Remission to normal blood pressure in older adults with hypertension who did not receive antihypertensive medication: analysis of data from two longitudinal cohorts

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Summary

Background How often hypertensive patients could achieve remission to normal blood pressure (BP) (i.e., <140/90 mmHg) in the absence of antihypertensive drugs, which is important for the management of hypertension, remains largely unknown. This observational study aimed to investigate the change of BP in older adults with hypertension who did not take antihypertensive drugs and preliminarily examine whether the remission from hypertension to normal BP observed in this setting was associated with lower risk of cardiovascular disease (CVD).

Methods 2760 participants aged 33–99 years (median 60 years, interquartile 54–68 years) from the Health and Retirement Study (wave 2006 to wave 2018) and the English Longitudinal Study of Ageing (wave 1998 to wave 2016), who had no major CVD, were hypertensive, and were not on antihypertensive drugs at the time of baseline BP measurement, and had at least one follow-up BP measurement before which no antihypertensive drugs were taken, were included for analysis. The main outcome was the proportion of patients who achieved remission of hypertension at the last wave of measurement.

Findings During a median follow-up of six years, 52% of the participants showed a reduction of ≥6 mmHg in systolic BP and 60% a reduction of ≥3 mmHg in diastolic BP. 1171 participants (42%, 95% CI: 41–44%) achieved remission at the last measurement, and by that time 67%, 43%, and 29% of them had maintained the normotensive state for around 4, 8, and 12 years, respectively. Various supplementary analyses that aimed to examine the impact of chance and bias yielded similar results. Preliminary analyses showed that being non-smokers at baseline, achieving a normal body mass index during follow-up, and quitting alcohol drinking during follow-up, among others, were associated with the remission of hypertension. Compared with the participants who remained hypertensive, those who achieved remission had a lower CVD risk (adjusted hazard ratio 0.66, 95% CI: 0.47–0.92).

Interpretation In many of this study population, hypertension could be reversed without the intervention of drug treatment in the first few years after diagnosis. This finding may have implications for more individualized management of hypertension. Further studies to identify the factors or algorithms predictive of such hypertension remission are warranted.

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Keywords: Blood pressure; Hypertension; Remission; Untreated; Longitudinal

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Research in context

Evidence before this study

We searched PubMed up to 10 Jan 2023 for longitudinal studies and clinical trials with investigation of blood pressure trajectories in adults. Search terms included "trajectory", "blood pressure", "hypertension", "longitudinal", "cohort", "follow-up", and "trial". We identified 54 studies, but in most of them varying proportions of participants received antihypertensive drugs at baseline and/or during follow-up, which made it impossible to quantify the changes of blood pressure and cardiovascular disease risk in the absence of drug treatment reliably. Eight of the studies investigated blood pressure trajectories in people who were never treated with antihypertensive drugs throughout the whole study periods, but their study populations were either normotensive at baseline or a mix of normotensive and hypertensive people, without separate analysis of the hypertensive ones. Thus, how often hypertensive patients could achieve remission to normal blood pressure level in the absence of antihypertensive drugs and whether the remission would translate into a lower cardiovascular disease risk remain largely unknown.

Added value of this study

This study found that more than 40% of the older adults with hypertension who did not receive antihypertensive drugs could achieve remission to normal blood pressure level during a median follow-up of six years and the remission was associated with a one-third lower cardiovascular disease risk, which challenge the commonly held view that hypertension is a lifelong condition that requires continuous drug treatment. Preliminary analyses suggested that achieving a normal body mass index and quitting alcohol drinking during follow-up, among other factors, might have contributed to the observed remission of hypertension.

Implications of all the available evidence

A less aggressive strategy for management may be desirable for many hypertensive patients, at least in the first few years after diagnosis. Further studies to identify the factors or algorithms predictive of the remission would be important for management of hypertension.

Introduction

High blood pressure (BP), or hypertension, affects nearly 30% of the world's adult population and is the most important modifiable risk factor for cardiovascular disease (CVD).[1,2] It is often considered as an irreversible chronic condition that requires lifelong management, particularly drug treatment.[3] However, previous randomized controlled trials (RCTs) showed that lifestyle interventions such as salt substitution, heart-healthy diet, and alcohol reduction could lower BP.[4–6] It has also been found that intensive weight management could help 42%–49% of the patients with type 2 diabetes, which shares some pathways and risk factors with hypertension, achieve diabetes remission.[7,8] An early study of a small number of hypertensive patients showed that those who achieved adequate BP control by drug treatment maintained their normal BP for at least 2 years without medications.[9] These available evidences lead naturally to the hypothesis that hypertension in adults may achieve remission in the absence of antihypertensive drugs. How often such remission to normal BP would occur and whether it can translate into a lower CVD risk are, however, largely unknown.

