)	<0.0001

A generalized estimating equation linear model was used to test differences in BP changes, and a generalized linear mixed-effects model was used to test differences in the proportions of participants with controlled BP and other binary outcomes. A two-sided *P* value of 0.05 was used as the significance level. [a]Accounted for cluster effects of villages and stratified by town, county and province. [b]Accounted for cluster effects of villages and stratified by town, county and province. Additionally, adjusted for age, sex, education, history of cigarette smoking, history of major CVD, use of antihypertensive medication, body mass index, SBP, LDL cholesterol and fasting plasma glucose at baseline.

Table 3 | Effectiveness of BP-lowering intervention on the primary, secondary and safety outcomes

Study outcomes	Intervention		Usual care		Unadjusted RR (95% CI)[a]	*P* value	Multiple-adjusted RR (95% CI)[b]	*P* value
	Number of events	Proportion of cumulative events, %	Number of events	Proportion of cumulative events, %				
Primary outcome								
All-cause dementia	668	4.59%	734	5.40%	0.85 (0.76, 0.95)	0.0035	0.88 (0.79, 0.98)	0.023
Secondary outcomes								
CIND	2,506	17.2%	2,808	20.7%	0.84 (0.80, 0.87)	<0.0001	0.85 (0.81, 0.89)	<0.0001
Composite outcome of dementia and CIND	3,174	21.8%	3,542	26.1%	0.84 (0.81, 0.87)	<0.0001	0.86 (0.83, 0.90)	<0.0001
Death from all causes	1,269	7.3%	1,392	8.4%	0.87 (0.80, 0.94)	0.0004	0.88 (0.82, 0.94)	0.0003
Composite outcome of dementia and deaths	1,908	12.1%	2,092	14.1%	0.86 (0.81, 0.92)	<0.0001	0.88 (0.83, 0.94)	<0.0001
Safety outcomes								
Serious adverse event[c]	6,201	35.7%	6,329	38.2%	0.94 (0.91, 0.98)	0.0006	0.94 (0.91, 0.97)	0.0001
Injurious falls[d]	166	0.96%	157	0.95%	1.01 (0.80, 1.28)	0.92	1.04 (0.82, 1.32)	0.77
Symptomatic hypotension[e]	201	1.16%	156	0.94%	1.20 (0.89, 1.62)	0.23	1.18 (0.88, 1.58)	0.28
Syncope[f]	127	0.73%	102	0.62%	1.20 (0.87, 1.66)	0.27	1.22 (0.89, 1.69)	0.22

A modified Poisson regression with a cluster-robust error variance was used to test the effect of the intervention at a two-sided *P* value of 0.05. [a]Accounted for cluster effects of villages and stratified by town, county and province. [b]Accounted for cluster effects of villages and stratified by town, county and province. Additionally, adjusted for age, sex, education, cigarette smoking, history of major CVD, use of antihypertensive medication, body mass index, SBP, LDL cholesterol and fasting plasma glucose at baseline. [c]Serious adverse events included deaths and hospitalizations in this analysis. [d]Self-reported injurious fall was defined as a fall that resulted in seeking medical care in a hospital, a primary care clinic or a village doctor's office. [e]Self-reported symptomatic hypotension was confirmed by SBP <90 mm Hg at a village doctor visit. [f]Self-reported temporary loss of consciousness that resulted in seeking medical care in a hospital, a primary care clinic or a village doctor's office.

effect of antihypertensive treatment on risk of dementia remained stable. Therefore, it is highly unlikely that the lack of baseline cognitive function assessment would bias the comparison between the two randomized groups.

Another limitation is the absence of repeated cognitive and functional assessments during the follow-up visits to identify incident dementia. Dementia is currently considered an irreversible condition. With careful clinical and neurological evaluations, as well as cognitive

