Intensive blood pressure control in isolated systolic hypertension: a post hoc analysis of a cluster randomized trial

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Summary

Background The isolated systolic hypertension (ISH) is of high prevalence, with a relatively poor prognosis. However, there is still no direct evidence to demonstrate the benefits of intensive blood pressure (BP) control among these patients. We aimed to evaluate intensive BP control with the target of <130/80 mmHg in ISH.

Methods This was a post hoc analysis of patients with ISH in the China Rural Hypertension Control Project (CRHCP), defined as systolic blood pressure (SBP) ≥ 140 mmHg and diastolic blood pressure (DBP) < 90 mmHg. The primary outcome was cardiovascular disease (CVD) including stroke, myocardial infarction, heart failure, and CVD death. Mixed-effect Cox proportional regression and generalized estimating equation models were used for analysis.

Findings In total, 7981 patients were randomly assigned to the intervention group and 8005 to the usual care group between May 8 and November 27, 2018. The median follow-up was 3.02 years (25–75%: 2.98–3.06). Mean systolic/diastolic BP at the end of 36 months follow-up was 126.5/71.2 mmHg in the intensive BP control group and 148.1/78.6 mmHg in the usual care group. The intervention group presented a substantially lower rate of composite CVD compared with the usual care group (1.52% versus 2.30%/year; multiple-adjusted hazard ratio (HR): 0.64; 95% confidence interval (CI): 0.57–0.72; $P < 0.001$), especially for stroke (multiple-adjusted HR: 0.61; 95% CI: 0.53–0.70; $P < 0.001$), HF (multiple-adjusted HR: 0.57; 95% CI: 0.36–0.91; $P = 0.017$) and CVD death (multiple-adjusted HR: 0.64; 95% CI: 0.50–0.83; $P < 0.001$). The primary composite outcome was substantially reduced by 36% in the intervention group compared with the usual care group. The further interaction analysis revealed that the reduction of primary outcome by intervention was consistent across subgroups of sex, age, education level, history of CVD, use of antihypertensive medication and baseline DBP ($P > 0.05$ for all interaction test). The incidences of symptomatic hypotension, syncope injurious falls and renal outcomes did not differ between the two groups, even though hypotension was increased in intervention group (RR:1.71; 95% CI: 1.28–2.28; $P < 0.001$).

Interpretation Intensive BP control (<130/80 mmHg) was effective and safe in patients with ISH for the prevention of CVD events.

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Keywords: Isolated systolic hypertension; Intensive blood pressure control; Cardiovascular disease

Introduction

Hypertension is widely recognized as an important risk factor for cardiovascular events.[1] It could be categorized into three subtypes: isolated systolic hypertension (ISH), isolated diastolic hypertension (IDH), and systolic and diastolic hypertension (SDH).[2] ISH, defined as systolic blood pressure (SBP) ≥140 mmHg and diastolic blood pressure (DBP) < 90 mmHg, is the most prevalent and high-risk type, which is common in patients with atherosclerosis and in older adults.[3–5] With the

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Research in context

Evidence before this study

We conducted a comprehensive search of the PubMed databases published up to March 6, 2024, using the search terms "blood pressure control [Title/Abstract]" OR "Antihypertensive [Title/Abstract]" OR "blood pressure management [Title/Abstract]" OR "blood pressure lowering [Title/Abstract]" AND "randomized controlled trial [Filter]" AND "isolated systolic hypertension [Title/Abstract]". No language restrictions were applied. Our search identified three relevant randomized clinical trials, namely the Systolic Hypertension in Europe Trial (Syst-Eur), Valsartan in Elderly Isolated Systolic Hypertension Study (VALISH) and Systolic Hypertension in the Elderly Program (SHEP). The Syst-Eur trial suggested that lowering systolic blood pressure (SBP) to between 140 and 150 mmHg was beneficial for patients with isolated systolic hypertension (ISH), and the VALISH trial indicated that targeting SBP to <140 mmHg was safe but not beneficial for patients with ISH. The SHEP trial demonstrated the ability of antihypertensive drug treatment to reduce the risk of stroke in isolated systolic hypertension. There is insufficient evidence to support intensive BP control aiming for a target of 130/80 mmHg in patients with ISH.

Added value of this study

As a post hoc analysis within the China Rural Hypertension Control Project, the current study is the first to evaluate intensive BP control (<130/80 mmHg) in patients with ISH, demonstrating a substantial reduction in cardiovascular events. These results contributed further evidence-based medical knowledge regarding antihypertensive treatment approaches for ISH.

Implications of all the available evidence

The outcomes of this study validated both the efficacy and safety of intensive BP control (<130/80 mmHg) among patients with ISH, which addressed the identified guidelines gaps where BP thresholds and targets in this specific population. Moreover, our research provided valuable insights into chronic disease management models applicable to low-resource settings.

development of the population aging, the prevalence and risk degree of ISH are gradually increasing.[4] The 2023 European Society of Hypertension (ESH) guidelines for the management of arterial Hypertension reveals a gap in identifying the optimal blood pressure (BP) target for ISH,[6] highlighting the importance of implementing safe and effective BP control methods.

Among ISH patients with SBP ≥160 mmHg, antihypertensive therapy led to substantial reductions of 13%, 18%, and 26% in all-cause death, cardiovascular death, and overall cardiovascular outcomes, respectively.[7] Several randomized controlled trials (RCT) (Syst-Eur, SHEP, Syst-China)[8–10] had suggested that maintaining SBP within the range of 140–150 mmHg confers a protective effect against cardiovascular disease (CVD) in ISH patients. However, the Valsartan in Elderly Isolated Systolic Hypertension Study (VALISH) trial demonstrated that SBP below 140 mmHg were deemed safe but did not provide additional benefits compared to levels between 140 and 150 mmHg in patients with ISH.[11] Thus, this scientific issue of BP lowering in the ISH patients remained controversial.