This question is important for the management of hypertensive patients, but the data that can be used to answer the question is rare. Previous cohort studies on this topic usually defined treatment status ("treated" or "untreated") based on the information collected at baseline[10–12]; antihypertensive drugs received during follow-up which may affect BP and CVD risk were not accounted for in their data analyses. The placebo arms of RCTs are theoretically less susceptible to this bias, but in previous RCTs the placebo was given on top of "usual treatment", with a substantial proportion of participants in the placebo arms receiving antihypertensive drugs at baseline and/or during follow-up.[13–16] A few studies did investigate the BP trajectories of people who never received antihypertensive drugs at baseline or during follow-up, but their study populations were either normotensive at baseline or a mix of normotensive and hypertensive people, without separate analysis of hypertensive patients.[17–24]

Against this background, we performed a pooled analysis of data from two cohorts (in which the researchers only observed and did not administer any intervention to participants) to investigate the change of BP among hypertensive patients who did not receive any antihypertensive drugs at baseline and during years of follow-up and preliminarily examine whether the remission from hypertension to normal BP observed in this setting was associated with a lower risk of CVD. Although we also made efforts to explore the factors contributing to the observed hypertension remission, it was not the primary focus of this study, because the data available for that purpose were very limited.

Methods

Data sources

Data from the Health and Retirement Study (HRS) and the English Longitudinal Study of Ageing (ELSA), both of which were ongoing, open cohorts with multiple

waves of enrolment and follow-up, were used in the present study. Both cohorts enrolled participants aged ≥50 years and their spouses/partners of any age.[25,26] Questionnaire interview was conducted every wave (two years apart on average), while physical examination including BP measurement was conducted every two waves (four years apart on average). All participants enrolled in HRS and ELSA have provided written informed consent. Details of the methods of HRS and ELSA have been published elsewhere,[25,26] and are briefly described in Supplementary Methods.

Study population

The participants enrolled in ELSA from the wave 1998 to the wave 2016 and in HRS from the wave 2006 to the wave 2018 were included in the present study if they fulfilled all the following criteria. First, they clearly reported that they had no CVD in or before the baseline wave. In this study, baseline wave was defined as the wave in which participants' BP was measured for the first time after enrolment, which may thus vary across individuals. Second, they clearly reported that they were not on antihypertensive drugs in or before the baseline wave. Third, they had at least one follow-up BP measurement and clearly reported "not taking antihypertensive drugs" before the first follow-up BP measurement. For those who reported "not taking antihypertensive drugs" in all their subsequent follow-up surveys, the last BP measurement marked the end of follow-up period. For those who initiated antihypertensive drug treatment or whose treatment status was unclear in a certain wave, the follow-up BP measurement immediately before that wave, which had not been affected by antihypertensive drugs, marked the end of follow-up period. Forth, their BP was ≥140/90 mmHg in the baseline wave. In total, 2760 participants aged from 33 to 99 years (95% of them ≥50 years) fulfilled the above criteria (Fig. 1).

Measurement of BP, antihypertensive drugs, and CVD

In both HRS and ELSA, BP was measured at the baseline (or wave 0), 2nd, 4th, 6th, and 8th waves, with an average of four years between two consecutive measurements. In each BP measurement, systolic and diastolic BP were measured three times on the participant's single arm in seated position using automated sphygmomanometer with appropriate cuff sizes for arm circumference by trained interviewers or nurses. The average of the three BP readings was then taken to represent the participant's BP level in that wave. The information on antihypertensive drugs was collected in every wave of interview by asking the participants whether they were currently taking medication to lower BP. The major CVD events of interest included angina, heart attack, heart failure, and stroke. In every wave of interview, the participants were asked whether they had any of the above CVD events diagnosed by doctors and, if yes, the date (or age in ELSA) of diagnosis. The participants who reported having doctor-diagnosed CVD