https://doi.org/10.1038/s41591-025-03616-8

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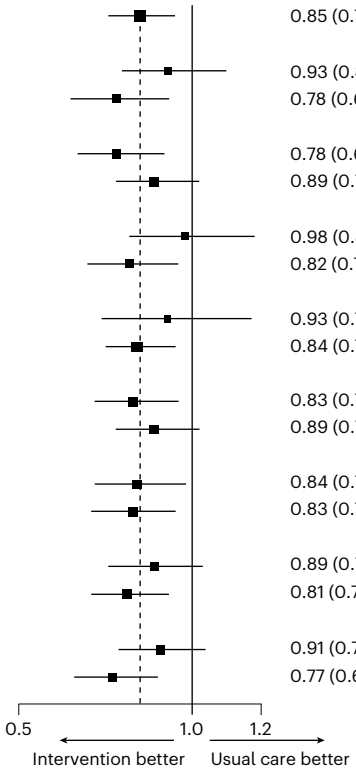
	Intervention		Usual care		Relative risk (95% CI)	*P* value for interaction
	Number of patients with dementia/total number (rate per year)					
Overall	668/14,541	(1.12%)	734/13,594	(1.31%)	0.85 (0.76, 0.95)	
Age						
≥69 years	382/3,670	(2.53%)	390/3,532	(2.68%)	0.93 (0.80, 1.10)	0.11
<69 years	286/10,871	(0.64%)	344/10,062	(0.83%)	0.78 (0.65, 0.93)	
Sex						
Male	217/5,508	(0.96%)	253/5,035	(1.22%)	0.78 (0.67, 0.92)	0.25
Female	451/9,033	(1.21%)	481/8,559	(1.37%)	0.89 (0.78, 1.02)	
Education						
<Primary school	307/2,920	(2.54%)	329/3,059	(2.59%)	0.98 (0.82, 1.18)	0.09
≥Primary school	359/11,505	(0.76%)	395/10,393	(0.93%)	0.82 (0.70, 0.96)	
Cigarette smoking						
Current	130/2,997	(1.06%)	133/2,855	(1.14%)	0.93 (0.74, 1.17)	0.44
Former or never	535/11,444	(1.14%)	590/10,600	(1.35%)	0.84 (0.75, 0.95)	
Body mass index, kg m^{-2}						
≥24.6	329/9,388	(0.85%)	366/8,518	(1.05%)	0.83 (0.72, 0.96)	0.29
<24.6	338/5,111	(1.61%)	367/5,046	(1.77%)	0.89 (0.78, 1.02)	
SBP, mm Hg						
≥157.2	351/6,135	(1.40%)	344/5,139	(1.63%)	0.84 (0.72, 0.98)	0.73
<157.2	317/8,406	(0.91%)	390/8,455	(1.12%)	0.83 (0.71, 0.95)	
Fasting plasma glucose, mg dl^{-1}						
≥101.3	345/7,085	(1.19%)	360/6,589	(1.33%)	0.89 (0.76, 1.03)	0.36
<101.3	323/7,455	(1.05%)	374/7,002	(1.30%)	0.81 (0.71, 0.93)	
10-year risk of ASCVD, %						
≥41.4	350/3,489	(2.44%)	348/3,157	(2.68%)	0.91 (0.79, 1.04)	0.11
<41.4	315/10,950	(0.70%)	385/10,345	(0.91%)	0.77 (0.66, 0.90)	