The traditional recommendation by major guidelines was maintaining a BP target of <140/90 mmHg due to its proven efficacy in reducing cardiovascular outcomes.[12] Then a comprehensive meta-analysis revealed that a reduction of 5 mmHg in SBP was associated with a noteworthy 10% decrease in the risk of major cardiovascular events, even among individuals with normal or high-normal BP levels.[13,14] Thus, intensive BP control was suggested, following by RCTs. In the Systolic Blood Pressure Intervention Trial (SPRINT), intensive BP control (SBP <120 mmHg) could lower risk of CVD than traditional treatment (SBP <140 mmHg) in high-risk individuals without diabetes mellitus or stroke.[15] The Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients (STEP) trial also demonstrated the effectiveness and safety of intensive BP control (110 mmHg < SBP < 130 mmHg) in hypertensive patients aged 60–80 years.[16] China Rural Hypertension Control Project (CRHCP), an implementation study testing safety and effective of intensive BP strategy with a target of <130/80 mmHg, enrolled a general population, having high representativeness.

However, no RCT has yet confirmed the safety and efficacy of intensive BP control in patients with ISH. In our CRHCP trial, the target of <130/80 mmHg was used to assess the effectiveness and safety in preventing CVD, according to the recommendation by the 2017 American College of Cardiology/American Heart Association (ACC/AHA) Hypertension Guideline.[17,18] Therefore, to fulfill the vacancy of evidence, our current post hoc analysis was performed to elucidate the effectiveness and safety of this intensive BP control strategy among patients with ISH.

Methods

Study population

In this study, we used data from the cluster-randomized trial of CRHCP, which has been extensively described in published articles.[17,18] Briefly, the trial aimed to evaluate the efficacy of a multifaceted BP intervention model led by non-physician community health care providers with

the goal of BP < 130/80 mmHg in reducing the risk of composite CVD among hypertensive patients, compared with usual care. The CRHCP study was a two-stage, cluster-randomized trial in 326 rural villages across three provinces of China (Liaoning, Shaanxi, and Hubei) using an open-label design with blind endpoints. The study received approval from the Ethics Committee of the First Hospital of China Medical University and all participating research institutes (KLS20181582). Informed consent forms were signed by all participants during the screening visit. The progress of the trial was monitored by an independent data and safety monitoring committee, with a focus on examining both safety and effectiveness. Inclusion and exclusion criteria have been published previously.[17] Among all eligible patients, a total of 15,986 hypertensive patients were diagnosed with ISH. The definition of ISH was SBP ≥140 mmHg and DBP < 90 mmHg, treated or untreated alike, similar to previous studies.[19–21] Of these, 7981 patients were in the intervention group and 8005 in the usual care group.

Randomization and masking

The randomization process was conducted at the Tulane University Translational Science Institute in the United States. SAS software was used for stratification by province, county, and township. A biostatistician allocated all enrolled villages to either the intervention group or the usual care group following a 1:1 ratio, based on the predetermined random allocation sequence. Details of the randomization were kept confidential until the completion of participant recruitment and collection of baseline data. Furthermore, members of the endpoint adjudication committee, as well as event adjudication coordinators, were systematically blinded to the allocation of study groups.

Intervention and measurements

The study implemented a stepwise management plan for hypertension. The intervention group received comprehensive treatment from trained non-physician community health providers targeting a BP goal of <130/80 mmHg, and the control group received usual care. These providers underwent detailed training in antihypertensive treatment, including drug selection, contraindications, dosage adjustments, and patient education on home BP monitoring, medication adherence, and lifestyle modifications with the guidance of primary care physicians. Their tasks also involved medication management, health coaching, home BP monitoring instruction, and organizing social support groups, with compensation of a base salary plus performance incentives from research grants. To improve adherence, the intervention group was offered monthly antihypertensive medications for free or at a reduced cost and home BP monitoring devices, along with regular health coaching, providing a strong support system.

All participants were enrolled between May 8 and November 27, 2018. Participants underwent follow-up every six months after enrollment. The 36 months follow-up for each participant concluded on October 29, 2021. Baseline demographic data were acquired via a standardized questionnaire. Subsequent follow-up visits entailed the measurement of BP and collection of data on lifestyle variables, antihypertensive medication use and compliance, costs associated with health care, and recording of adverse events and trial outcomes. BP was measured using an Omron HBP-1100U automatic BP monitor (Omron Corporation, Tokyo, Japan), with cuff size selected according to arm circumference measurements. After a resting for 5 min, three consecutive BP readings were obtained while the participant was seated, in accordance with a predefined protocol. To mitigate observer bias, the BP data were immediately transmitted to the central research data repository using mobile technology. During each follow-up visit, BP were monitored for two days, three times daily. The mean of these six values were used for the final analysis. Participants provided overnight fasting blood samples in the morning at both the baseline and 36 months follow-up consultations for the analysis of glucose levels, lipid profiles, electrolytes, liver and kidney functions, and other standard blood biochemical parameters. The estimated glomerular filtration rate (eGFR) was determined using the newly updated Chronic Kidney Disease Epidemiology Collaboration creatinine equation.[22]

Outcomes

Follow-up assessments were performed every six months. The primary outcome of the CRHCP was the incidence of composite CVD, including myocardial infarction, stroke, heart failure necessitating hospitalization, or cardiovascular death, within the 36 months follow-up period. Each case was independently evaluated by two members of the endpoint adjudication committee, who were unaware of the randomization assignments. In cases of disagreement, a third adjudicator was consulted to reach a consensus. The detailed events adjudication had been described in previous article[17,23] For cardiovascular events, only definite cases are included in the final analysis. For CVD deaths, both definite and probable cases are included in the analyses. Classification of cause of death evidence was shown in Supplementary eTable S1. In this analysis, serious adverse events were defined as hospitalization or death. Injurious falls was self-reported and defined as a fall that resulted in seeking medical care. Hypotension was defined as SBP <90 mmHg at a village doctor visit or a study data a collection visit at months 6, 12, 18, 24, 30, and 36. Symptomatic hypotension was self-reported and confirmed by SBP <90 mmHg at a village doctor visit. Syncope was defined as self-reported temporary loss of consciousness that resulted in seeking medical care.