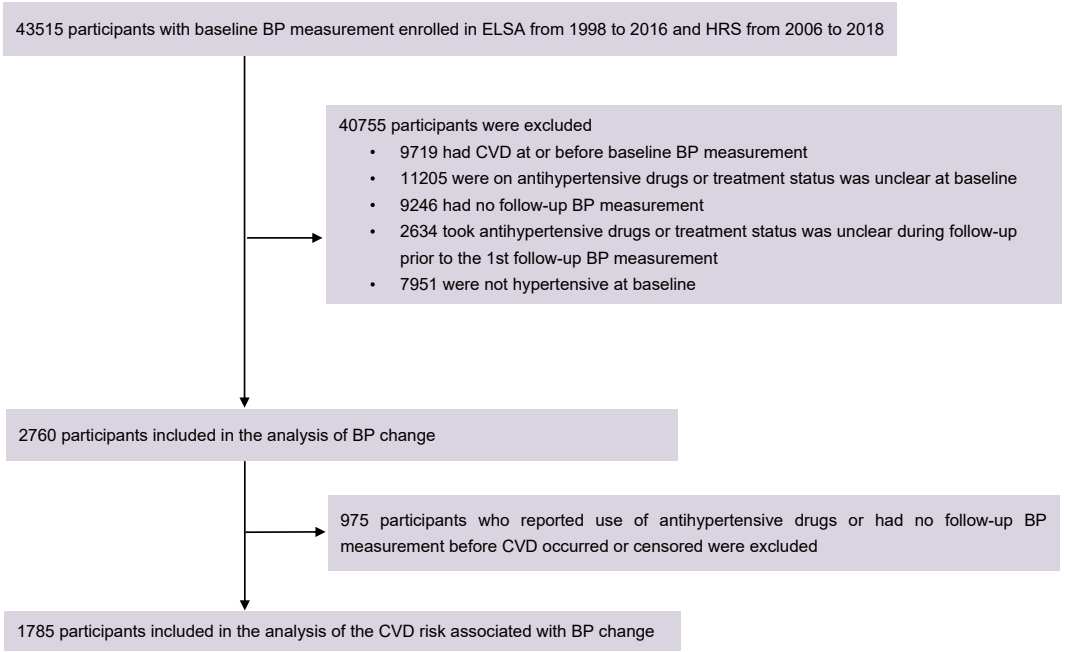

Fig. 1: Flow chart of the inclusion and exclusion of the study participants.

were asked to confirm the reported heart condition again in the following wave of interview to guarantee the accuracy of their previous reports.

Covariates

Covariates of interest included sociodemographic characteristics (age, gender, race, marital status, education), health behaviors related covariates (smoking status, drinking status, physical activity) and health status related covariates (body mass index (BMI), waist circumference, presence of comorbidity, antidiabetic treatment, total cholesterol to high-density lipoprotein ratio, use of lipid-lowering drugs, emotional problems, sleep quality, and self-reported general health) (see Supplementary Methods for details). These covariates were used to describe the baseline characteristics of participants and analyzed as potential factors contributing to the change of BP, but were not involved in the categorization of BP level or calculation of BP change per se.

Statistical analysis

The design and analytical framework of the study were presented in Fig. 2. In the main analysis on change of BP over time, BP was categorized into four levels, i.e., optimal BP (BP < 120/80 mmHg), prehypertension (120/80 mmHg ≤ BP < 140/90 mmHg), stage 1 hypertension (140/90 mmHg ≤ BP < 160/100 mmHg), and stage 2 hypertension (≥160/100 mmHg) as defined by the JNC-7 guidelines.[27] Optimal BP and prehypertension were collectively referred to as normal BP. The JNC-7 definition was adopted because the diagnosis of hypertension and prescription of antihypertensive drugs (if any) in HRS and ELSA between 1998 and 2018, during which the participants for the present study were enrolled, were based on it. To describe the change of BP over time, the participants were divided into two groups according to their baseline BP level, i.e., stage 1 hypertension or stage 2 hypertension. Within each group, the before-after change of BP (= BP at the last measurement—baseline BP) was calculated for every participant and tested for statistical significance with paired t-test. The changes of systolic and diastolic BP were quantified separately.

Change of systolic BP was categorized into four levels: decrease ≥6 mmHg, decrease <6 mmHg, increase <6 mmHg, and increase ≥6 mmHg. Change of diastolic BP during the follow-up was also divided into four levels: decrease ≥3 mmHg, decrease <3 mmHg, increase <3 mmHg, and increase ≥3 mmHg. We adopted 6 mmHg and 3 mmHg as cut-off values because they represented the average effects of antihypertensive drugs demonstrated in placebo-controlled trials conducted in those who were not on antihypertensive drugs at baseline.[28] Remission of hypertension was defined as having a normal BP (i.e., BP < 140/90 mmHg) at the last measurement, with no requirement for how long the normal state had been maintained.[29] This does not imply that we thought the duration of maintaining a normal BP was unimportant for the definition of hypertension remission. Rather, it was a realistic choice, because in the HRS and ELSA cohorts the average time interval between two consecutive BP measurements was 4 years (too long for defining hypertension remission, taking reference to the definition of diabetes remission for which only 3