b

	Intervention		Usual care		Relative risk (95% CI)	*P* value for interaction
	Number of patients with dementia/total number (rate per year)					
Overall	2,506/14,541	(4.19%)	2,808/13,594	(5.02%)	0.84 (0.80, 0.87)	
Age						
≥67 years	1,275/4,812	(6.44%)	1,396/4,720	(7.18%)	0.90 (0.85, 0.95)	0.019
<67 years	1,231/9,729	(3.08%)	1,412/8,874	(3.87%)	0.79 (0.74, 0.84)	
Sex						
Male	735/5,508	(3.25%)	809/5,035	(3.92%)	0.83 (0.76, 0.90)	0.91
Female	1,771/9,033	(4.77%)	1,999/8,559	(5.67%)	0.85 (0.80, 0.89)	
Education						
<Primary school	939/ 2,920	(7.77%)	1,089/3,059	(8.58%)	0.90 (0.84, 0.96)	0.11
≥Primary school	1,549/11,505	(3.28%)	1,686/10,393	(3.96%)	0.82 (0.78, 0.87)	
Cigarette smoking						
Current	420/2,997	(3.41%)	519/2,855	(4.44%)	0.78 (0.70, 0.86)	0.15
Former or never	2,074/11,444	(4.41%)	2,256/10,600	(5.17%)	0.85 (0.81, 0.90)	
Body mass index, kg m^{-2}						
≥25.3	1,275/8,369	(3.71%)	1,374/7,435	(4.50%)	0.83 (0.78, 0.88)	0.40
<25.3	1,225/6,130	(4.86%)	1,425/6,129	(5.65%)	0.86 (0.81, 0.91)	
SBP, mm Hg						
≥154.7	1,323/6.976	(4.64%)	1,328/5,869	(5.52%)	0.84 (0.79, 0.89)	0.67
<154.7	1,183/7.565	(3.78%)	1,480/7,725	(4.65%)	0.82 (0.77, 0.87)	
Fasting glucose, mg dl^{-1}						
≥101.6	1,287/7.018	(4.47%)	1,383/6,532	(5.16%)	0.86 (0.81, 0.91)	0.16
<101.6	1,219/7,522	(3.93%)	1,424/7,059	(4.90%)	0.81 (0.76, 0.87)	
10-year risk of ASCVD, %						
≥23.2	1,333/5,443	(5.96%)	1,310/5,030	(6.33%)	0.94 (0.89, 0.99)	<0.0001
<23.2	1,160/8,996	(3.14%)	1,478/8,472	(4.24%)	0.75 (0.70, 0.80)	

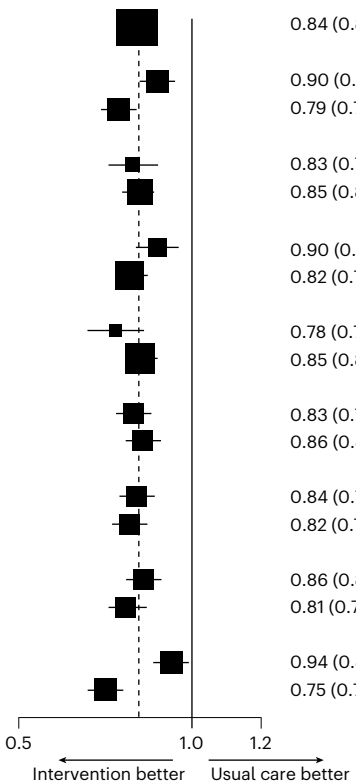


Fig. 3 | Forest plot of the primary and main secondary outcomes according to subgroups. a, All-cause dementia. **b**, CIND. The dashed vertical line represents the RR for the overall study population. The box sizes are proportional to the precision of the estimates (with larger boxes indicating a greater degree of precision). Error bars represent 95% CIs. The heterogeneity of effect sizes across predefined subgroups was tested using a treatment-by-covariate interaction term in a modified Poisson regression. The Bonferroni correction method was used to adjust the critical value (0.05/16 = 0.003) for the interaction tests.

and functional assessments conducted at the 48-month follow-up visits, all cumulative dementia events should be identified and diagnosed. Additionally, the follow-up schedule and cognitive and functional assessment procedures were uniformly applied to both groups by masked observers. Thus, the lack of repeated cognitive and functional assessments is unlikely to bias the comparison of cumulative dementia events between the two randomized groups. Cognitive and functional data were not available for participants who died during the follow-up period. However, antihypertensive treatment was associated with a significant 14% reduction in the composite outcome of dementia and deaths compared to a 15% reduction in dementia alone, suggesting that deaths did not bias the effect of antihypertensive treatment on dementia.

Additionally, potential intervention contamination among villages is a concern in this cluster trial. We took several steps to prevent this bias, such as excluding villages that shared NPCHPs, limiting protocol-based treatment training among providers in intervention villages, and providing discounted or free antihypertensive medications, as well as free home BP monitors, only to participants in the intervention group. Furthermore, if contamination occurred, it could have diluted the intervention effect.

Furthermore, the CRHCP-3 trial was exclusively conducted in patients with hypertension in rural China. While the NPCHP-led multifaceted implementation strategy should be adapted to suit local contexts, the risk-lowering effect of antihypertensive treatment on dementia could be generalized to other populations directly. Importantly, a meta-analysis of four previous trials in western populations, along with the CRHCP-3 trial, demonstrated a similar 15% reduction in dementia events, supporting BP lowering as a widespread intervention for the global prevention of dementia[10–13].