Statistical analysis

As a post-hoc analysis of CRHCP, participants with ISH were categorized into groups based on whether they received an intervention. The statistical power was estimated for the available sample size and directly calculated by PASS software with a result of 0.94. The comprehensive calculation process of statistical power can be found in the Supplementary Appendix. Continuous variables are presented as mean ± standard deviation, while categorical variables are shown as frequency counts (percentage). To compare differences in continuous variables between groups, we used the Student's T-test. For categorical variables, we employed the $\chi 2$ or Fisher exact test, and for differences between medians, the Mann–Whitney U test was applied. The propensity score has been used as part of the sensitivity analyses, and the detailed description was shown in the Supplementary Appendix. We conducted intention-to-treat analyses to compare study outcomes between groups based on village randomization, regardless of actual intervention adherence. We used a generalized estimating equation linear model with an exchangeable correlation structure to assess differences in BP. The ΔSBP and ΔDBP between baseline and the 36 months follow-up were calculated for each group. Subsequently, group net differences were compared after adjusting for age, sex and baseline SBP/DBP. Before the construction of the Cox proportional regression models, we systematically assessed the adherence to the Proportional Hazards (PH) assumption. The village variable was treated as a random effect in the mixed-effect Cox proportional regression model. Marginal Cox proportional hazards models were used to estimate the cardiovascular event hazard ratios (HRs) and 95% confidence intervals (CIs) at a significance level of 0.05. In these models, village was treated as a random effect while province, county, and township were treated as fixed effects. A robust sandwich covariance matrix was applied to address village clustering. Preliminary adjusted model adjusted for province, county, and township to calculate HR. In multiple-adjusted analysis, we adjusted for province, county, township, baseline covariates such as age, sex, smoking, antihypertensive medication use, CVD history, baseline SBP, low-density lipoprotein cholesterol, fasting plasma glucose. The Kaplan–Meier curves were used to compare the cumulative incidence of primary outcome and secondary outcomes between groups, followed by the log-rank tests. The dose–response interactive effect between baseline DBP and the intervention on the hazard ratio of the primary outcome was illustrated using the "interaction RCS" R package. We censored follow-up time at loss to follow-up or the last event. The reported CIs were not adjusted for multiple comparisons and were therefore unsuitable for hypothesis testing. We also calculated event rates per 100 person-years. Two-tailed P values < 0.05 were considered statistically substantial for all analyses. Statistical analysis was conducted with SAS 9.4 (SAS Institute, Cary, NC, USA), R version 4.2.0 (R Project for Statistical Computing, Vienna, Austria) and SPSS 25.0 software (IBM Corporation).

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or report writing.

Results

Baseline characteristics of study participants

In this post hoc analysis of the CRHCP, 15,986 patients with ISH (SBP ≥140 mmHg and DBP <90 mmHg) were ultimately included in the final analysis, in which 7981 patients were randomly assigned to the intervention group and 8005 patients in the usual care group, the median follow-up time was 3.02 years (25–75%: 2.98–3.06) (Fig. 1). Table 1 shows the demographic and clinical characteristics of the study population in two groups. The mean age of participants was 65.7 years in the intervention group and 66.1 years in the usual care group, with women comprising 66.3% and 66.5% of each respective group. Among patients with ISH, more participants had history of diabetes, use of antihypertensive drugs, and higher levels of body mass index, SBP, DBP, total cholesterol, low-density lipoprotein cholesterol, and blood glucose were found at baseline. These imbalanced covariates were adjusted in subsequent analysis, as appropriate.

Blood pressure and antihypertensive medications during follow-up

After the 36 months follow-up, the mean BP of the intervention group reached 126.5/71.2 mmHg, from 155.9/81.3 mmHg at baseline; the mean BP of the usual care group decreased from 155.1/81.0 mmHg at baseline to 148.1/78.6 mmHg (Fig. 2). We observed net differences in the reduction of SBP of 21.7 mmHg (95% CI: 20.8–22.66; P < 0.001) and a decrease in DBP of 7.7 mmHg (95% CI: 7.1–8.2; P < 0.001). ; After multiple imputation for missing data, the proportion of ISH patients who had a BP of less than 130/80 mmHg at 36 months was 73.9% in the intervention group and 12•0% in the usual care group (Supplementary eFig. S1). In the intervention group, a gradual reduction in both SBP and DBP was observed, with the target <130/80 mmHg during the 36 months follow-up (Fig. 2). SBP reached 130.6 mmHg at 18 months and remained approximately 130 mmHg thereafter. DBP quickly reached 80 mmHg after the intervention and remained below this threshold until the end of the study. The mean DBP in the usual care group dropped to 80 mmHg at approximately the same time as in the intervention group but remained at a higher level. Types and dosages of antihypertensive medications used by study participants during the follow-up were shown in Supplementary eTable S2.

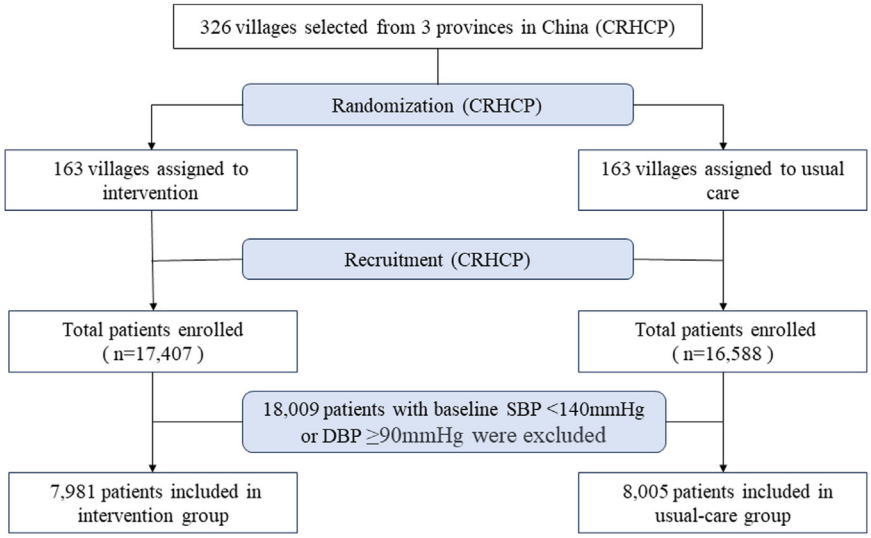

Fig. 1: Flowchart of the study. Abbreviations: SBP = systolic blood pressure; DBP = diastolic blood pressure; CRHCP = China Rural Hypertension Control Project. The randomization, recruitment, and enrollment of this study are shown.