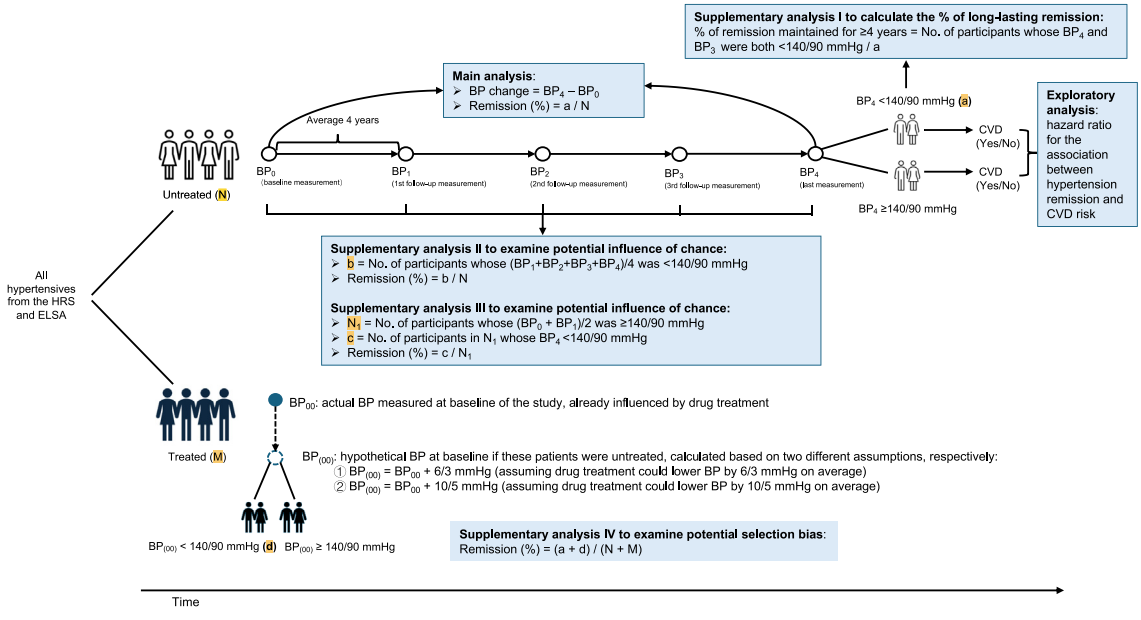

Fig. 2: Design and analytical framework of the study.

months are required[30]), and there were no repeated measurements within a shorter period, for example, 3–6 months (the recommended interval for follow-up evaluation after non-pharmacological intervention for hypertension[3] and diabetes[30]).

Remission rate was calculated as the number of patients who achieved remission of hypertension divided by the total sample size (i.e., 2760). In view of the lack of consensus on how to define hypertension remission, the robustness of remission rate calculated based on our definition was examined by multiple supplementary analyses described below. BP changes by the end of the 2nd, 4th, 6th, and 8th waves (corresponding to a median follow-up of 4, 8, 12, and 16 years) respectively, as compared with baseline, were also calculated and tested for statistical significance with paired t-test to depict the BP change at different time points. The number of waves rather than the exact years after baseline BP measurement was used to denote the timing of follow-up BP measurements for simplicity. This approach was adopted due to variations in the number of participants available for analysis across different time points, as not all participants were able to participate in all waves of follow-up. Additionally, each wave of data collection took more than one year to complete. As a result, the interval between two consecutive BP measurements for an individual participant may not be exactly four years, but averaged out to approximately four years when taking all participants collectively. The linear fixed effects model that accounted for the clustering effect within the same individuals in the repeated measures was used to test the overall trend of BP across multiple waves, adjusting for baseline age and gender.

To explore potential reasons for hypertension remission, selected factors and their changes during the follow-up (where applicable) were compared between those who achieved remission from hypertension to normal BP and those who remained hypertensive at the last measurement. Multivariable regression analysis adjusting for all these factors was also conducted. The selected factors included health behaviors related covariates, BMI, comorbidity, sleep quality, emotional problems, antidiabetic treatment, and lipid-lowering drugs. To be consistent with the approach to defining BP change, the change of factors was also determined by comparing the information collected at baseline and that from the last follow-up survey.