Comparison with other studies

Several randomized trials have compared antihypertensive medications versus placebo or intensive versus standard BP treatment on the risk of dementia[10–13]. In the Systolic Hypertension in Europe trial, nitrendipine with the possible addition of enalapril or hydrochlorothiazide was associated with a non-significant 50% reduction in dementia ($P = 0.06$) compared to placebo in 2,418 patients aged ≥60 years with SBP 160–219 mm Hg and DBP <95 mm Hg over 2 years[10]. The Perindopril Protection Against Recurrent Stroke Study found that perindopril with possible addition of indapamide was associated with a non-significant 11% reduction in dementia ($P = 0.22$) compared to placebo among 6,105 patients with previous stroke or transient ischemic attack over 3.9 years[12]. The Hypertension in the Very Elderly trial showed that indapamide with the option of perindopril was associated with a non-significant 14% reduction in dementia ($P = 0.21$) compared to placebo among 3,336 patients ≥80 years of age with SBP 160–200 mm Hg and DBP <110 mm Hg over 2.2 years[11]. In these trials, dementia was a secondary outcome[10–12]. The SPRINT-MIND trial found that intensive antihypertensive treatment targeting an SBP goal <120 mm Hg was non-significantly associated with a 17% reduction in dementia compared to standard treatment targeting an SBP goal <140 mm Hg in 9,361 patients ≥50 years of age with hypertension and a high risk for CVD[13]. Although these trials suggested a potential benefit of antihypertensive treatment on dementia, none demonstrated a statistically significant risk reduction. With the largest sample size and BP separation between randomization groups, our study demonstrated that antihypertensive treatment significantly reduced all-cause dementia and CIND in patients with hypertension.

A recent meta-analysis of 12 antihypertensive clinical trials reported that BP lowering with antihypertensive agents, compared to control, was significantly associated with a 7% reduction in the odds of dementia or cognitive impairment over an average of 4.1 years (odds ratio 0.93; 95% CI 0.88 to 0.98)[15]. It is worth noting that dementia and cognitive impairment were not primary outcomes in most of these trials. Furthermore, these trials used various criteria to define study outcomes, including ICD-10 codes and investigator reports without adjudication[15]. In the CRHCP trial, antihypertensive treatment was significantly associated with a 16% reduction in adjudicated CIND and a 16% reduction in the composite outcome of adjudicated dementia or CIND.

The CRHCP-3 trial was not designed to compare the effect of antihypertensive medication classes on dementia or cognitive impairment. Based on clinical guidelines, the study protocol recommended ACEIs or ARBs, CCBs, and/or thiazide or thiazide-like diuretics as the first-line medication[19–21]. In addition, CCBs and ARBs were commonly used in routine clinical practice in China due to fewer side effects[22]. A network meta-analysis of 15 observational studies showed that treatment with either CCBs or ARBs was associated with lower dementia risks than treatment with other antihypertensive agents[23]. However, two recent meta-analyses of prospective cohort studies showed that, although antihypertensive treatment was associated with a reduced risk of dementia, no evidence was found that any specific antihypertensive medication class was more effective than others in lowering this risk[14,24]. Future studies are warranted to understand the underlying mechanism of the protective effect of antihypertensive treatment on dementia and cognitive impairment[13,15,25].

In conclusion, the findings from the CRHCP-3 trial demonstrated that BP reduction is effective in reducing the risk of dementia in patients with uncontrolled hypertension. This proven-effective intervention should be widely adopted and scaled up to reduce the global burden of dementia.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-025-03616-8.