Clinical outcomes

During the 36 months follow-up period, 348 participants in the intervention group (1.52% rate per year) reported primary outcomes and the usual care group witnessed 523 participants (2.30% rate per year) with primary outcomes (Table 2). A statistically meaningful disparity could be observed between the two groups (multiple-adjusted HR: 0.64; 95% CI: 0.57–0.72; $P < 0.001$). The event rates for secondary outcomes were also calculated, with notable risk reductions for stroke (multiple-adjusted HR: 0.61; 95% CI: 0.53–0.70; $P < 0.001$), heart failure (multiple-adjusted HR: 0.57; 95% CI: 0.36–0.91; $P = 0.017$), and cardiovascular death (multiple-adjusted HR: 0.64; 95% CI: 0.50–0.83; $P < 0.001$) (Table 2). The risk reduction by intervention in cumulative incidence of composite CVD, stroke and cardiovascular death was also presented in Kaplan–Meier curves ($P < 0.05$ for all) (Fig. 3).

Subgroup analysis of the primary outcome was conducted, revealing that the reduction of primary outcome by intervention was consistent across subgroups of sex, age, education level, history of CVD, and use of antihypertensive medication ($P < 0.05$ for all). In the subgroup of baseline DBP, the benefits were substantial in patients with DBP between 70 and 80 mmHg (multiple-adjusted HR: 0.68; 95% CI: 0.54–0.87; $P = 0.002$) or ≥80 mmHg (multiple-adjusted HR: 0.59; 95% CI: 0.51–0.69; $P < 0.001$) (Fig. 4). The further analysis revealed that the interactions between each subgroup and intervention were all negative ($P > 0.05$ for all interaction test). Secondary outcomes by subgroup analysis were also compared (Supplementary eFigs. S2–S6), and similar trends were also reported for stroke and cardiovascular death.

To explore the possible difference of benefits across baseline DBP, we further investigated the underling BP changes in the subgroup of patients with baseline DBP < 70 mmHg during follow-up. As a result, the intervention group had a decrease of SBP from 153.2 ± 11.7 mmHg to 127.7 ± 11.2 mmHg and DBP from 65.8 ± 3.7 mmHg to 65.5 ± 9.3 mmHg. In contrast, SBP in the usual care group changed from 153.9 ± 12.2 mmHg to 148.1 ± 12.8 mmHg, and DBP from 65.6 ± 4.0 mmHg to 69.7 ± 10.5 mmHg. DBP remained stable whereas SBP decreased substantially following intensive BP lowering (Supplementary eFig. S7). Beside the interaction test mentioned above, the dose–response interactive effect between baseline DBP and intervention on the HR of the primary outcome was also presented in Supplementary eFig. S8 (P for interaction = 0.114). Thus, the interactive effective was non-substantial.

Safety and renal outcomes

We conducted a comprehensive evaluation of the safety endpoints in this study (Fig. 5). The intervention group showed a substantially protective effect against serious adverse events, including death and hospitalization, compared with the usual care group (RR: 0.92; 95% CI: 0.86–0.98; $P = 0.011$). The results indicated no statistically meaningful differences in symptomatic hypotension between the groups (RR: 0.84; 95% CI: 0.57–1.24; $P = 0.364$), despite a statistically higher incidence of hypotension observed in the intervention group (RR: 1.71; 95% CI: 1.28–2.28; $P < 0.001$). Compared to the usual care group, the intervention group had a lower incidence of hypernatremia with serum sodium >150 mmol/L (RR: 0.35; 95% CI: 0.25–0.47; $P < 0.001$) and a higher incidence of hypokalemia with serum

Characteristics	Intervention (n = 7981)	Usual care (n = 8005)	P value
Age (SD), years	65.7 (8.6)	66.1 (8.6)	0.004
Female, n (%)	5290 (66.3)	5321 (66.5)	0.801
Education, n (%)			
Primary school or less	5725 (72.3)	5881 (74.2)	0.019
Junior high school	1812 (22.9)	1662 (21.0)	
High school	344 (4.3)	354 (4.5)	
College or higher	37 (0.5)	28 (0.4)	
Cigarette smoking, n (%)			
Never smoked	5842 (73.7)	5765 (72.8)	0.062
Former smokers	628 (7.9)	591 (7.5)	
Current smokers	1455 (18.4)	1564 (19.7)	
Weekly alcohol drinking, n (%)	999 (12.6)	1101 (13.9)	0.016
Physical activity ≥5 times/week, n (%)[a]	3671 (46.4)	3760 (47.6)	0.124
Median duration of hypertension (IQR), years	8 (5, 12)	8 (4, 11)	0.229
Use of antihypertensive medications, n (%)	4503 (56.4)	3866 (48.3)	<0.001
History of major cardiovascular disease, n (%)[b]	1628 (20.4)	1535 (19.2)	0.052
History of previously diagnosed diabetes, n (%)	833 (10.4)	726 (9.1)	0.004
History of chronic kidney disease, n (%)	57 (0.7)	39 (0.5)	0.063
Body mass index (SD), kg/m^2	25.6 (3.8)	25.3 (3.7)	<0.001
Systolic blood pressure (SD), mmHg	155.9 (13.3)	155.1 (12.9)	<0.001
Diastolic blood pressure (SD), mmHg	81.3 (6.5)	81.0 (6.6)	0.011
Total cholesterol (SD), mg/dL	195.9 (39.7)	194.5 (38.9)	0.023
Low-density lipoprotein cholesterol (SD), mg/dL	106.3 (32.7)	104.8 (31.4)	0.003
High-density lipoprotein cholesterol (SD), mg/dL	56.3 (13.3)	56.3 (13.3)	0.858
Plasma glucose (SD), mg/dL	112.4 (37.5)	111.3 (35.8)	0.050
Uric acid (SD), mg/dL	5.0 (1.4)	5.0 (1.4)	0.257
Estimated glomerular filtration rate (SD), mL/min/1.73 m^2[c]	94.1 (12.6)	93.7 (12.5)	0.085
10-year risk for atherosclerotic cardiovascular disease (SD), %[d]	16.4 (12.3)	16.1 (11.8)	0.155

SD = standard deviation; IQR = interquartile range. [a]Moderate or heavy physical activity ≥30 min/time. [b]Major cardiovascular disease includes myocardial infarction, stroke, and heart failure requiring hospitalization. [c]Estimated glomerular filtration rate was calculated based on the 2021 Chronic Kidney Disease Epidemiology Collaboration creatinine equations. [d]Atherosclerotic cardiovascular disease risk was calculated based on the American College of Cardiology/American Heart Association Pooled Cohort Equations.