In the main analysis described above, remission of hypertension was defined based on BP levels at baseline and the last measurement, each of which was measured at one time point only, and might be subject to random error of BP measurement (chance). To examine the robustness of remission rate, several supplementary analyses were conducted. First, for the participants who achieved remission, the proportion of those who had maintained the normotensive state for two consecutive waves (four years apart on average) or more by the end of follow-up was calculated. Remission of those people was unlikely caused by chance alone. Second, "BP at the last measurement" was replaced with "the mean BP of all follow-up measurements" in the calculation of BP change from baseline, and then remission rate was re-calculated based on this new result. Third, "baseline BP" was replaced with "the mean BP of the first two measurements" in the calculation of BP change from baseline, and then remission rate was re-calculated based on this new result, but this analysis was conducted only in the participants with three or more BP measurements. Fourth, the participants who reported having doctor-diagnosed hypertension but had a BP < 140/90 mmHg (possibly due to random fluctuation) in the baseline wave were additionally included to re-calculate the remission rate.

We also performed supplementary analyses to examine potential selection bias caused by only including the untreated participants in the main analysis. The reason selection bias might arise was that the present study intended to yield findings generalizable to all hypertensive patients, whereas the untreated participants might differ with the treated ones in terms of BP-related factors and thus might not be representative of all hypertensive patients. In other words, had all patients been untreated and included for our analysis, the results could be different. To examine whether and to what extent such selection bias had occurred, the participants who were already on antihypertensive drug treatment at baseline or initiated treatment before their first follow-up BP measurements were additionally included in supplementary analyses, with correction for the effects of drugs on BP (see Supplementary Methods for details). The results of all the above supplementary analyses were compared with those from the main analyses.

An exploratory analysis on association between remission of hypertension and CVD risk was conducted, with a subset of 1785 participants who did not take antihypertensive drugs and had at least two BP measurements before CVD occurred or censored, whichever earlier, included (Fig. 1). CVD risk was defined as the incidence rate of major CVD events (including angina, heart attack, heart failure, and stroke) during follow-up, and the remission of hypertension was considered as a surrogate marker for it. To assess the association between these two, the 1785 participants were divided into two groups, one group being those who achieved remission of hypertension and the other being those who remained hypertensive, and Cox regression model was adopted to estimate the hazard ratio (HR), adjusting for the covariates mentioned above as well as cohort source (i.e., HRS or ELSA). The assumption of proportional hazards in the Cox model was tested variable by variable using the graphical and numerical methods with cumulative sums of martingale-based residuals described by Lin et al.,[31] which showed that the assumption was fulfilled (details not shown).

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc). A 2-sided P value < 0.05 was considered statistically significant.

Ethics statement

The study was approved by the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee (ref. no.: 2022.002).

Role of the funding source

The funders of this study have no role in study design, data collection, data analysis, and results interpretation.

Results

Baseline characteristics

Table 1 shows the baseline characteristics of the 2760 participants included in this study. The median age was 60 years (interquartile 54 to 68), and the percentages of men, White people, people with comorbidity, people receiving diabetic treatments, and people receiving lipid-lowering drugs were 49.49%, 88.40%, 14.49%, 3.01%, and 8.80%, respectively. With a median of 147/87 mmHg, the baseline BP was stage 1 hypertensive in 81.27% and stage 2 hypertensive in 18.73% of the participants. Compared with those who had stage 2