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[1]Department of Epidemiology, Peter O'Donnell Jr. School of Public Health, UT Southwestern Medical Center, Dallas, TX, USA. [2]Department of Internal Medicine, UT Southwestern Medical Center, Dallas, TX, USA. [3]Department of Neurology, UT Southwestern Medical Center, Dallas, TX, USA. [4]Peter O'Donnell Jr. Brain Institute, UT Southwestern Medical Center, Dallas, TX, USA. [5]Department of Neurology, First Hospital of China Medical University, Shenyang, China. [6]Department of Cardiology, First Hospital of China Medical University, Shenyang, China. [7]Hanzhong People's Hospital, Hanzhong, China. [8]Division of Cardiology, Department of Internal Medicine, Tongji Hospital, Tongji Medical College of Huazhong University of Science and Technology, Wuhan, China. [9]Tulane University Translational Science Institute, New Orleans, LA, USA. [10]Sticht Center for Healthy Aging and Alzheimer's Prevention, Department of Internal Medicine, Section on Geriatric Medicine, Wake Forest University School of Medicine, Winston-Salem, NC, USA. [11]These authors contributed equally: Jiang He, Chuansheng Zhao, Shanshan Zhong, Nanxiang Ouyang, Guozhe Sun, Lixia Qiao.
✉e-mail: jiang.he@utsouthwestern.edu; yxsun@cmu.edu.cn

Methods

Trial design and participants

The details of the CRHCP trial design and participants were published previously[17,18,26]. The CRHCP trial was originally designed as a two-phase effectiveness trial, with the primary outcome being BP control at 18 months and CVD events over 36 months (ref. 26). Due to the increasing public health importance of dementia and evidence from previous clinical trials suggesting a beneficial effect of lowering BP on dementia, the CRHCP steering committee decided, in October 2021, to extend the intervention and follow-up period to 48 months to study dementia outcomes. The revised trial protocol was approved by the ethics committees of the First Hospital of China Medical University and all participating institutes, and by an independent data and safety monitoring board. The decision to extend the CRHCP trial was independent of knowledge about dementia events in the trial participants, and cognitive function data were not available at that time. Informed consent was obtained from all participants.

Villages with a regular NPCHP that were located at least 2 km apart from each other were eligible for the CRHCP study. Residents ≥40 years of age with a mean untreated SBP ≥140 mm Hg and/or a DBP ≥90 mm Hg (or ≥130 mm Hg and/or ≥80 mm Hg among those with clinical CVD, diabetes or chronic kidney disease) or a mean treated SBP ≥130 mm Hg and/or a DBP ≥80 mm Hg, based on six measurements taken on two different days, were eligible for the study. Additional eligibility criteria are provided in Supplementary Information. Demographic information, including self-reported sex, was collected at baseline.

Randomization and masking

The randomization was conducted by a biostatistician using a random allocation sequence generated with SAS software and was stratified by province, county and township to ensure group balance in geographic and socioeconomic conditions. The randomization assignments were concealed until recruitment and baseline data collection were completed for all participating villages within each township, with half the villages assigned to the intervention group and the other half to usual care group.

Due to the cluster design and the nature of the intervention program, the study participants, NPCHPs and research staff who collected BP data were unmasked. However, all the research staff responsible for collecting cognitive outcome data and the members of the endpoint adjudication committee were masked to the randomization assignments.

Intervention and implementation strategy

In the intervention group, trained NPCHPs implemented intensive antihypertensive treatment using a simple stepped-care protocol aimed at achieving a target SBP of <130 mm Hg and a DBP of <80 mm Hg (refs. 19,26). NPCHPs, often called 'village doctors', most of whom have some medical training, provided basic health services to rural residents in China[18,27]. They initiated and titrated antihypertensive medications according to the treatment protocol, delivered these medications to patients at a discount or at no cost, conducted health coaching for lifestyle modifications and medication adherence, and provided monitors and instructions to participants for home BP monitoring[18,26]. Based on clinical guidelines, the study protocol recommended ACEIs or ARBs, CCBs, and/or thiazide or thiazide-like diuretics as the first-line medication[19–21]. Primary care physicians at township hospitals routinely reviewed patients' clinical BP data and provided monthly feedback to NPCHPs.

In the usual care group, NPCHPs received training in standard BP measurement but not in protocol-based hypertension management. Participants in control villages had their BP managed at their usual healthcare settings by either NPCHPs or primary care physicians in township hospitals. They did not receive free home BP monitors or antihypertensive medications. However, participants in both groups had the same health insurance plan (the China New Rural Cooperative Medical Scheme) and received similar healthcare excepting BP management.