Table 1: **Baseline characteristics of the subjects.**

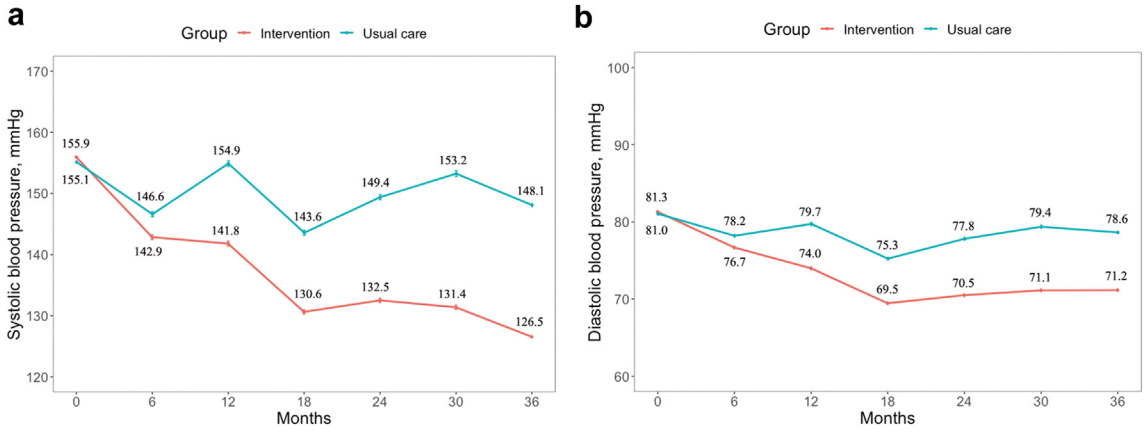

Fig. 2: Systolic and diastolic blood pressure in the intervention and usual care groups over 36 months of follow-up. Notes: Error bars indicate 95% confidence intervals.

Study outcomes	Intervention		Usual care		Hazard ratio (95% CI)[a]	P value	Multiple-adjusted hazard ratio (95% CI)[a,b]	P value
	No. of events	Rate, % per year	No. of events	Rate, % per year				
Primary outcome								
Cardiovascular disease	348	1.52	523	2.30	0.65 (0.57, 0.73)	<0.001	0.64 (0.57, 0.72)	<0.001
Secondary outcomes								
Stroke	257	1.12	406	1.78	0.62 (0.54, 0.71)	<0.001	0.61 (0.53, 0.70)	<0.001
Myocardial infarction	55	0.24	57	0.25	0.94 (0.65, 1.35)	0.729	0.94 (0.65, 1.39)	0.784
Heart failure	25	0.11	41	0.18	0.59 (0.38, 0.93)	0.023	0.57 (0.36, 0.91)	0.017
Death from cardiovascular causes	89	0.38	137	0.59	0.64 (0.49, 0.82)	<0.001	0.64 (0.50, 0.83)	<0.001
Death from all causes	356	1.53	396	1.70	0.91 (0.79, 1.05)	0.191	0.93 (0.81, 1.07)	0.321

BP = blood pressure; ISH = isolated systolic hypertension; CI = confidence interval. [a]In the marginal Cox models, village was used as a random effect. [b]Additionally adjusted for age, sex, cigarette smoking, use of antihypertensive medication, history of cardiovascular disease, baseline systolic blood pressure, low-density lipoprotein cholesterol, and fasting plasma glucose.

Table 2: **Effectiveness of the intensive BP control strategy on the primary and secondary outcomes in ISH patients.**

potassium <3.5 mmol/L (RR: 1.61; 95% CI: 1.29–2.02; $P < 0.001$), but, no substantial difference between the intervention group and the usual care group of hypokalemia with serum potassium <3.0 mmol/L (RR: 1.51; 95% CI: 0.48–5.14; $P = 0.451$). Thus, most hypokalemia cases with were 3.0 and 3.5 mmol/L (198/207). Among patients with CKD at baseline, three out of 137 in the intervention group experienced a reduction in eGFR of 50% or more, representing 2.19%, compared to five out of 139 in the usual care group, which accounted for 3.60% (RR: 0.61; 95% CI: 0.10–3.13; $P = 0.521$). In patients without CKD, those experiencing a 30% or more reduction in eGFR to below 60 ml/min/1.73 m^2 were 123 out of 7023 in the intervention group (1.75%) and 104 out of 6935 in the usual care group (1.50%) (RR: 1.17; 95% CI: 0.89–1.53; $P = 0.245$).

Sensitivity analysis

As a post hoc analysis for ISH patients of CRHCP, propensity score matching strategy successfully matched a total of 7165 pairs of ISH patients in the two groups (Supplementary eTable S3). The result for the primary outcome was robust and similar to that of unmatched population (multiple-adjusted HR for primary outcome: 0.64; 95% CI: 0.56–0.74; $P < 0.001$) (Supplementary eTable S4). Additionally, sensitivity analysis on BP change, outcomes, subgroup analysis and serious adverse events were conducted by restricted ISH patients as untreated ones (Supplementary eFigs. S9–S12 and Tables S5 and S6). Similar finding was found in the primary outcome (multiple-adjusted HR: 0.69; 95% CI: 0.57–0.84; $P < 0.001$).

Discussion

This was a post hoc analysis of CRHCP aiming to verify the effectiveness and safety of the intensive BP control in patients with ISH. At the 36 months follow-up, the reduction in SBP was 21.5 mmHg (95% CI: 20.6–22.3; $P < 0.001$), and DBP decreased by 7.6 mmHg (95% CI: 7.0–8.1; $P < 0.001$). Intensive BP control reduced composite CVD events by 36%. The secondary outcomes also declined in the intervention: there was a 6% reduction in myocardial infarction, a 39% reduction in stroke, a 43% reduction in hospitalized heart failure, a 36% reduction in CVD death, and a 7% reduction in all-cause death. Subgroup analysis indicated that the effect of intervention was consistent across age, sex, education level, history of CVD, and antihypertensive medication use. However, different from patients with DBP between 70 and 80 mmHg and above 80 mmHg, those with a baseline DBP less than 70 mmHg did not show substantial protection against CVD events by intensive BP control.