Follow-up data collection

At the 48-month follow-up visit, trained and certified neurologists, masked to randomization assignments, collected medical history data and conducted neurological assessments, including a mental status evaluation. They administered the MMSE, a widely used 30-point questionnaire for screening cognitive impairment, to all participants[28]. Regardless of the participants' MMSE scores, knowledgeable informants (family members and/or village doctors) were asked to complete the FAQ and QDRS scales during an in-person visit. Family members of 786 participants were unavailable for the in-person visit and were interviewed over the phone. The FAQ is a brief inventory of 10 measures assessing difficulties in instrumental activities of daily living and has demonstrated excellent reliability and validity for distinguishing functional independence in patients with dementia and mild cognitive impairment[29,30]. The QDRS is a 10-domain questionnaire designed to capture prominent symptoms of cognitive impairment and dementia, reliably differentiating between those who do and those who do not have dementia[31–33]. These instruments have been translated into Chinese, culturally adapted, and validated in the Chinese population[34–37].

Central training in cognitive and functional status assessments included two stages. In the first stage, key investigators were trained and certified by unpaid consulting US-based researchers who were fluent in Chinese. In the second stage, all data collectors were trained and certified to administer the assessments by the previously trained and certified key investigators.

Study outcomes

All-cause dementia was the primary outcome and CIND was the main secondary outcome. The diagnostic criteria for all-cause dementia and CIND were adopted from the Recommendations of the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease[38,39]. Specifically, a diagnosis of dementia requires the simultaneous presence of four conditions, which are (1) an expert adjudication panel confirming the presence of significant cognitive impairment, (2) cognitive or neuropsychiatric symptoms interfering with the ability to function at work or in usual activities, (3) cognitive and physical function representing a decline from previous levels of functioning and performance and (4) cognitive impairments that are not explained by delirium or major psychiatric disorders. Likewise, the four conditions that need to be met for the diagnosis of CIND are (1) an expert adjudication panel confirming the presence of cognitive impairment, (2) evidence of concern regarding a decline in cognition from previous levels, (3) preserved functionality and independence at work or in usual activities and (4) not suffering from dementia.

The final diagnosis of all-cause dementia or CIND was determined by an expert adjudication panel that was blinded to the intervention assignment. All adjudicators were clinical neurologists with five or more years of experience in the diagnosis and management of dementia. They were trained and supervised on the adjudication protocol by dementia clinical trial experts from the United States. The adjudication panel used all available data relevant to cognitive function, including medical and psychiatric history, physical and neurological examination findings, and standardized cognitive and functional assessments to adjudicate cognitive status among all study participants (Supplementary Fig. 1). Participants were categorized into one of three primary groups: having no cognitive impairment, having a CIND diagnosis or having a diagnosis of dementia. Unclassifiable cases were placed in a 'cannot classify' category and were treated as missing data in all analyses. Each case was independently reviewed by two adjudicators using standardized diagnostic criteria. If the two reviewers concurred on the

diagnosis, it was recorded as the final diagnosis. If the two reviewers disagreed, a third more experienced adjudicator joined the review and discussion. If a consensus could not be reached through this additional process, the case was discussed by the entire adjudicating panel during regularly scheduled meetings. The classification decision in these cases was decided by a majority vote of the panel members. No attempt was made to classify dementia subtypes.

Sample size and power

The number of clusters and participants was fixed for the CRHCP trial[17,18]. We calculated statistical power based on the following assumptions: 163 clusters in each group, an average of 104 participants per cluster, a 5.0% cumulative proportion of dementia at 48 months, a 15% risk reduction, an average follow-up duration of 4 years, a lost-to-follow-up rate of 1.6% per year, an intracluster correlation of 0.001 and a two-sided significance level of 0.05. The prevalence of dementia was informed by previous studies of the Chinese population[40,41], and the effect size was derived from a meta-analysis of four previous trials[10–13]. The statistical power for the primary outcome was determined to be 85.8%, based on a Score test implemented with PASS software v.2008 (ref. 42).

Statistical analysis

Intention-to-treat analyses were conducted. A modified Poisson regression with a cluster-robust error variance was used to calculate RR and 95% CI for dementia and secondary clinical outcomes associated with the intervention[43]. A generalized estimating equation linear model was employed to test differences in BP changes, and a generalized linear mixed-effects model was used to test differences in the proportions of patients with controlled BP and other binary outcomes[44,45]. A compound symmetric working correlation structure accounted for the clustering effect, and the analyses were stratified by township, county and province. The modified Poisson regression analysis, generalized estimating equation linear model and mixed-effects models were implemented using SAS Proc GENMOD. Also, rates of adverse events were compared using a chi-square test at a significance level of 0.0125 (0.05 of 4).

In a sensitivity analysis, predefined covariables, including age, self-reporetd sex, education, history of cigarette smoking, history of major CVD, use of antihypertensive medication, body mass index, SBP, LDL cholesterol and fasting plasma glucose at baseline, were adjusted. Multiple imputation for missing data was performed using Markov Chain Monte Carlo method with 20 cycles, incorporating study outcomes and all the covariates mentioned above[46,47]. Additionally, multiple imputation using the pattern-mixture method with a delta ranging from 0.5 to 5 was also performed[48]. Predefined subgroup analyses were conducted. For continuous covariates, subgroups were divided by the median values among participants with dementia or CIND to ensure sufficient events in each subgroup. The heterogeneity of effect sizes across predefined subgroups was tested using a treatment-by-covariate interaction term at a significance level of 0.003 (0.05 of 16).

ICC was calculated using the analysis of variance estimator and implemented with the ICCbin package in R[49].

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Since patients have not explicitly consented to data sharing, we are not allowed to post individual participant data in a public data repository for legal reasons. However, researchers with a valuable research question can request study data from the corresponding authors. If the proposal is approved by the CRHCP Study Steering Committee, deidentified individual data may be shared after consultation with the data protection officers and legal representatives of the participating institutions and after signing a data-sharing agreement. All data sharing will abide by the rules and policies defined by the sponsor, relevant ethics committees, and government laws and regulations. A response to requests for data access can be expected within 4 weeks. Source data are provided with this paper.

Code availability

The modified Poisson regression analysis and generalized estimating equation linear model were implemented using Proc GENMOD in SAS v.9.4.

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Acknowledgements

This work was supported by the National Key Research and Development Program of the Ministry of Science and Technology of China (grant no. 2017YFC1307600, Y.S.), Chinese Society of Cardiology Foundation (grant no. CSCF2022B02, Y.S.), and the Science and Technology Program of Liaoning Province, China (grant no. 2020JH1/10300002, Y.S.). The funder of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report. The US investigators did not receive any financial support from this study. We are grateful to the NPCHPs, primary care physicians, hypertension specialists and research staff at all participating institutes for their support throughout the study. A full list of the committee members and study group members of the China Rural Hypertension Control Project is provided in Supplementary Information. We acknowledge C. Li from the Alzheimer's Disease Research Center at the Icahn School of Medicine at Mount Sinai and J. S.-Lemus from the Department of Psychology at Montclair State University for their advice and recommendations on cognitive and functional status screening tools and diagnostic guidelines for dementia and CIND. We thank C. Li and X. Zeng for providing training and certification on cognitive and functional status assessment to the key investigators. Furthermore, we express our gratitude to H. He and S. Geng from the Tulane University Translational Science Institute for their advice and assistance in statistical analyses.

Author contributions

J.H., Chuansheng Zhao, S.Z., N.O., G.S., J.D.W. and Y.S. conceived and designed the study. J.H., Chuansheng Zhao, S.Z., N.O., G.S., L.Q., R.Y., Chunxia Zhao, H.L., W.T., X.L., C.W., S.L. and Y.S. supervised the data collection. J.H., Chuansheng Zhao, S.Z., N.O., G.S., L.Q., C.-S.C., J.D.W. and Y.S. analyzed and interpreted the data. J.H. drafted the paper. All authors revised the paper for important intellectual content and approved the final submitted version. J.H., Chuansheng Zhao, S.Z., N.O., G.S., C.-S.C. and Y.S. accessed and verified the data. J.H. and Y.S. had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41591-025-03616-8.

Correspondence and requests for materials should be addressed to Jiang He or Yingxian Sun.

Peer review information *Nature Medicine* thanks Josef Coresh, Ruth Peters and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Primary Handling Editor: Jerome Staal, in collaboration with the *Nature Medicine* team.