The 2022 Annual Report on Cardiovascular Health and Disease in China indicates that CVD deaths accounted for 48.0% of all causes of death in rural areas and 45.9% in urban areas,[24] while the proportion of cardiovascular deaths in the control group was only 34.6%. The possible reasons perhaps lie in the lack of detailed information for the cause of death, for most deaths in rural China occur at home without medical attention.[25,26] Only definite and probable cases were included in the analyses, leading to a lower rate of CVD deaths. For the CVD events, the confirmation of CVD events in our study was also strict, and TIA and lacunar infarction were not included in the stroke. In our trial, the intervention group had protective effect on stroke (HR: 0.60; 95%CI: 0.52–0.70), but not myocardial infarction (HR: 0.94; 95%CI: 0.65–1.39), which is similar with the ACCORD trial.[27] However, there was substantial difference in all CVD events between the intervention group and the usual care group in our main study.[17] It is noteworthy that the current study included a population with ISH, whereas the results from SPRINT study and ACCORD study were based on the total enrolled population.[15,27]

Several studies have been conducted about the BP lowering in ISH. The Systolic Hypertension in Europe Trial (Syst-Eur) suggested that lowering SBP to between 140 and 150 mmHg was beneficial for patients with ISH.[9] The VALISH trial showed that SBP values below

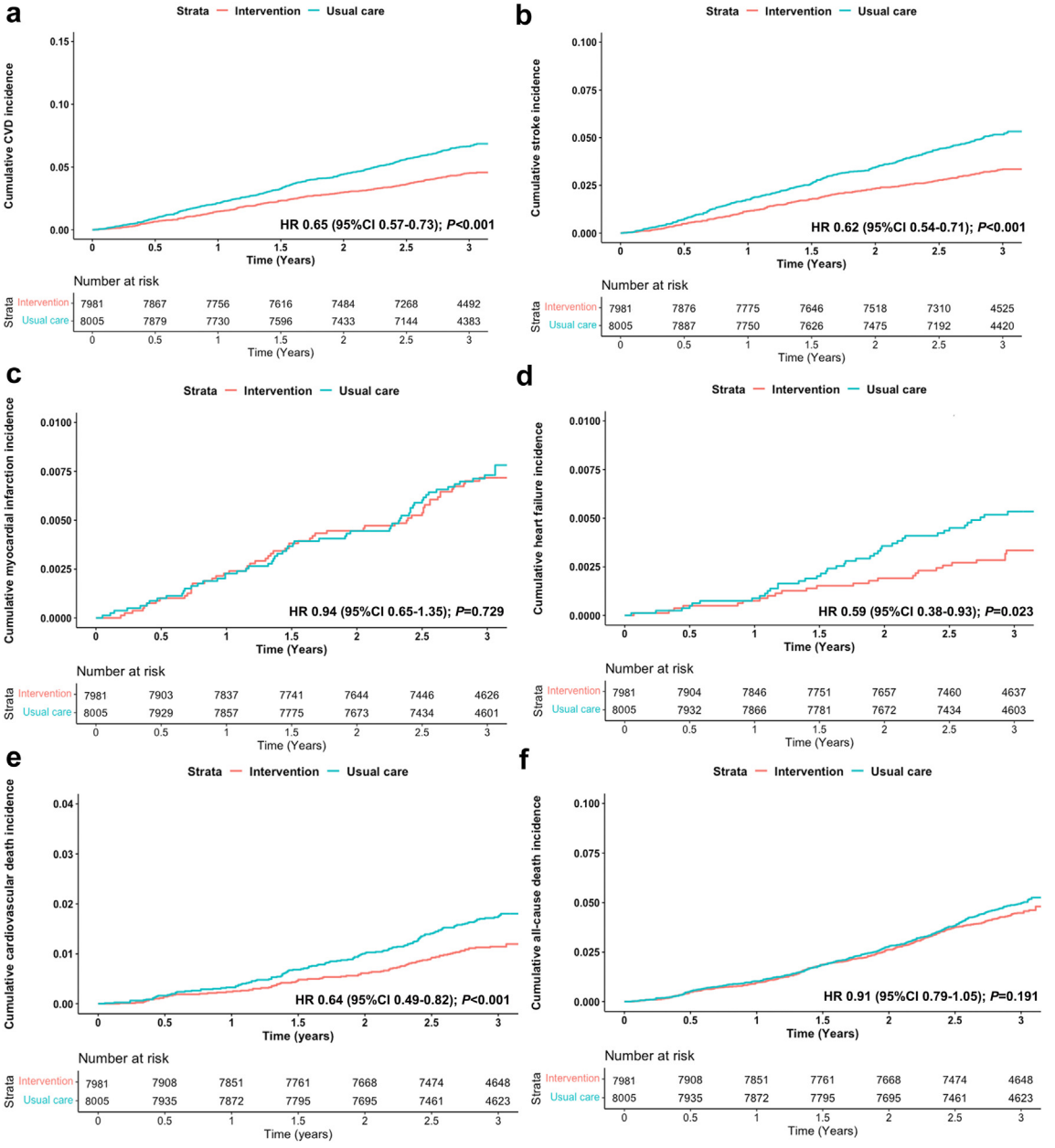

Fig. 3: Cumulative incidence of primary and secondary outcomes for intervention versus usual care. Abbreviations: CVD = cardiovascular disease; HR = hazard ratio. Cumulative incidence of primary outcome (a), stroke (b), myocardial infarction (c), heart failure (d), cardiovascular death (e), and all-cause death (f) for intervention versus usual care.