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Last updated by author(s): Feb 26, 2025

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☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
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Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	No software was used for the data collection process.
Data analysis	The statistical power for the primary outcome was determined using a Score test implemented in PASS 2008. The modified Poisson regression analysis and the generalized estimating equation linear model were conducted using Proc GENMOD in SAS 9.4.

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Since patients have not explicitly consented to data sharing, we are not allowed to post individual participant data in a public data repository for legal reasons. However, researchers with a valuable research question can request study data from the corresponding authors: Prof. Sun at yxsun@cmu.edu.cn or Prof. He at jiang.he@utsouthwestern.edu. If the proposal is approved by the CRHCP Study Steering Committee, de-identified individual data may be shared after consultation

with the data protection officers and legal representatives of the participating institutions and after signing a data-sharing agreement. All data sharing will abide by the rules and policies defined by the sponsor, relevant ethics committees, and government laws and regulations. A response to requests for data access can be expected within 4 weeks.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Subgroup analysis by sex is presented in Figure 3.
Reporting on race, ethnicity, or other socially relevant groupings	All study participants are Chinese ethnicity.
Population characteristics	On average, study participants were 62.8 years old in the intervention group and 63.3 years old in the usual care group. In the intervention group, 60.8% of participants were female, compared to 61.6% in the usual care group.
Recruitment	From May 8, 2018, to November 28, 2018, a total of 46,740 individuals were assessed for eligibility from 326 villages in rural China. Of these, 33,995 participants (17,407 in 163 intervention villages and 16,588 in 163 usual care villages) were enrolled. Of these participants, 15,972 (91.8%) in the intervention group and 15,072 (90.9%) in the usual care group were followed up for clinical outcomes at the 48-month visit, which concluded on March 26, 2023.
Ethics oversight	The trial protocol was approved by the ethics committees of the First Hospital of China Medical University and all participating institutes and by an independent data and safety monitoring board. Informed consent was obtained from all participants.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

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Life sciences study design

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Sample size	We calculated statistical power based on the following assumptions: 163 clusters in each group, an average of 104 participants per cluster, a 5.0% cumulative proportion of dementia at 48 months, a 15% risk reduction, an average follow-up duration of four years, a lost-to-follow-up rate of 1.6% per year, an intra-cluster correlation of 0.001, and a two-sided significance level of 0.05. The dementia prevalence was informed by previous studies in the Chinese population, and the effect size was derived from a meta-analysis of four prior trials. The statistical power for the primary outcome was determined to be 85.8%, based on a Score test implemented with PASS software.
Data exclusions	No data were excluded.
Replication	Since this study is a large cluster-randomized trial, replication is not necessary.
Randomization	The randomization was conducted by a biostatistician using a random allocation sequence generated with SAS software and was stratified by province, county, and township to ensure group balance in geographic and socioeconomic conditions. The randomization assignments were concealed until recruitment and baseline data collection were completed for all participating villages within each township.
Blinding	Due to the cluster design and the nature of the intervention program, the study participants, NPCHPs, and research staff who collected BP data were unmasked. However, all research staff responsible for collecting cognitive outcome data and the members of the endpoint adjudication committee were masked to the randomization assignments.

Reporting for specific materials, systems and methods

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☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	ClinicalTrials.gov: NCT03527719
Study protocol	The full trial protocol is available upon request.
Data collection	From May 8, 2018, to November 28, 2018, a total of 33,995 participants (17,407 in 163 intervention villages and 16,588 in 163 usual care villages) were enrolled from rural China. Of these participants, 15,972 (91.8%) in the intervention group and 15,072 (90.9%) in the usual care group were followed up for clinical outcomes at the 48-month visit, which concluded on March 26, 2023.
Outcomes	All-cause dementia was the primary outcome, and cognitive impairment no dementia (CIND) was the main secondary outcome. These outcomes were pre-defined before follow-up data collection. At the 48-month follow-up visit, trained and certified neurologists, who were masked to randomization assignments, collected medical history data and conducted neurological assessments, including a mental status evaluation. The final diagnosis of all-cause dementia or CIND was determined by an expert adjudication panel that was blinded to the intervention assignment.

Plants

Seed stocks	N/A
Novel plant genotypes	N/A
Authentication	N/A