140 mmHg were considered safe but not beneficial than level between 140 and 150 mmHg.[11] Recent evidence showed that intensive BP control (SBP <120 mmHg or BP < 130/80 mmHg) had additional benefits in reducing the incidence of cardiovascular events compared with traditional target of 140/90 mmHg.[15,16] In studies of intensive BP control, the SPRINT and Cardio-Sis trials focused on the population with high cardiovascular risk,[15,28] the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study only enrolled the patients with type 2 diabetes,[27] and the SPS3 study restricted to the people with recent lacunar infarctions.[29] However, there was still no evidence of RCT for intensive BP reduction in patients with ISH until now, there was no recommendation of guidelines either. As an intensive BP implementation study, CRHCP is also the

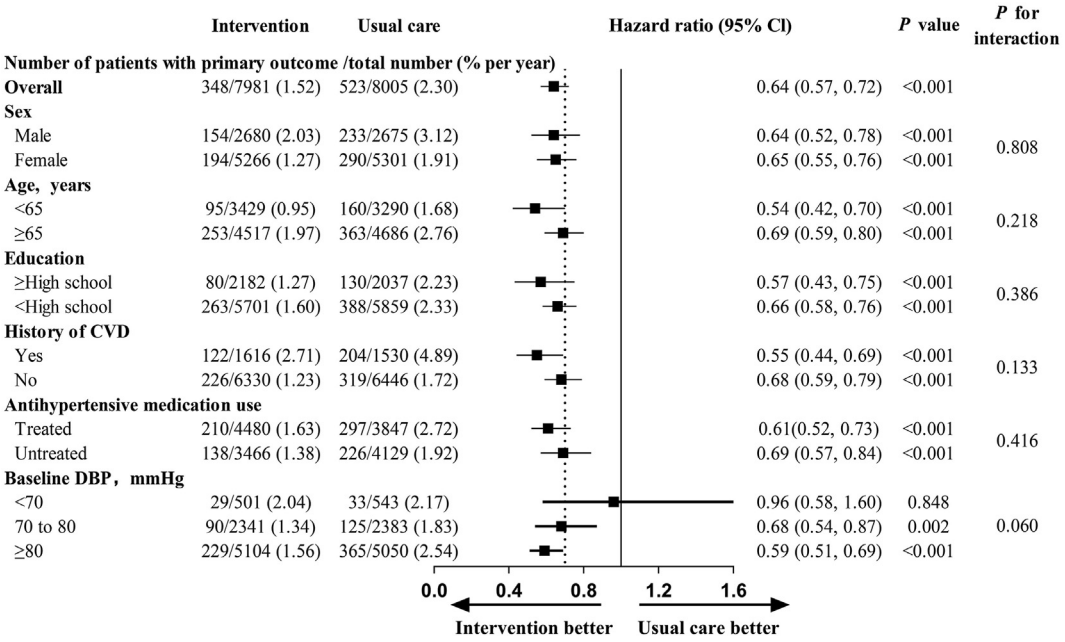

Fig. 4: Forest plot of the primary outcome according to subgroups. Abbreviations: CVD = cardiovascular disease; CI = confidence interval; DBP = diastolic blood pressure.

first RCT in the general population with higher representativeness. The current post hoc analysis of CRHCP firstly demonstrated that intensive BP control with the target of <130/80 mmHg provided lager benefits in CVD among these patients. It is worth noting that the mean SBP reached 126.5 mmHg in the intervention group and 148.1 mmHg in the usual care group at the end of 36 months follow-up, which could be interpreted that targeting a SBP of 130 mmHg is preferable to 150 mmHg in this trial. During the follow-up period, the compliance and doses of antihypertensive medications increased in the intervention group, while remained basically unchanged in the usual care group. This suggests that achieving more stringent BP targets in practice requires not only a higher treatment rate, but also a higher dosages intensity.

In our study, the mean age of ISH patients is 65.9 years, which is higher than 63.0 years in the whole enrolled participants in CRHCP, indicating that this study is aligned with phenomenon that patients with ISH exhibit aging characteristic. More notably, the 10-year risk of CVD in individuals with ISH was 16.2%,

Variables	Intervention	Usual care	Risk Ratio (95% CI)	*P* value
Serious adverse events	1820/7981(22.80)	1983/8005(24.77)	0.92 (0.86, 0.98)	0.011
Injurious falls	51/7981(0.64)	46/8005 (0.57)	1.11 (0.73, 1.69)	0.603
Hypotension	136/7981(1.70)	80/8005 (1.00)	1.71 (1.28, 2.28)	<0.001
Symptomatic hypotension	53/7981(0.66)	63/8005(0.79)	0.84 (0.57, 1.24)	0.364
Syncope	40/7981(0.50)	31/8005(0.3)	1.29 (0.79, 2.13)	0.283
Electrolyte at 36 months				
Serum sodium <130 mmol/L	5/7981(0.06)	3/8005(0.04)	1.67 (0.54, 3.90)	0.266
Serum sodium >150 mmol/L	39/7981(0.49)	113/8005(1.41)	0.35 (0.25, 0.47)	<0.001
Serum potassium <3.5 mmol/L	207/7981(2.59)	129/8005(1.61)	1.61 (1.29, 2.02)	<0.001
Serum potassium >5.5 mmol/L	42/7981(0.53)	47/8005(0.59)	0.90 (0.58, 1.39)	0.608
Renal outcomes, number of events/number of participants (%)				
≥50% eGFR reduction in patients with CKD at baseline	3/137(2.19)	5/139(3.60)	0.61 (0.10, 3.13)	0.521
≥30% eGFR reduction to <60 ml/min/1.73 m2 in patients without CKD	123/7023(1.75)	104/6935(1.50)	1.17 (0.89, 1.53)	0.245

Fig. 5: Safety and renal outcomes by randomization groups. Abbreviations: CI = confidence interval; eGFR = estimated glomerular filtration rate; CKD = chronic kidney disease. Notes: Serious adverse events include deaths and hospitalizations in this analysis. Injurious falls was self-reported and defined as a fall that resulted in seeking medical care. Hypotension was defined as systolic blood pressure <90 mmHg at a village doctor visit or a study data a collection visit at months 6, 12, 18, 24, 30, and 36. Symptomatic hypotension was self-reported and confirmed by systolic blood pressure <90 mmHg a at a village doctor visit. Syncope was defined as self-reported temporary loss of consciousness that resulted in seeking medical care.

higher than 14.5% in the overall population recruited by CRHCP. This suggests that ISH patients require increased attention and timely intervention for better prognosis. With age increasing, physiological changes occur in human tissues, including increased arterial stiffness, impaired endothelial structure and function, and altered intravascular inflammation.[30] Owing to the presence of atherosclerosis and small arterial wall hypertrophy in older people, the elasticity of large arteries decreases linearly, resulting in increased SBP and decreased DBP. This makes the intima more vulnerable to damage and further reduces vascular elasticity.[8,31] SBP gradually increases with age whereas DBP shows a period of stability between the ages of 50 and 60 years, followed by a decrease.[32,33] Therefore, we conducted subgroup analyses based on age, sex, education level, history of CVD, and use of antihypertensive medications. The results were consistent across these subgroups, further confirming the reliability of our findings.

The major problem of intensive BP control in ISH located at the low DBP. For ISH, when implementing intensive BP control, there remains concern regarding the discrepancy between SBP and DBP. The intensive treatment of SBP often entails reductions in DBP, necessitating careful consideration while treatment, especially in patients with lower DBP at baseline. A post hoc analysis within the SPRINT study revealed that low baseline DBP didn't weaken the benefits of intensive SBP control,[34] yet the benefit of BP reduction was not statistically meaningful across all stratifications. In contrast, the result in our study suggested a substantial benefit in patients with baseline DBP of 70–80 mmHg or ≥80 mmHg. However, there's not statistically meaningful difference in those with baseline DBP below 70 mmHg.[32] In comparison to the SPRINT study, we found that: 1) The study population were different. Our study specifically focused on individuals with ISH, while SPRINT encompassed all hypertension subtypes. 2) In contrast to SPRINT, which excluded individuals with a history of stroke or diabetes, this study included these patients. 3) For individuals with a DBP greater than 70 mmHg, the CRHCP had a larger sample size, potentially increasing its statistical power." At the same time, some studies report a higher prevalence of low DBP in patients with ISH undergoing antihypertensive treatment, which will also increase the risk of CVD.[9,35] Thus, greater attention is needed regarding the harm caused by excessively low DBP when treating patients with ISH. The relationship between insufficient perfusion and the increasing of the incidence of adverse events afterward remains controversial. Studies have shown that the relationship between DBP and CVD is a J-shaped curve.[36,37] Evidence from prior studies indicated that low DBP correlated with decreased myocardial perfusion and a higher rate of CVD events in patients with coronary artery disease.[38,39] In addition to potentially leading to decreased perfusion, the increased rate of CVD events in low DBP levels may also be due to clinical features associated with low DBP, such as aging and complications.[32,40] In our study, patients with the lowest DBP levels averaged 70.9 years old, and 20.6% had a history of CVD. Compared to patients with higher baseline DBP levels, those with lower baseline DBP have older age, lower eGFR, and a higher risk of developing CVD. Therefore, low DBP may serve as a risk marker for an increase in CVD events.[41] Farnett et al. suggested that the optimal DBP range for avoiding coronary heart disease death is between 85 mmHg and 90 mmHg.[42] The international Verapamil-Trandolapril Study (Invest study) further supported this, showing an increased risk of death and myocardial infarction with decreasing DBP.[43,44] Our subgroup and dose–response interactive effect analyses both indicated that the effect of intensive BP control became non-substantial and even an increased risk in patients with ISH and DBP <70 mmHg, which was consistent with previous studies. But the interactions between DBP subgroup and intervention showed no statistical difference, requiring to be verified by additional RCTs with a larger sample. We further examined the BP trends in this subgroup and found that these patients experienced a continuous reduction in SBP but maintained a relatively stable DBP level. Therefore, the non-substantial effect of intensive BP control might be attributed to insufficient tissue perfusion, which may potentially negate the benefits of intervention.[38,39] In terms of safety of the intervention, compared with the usual care group, the intervention group exhibited a higher propensity for hypotension but not symptomatic hypotension, which may be due to following reasons: 1) The connection between village doctors and patients was tighter in the intervention group. When hypotension occurred, village doctors promptly adjusted the treatment plans before the occurrence of symptomatic hypotension. 2) Better control and less fluctuation of a patient's BP improve tolerance to hypotension. So, it's less likely to become symptomatic in intervention group. Moreover, the intervention group had a higher rate of hypokalemia. However, most patients with hypokalemia had their serum potassium levels between 3.0 and 3.5 mmol/L, a relatively mild level. In the SPRINT trial, the SBP target was set below 120 mmHg, with participants achieving this goal rapidly within a three-month period.[15] In contrast, our implementation study set a BP target of less than 130/80 mmHg, with a gradual reduction strategy that only about half of the participants reaching the target over an 18-month duration. Thus, the differences in the speed of BP reduction and BP targets might explain the differing impacts on renal function observed across the two studies.

This is an implementation study, in which, we confirmed the effectiveness of intensive BP control procedures on population with ISH on low to middle

income areas with the target of 130/80 mmHg. Health care providers and patients are two vital aspects of implementation. In CRHCP, community health care providers received systematically training. In our study, the basic ability of medication of health care providers was limited, the final degree among which was junior medical college. The education level of patients is majorly in primary school or lower, which is also a relatively lower level.[45,46] Yet, these training measures have been proved effective and easy to implement, remaining effective for achieving optimal BP control and reducing the rate of cardiovascular events. The results of our trial provide practical supported for global public health management and encouraged a wide range of community health providers to be trained to provide superior BP management for patients with ISH.

This study has some limitations. The current study is an post hoc analysis was not prespecified, which means that the results might be subject to unmeasured bias and limited sample. However, both the statistical power calculation for the sample size (94%) and the results of propensity scores matching analysis indicated that our post hoc analyses are representative. Additionally, the limited number of ISH patients with DBP <70 mmHg included in analysis weakened the statistical power in this subgroup, necessitating further research to explore the effects of intensive BP reduction in patients with low DBP. Finally, as an implementation study, we did not set a fixed BP target in the usual care group.

Conclusion

Intensive BP control (<130/80 mmHg) was effective and safe in patients with ISH for the prevention of CVD events. However, for those with a baseline DBP below 70 mmHg, this conclusion should be further confirmed in the future.

Contributors

GS and YS served as principal investigators for the project. CW, SL, WM, NY and ZX did data collection and designed this study. NY, NO and LQ assisted data collection and conducted laboratory work. ZX and YY did data entry and archiving. CW, WM developed the data analysis plan in consultation with other authors. CW and SL conducted data analysis and verified all the data. CW and ZX drafted the manuscript. WM and ZX conducted manuscript editing and revisions. GS and YS had full access to the raw data and were responsible for final submission. All authors read the final version of manuscript and contributed intellectually.

Data sharing statement

The data used in this study can be requested from Prof Guozhe Sun (gzhsun66@163.com) and Prof Yingxian Sun (yxsun@cmu.edu.cn) after the publication of this study. Specific requests for data will require the submission of a proposal with a valuable research question as assessed by the study steering committee and may require the signing of a data access agreement.

Declaration of interests

We declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2024.101127.

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