Baseline characteristics	Baseline blood pressure level, mmHg		Total (n = 2760)
	140–159/90–99 (Stage 1 hypertension, n = 2243)	≥160/100 (Stage 2 hypertension, n = 517)	
Age, median (IQR)	60 (54–68)	62 (55–71)	60 (54–68)
Male, n (%)	1125 (50.2)	241 (46.6)	1366 (49.5)
White, n (%)[a]	1999 (89.2)	439 (84.9)	2438 (88.4)
Married, n (%)	1615 (72.0)	330 (63.8)	1945 (70.5)
College degree or higher, n (%)[b]	478 (21.6)	88 (17.4)	566 (20.9)
Smoking status, n (%)			
Non-smoker	1284 (57.2)	316 (61.1)	1600 (58.0)
Former smoker	709 (31.6)	150 (29.0)	859 (31.1)
Current smoker	250 (11.2)	51 (9.9)	301 (10.9)
Current drinker, n (%)[c]	1801 (80.4)	413 (79.9)	2214 (80.3)
Physical activity, n (%)			
High	585 (26.1)	122 (23.6)	707 (25.6)
Moderate	1242 (55.4)	283 (54.7)	1525 (55.3)
Low	416 (18.6)	112 (21.7)	528 (19.1)
General health, n (%)			
Excellent	262 (11.7)	45 (8.7)	307 (11.1)
Very good	830 (37.0)	203 (39.3)	1033 (37.4)
Good	768 (34.2)	177 (34.2)	945 (34.2)
Fair	315 (14.0)	78 (15.1)	393 (14.2)
Poor	68 (3.0)	14 (2.7)	82 (3.0)
Sleep quality, n (%)[d]			
Optimal	466 (22.6)	117 (25.4)	583 (23.1)
Suboptimal	1594 (77.4)	343 (74.6)	1937 (76.9)
BMI category, n (%)			
Underweight	34 (1.5)	13 (2.5)	47 (1.7)
Normal	616 (27.5)	122 (23.6)	738 (26.7)
Overweight	943 (42.0)	203 (39.3)	1146 (41.5)
Obesity	650 (29.0)	179 (34.6)	829 (30.0)
Waist circumference (cm), median (IQR)[e]	96.2 (86.8–104.8)	96.7 (87.6–106.7)	96.3 (87.0–105.4)
Had comorbidity, n (%)	322 (14.4)	78 (15.1)	400 (14.5)
Emotional problems, n (%)	213 (9.5)	33 (6.4)	246 (8.9)
Diabetic treatment, n (%)	68 (3.0)	15 (2.9)	83 (3.0)
TC to HDL ratio, median (IQR)[f]	3.9 (3.3–4.8)	3.9 (3.2–4.7)	3.9 (3.3–4.8)
Lipid-lowering drugs, n (%)	212 (9.5)	31 (6.0)	243 (8.8)
Systolic BP (mmHg), median (IQR)	145 (141–150)	165 (160–172)	147 (142–154)
Diastolic BP (mmHg), median (IQR)	86 (79–91)	96 (87–102)	87 (80–93)

Abbreviations: IQR, interquartile range; BMI, body mass index; TC, total cholesterol; HDL, high-density lipoprotein; BP, blood pressure. [a]2758 participants without missing data were included. [b]2714 participants without missing data were included. [c]2757 participants without missing data were included. [d]2520 participants without missing data were included. [e]2757 participants without missing data were included. [f]2585 participants without missing data were included.

Table 1: **Baseline characteristics of participants stratified by blood pressure levels.**

hypertension, those with stage 1 hypertension were more likely to have a college degree, be engaged in high-level physical activities and have normal BMI and better self-rated general health.

Change of BP over time

The median follow-up of the 2760 participants was 6 years (range, 2–19 years). From baseline to the end of follow-up, the mean change of BP was –6.06/–5.43 mmHg (systolic/diastolic BP) and more pronounced in those with stage 2 hypertension. At the 2nd, 4th, 6th and 8th waves (corresponding to a median follow-up of 4, 8, 12 and 16 years), the mean changes of BP from baseline in those who remained in the cohort at these time points were –6.30/–4.23, –6.71/–6.20, –7.11/–6.43, and –9.54/–7.54 mmHg, respectively (all $P < 0.001$), and also more pronounced in those with stage 2 hypertension (Fig. 3). The linear fixed effects model adjusting for baseline age and gender showed that the decreasing trend of BP was statistically significant ($P < 0.001$), with an average annual change of –0.71/–0.82 mmHg. At the last measurement, 25% and 24% of the participants showed ≥6 mmHg and ≥3 mmHg increases in systolic and diastolic BP, respectively (Table 2), and the BP in 15% of the participants increased from stage 1 to stage 2 hypertension (Table 3). On the other hand, 66% and 70% of the participants showed reductions in systolic and diastolic BP, respectively (Table 2), with 52% showing ≥6 mmHg reduction in systolic BP and 60% showing ≥3 mmHg reduction in diastolic BP. BP returned to normal level (including pre-hypertension and optimal BP) in 1171 participants (42%, 95% CI: 41–44%, Table 3). Among these 1171 participants, 67% (95% CI: 63–71%), 43% (95% CI: 36–49%), and 29% (95% CI: 20–40%) of those with multiple BP measurements had maintained the normotensive state for an average of 4 years, 8 years, and 12 years, respectively, by the time of the last measurement (Table 4).

Factors associated with the remission of hypertension

The results of comparison between the participants who achieved remission of hypertension and those who remained hypertensive are shown in Supplementary Tables S1 & S2. Univariable analysis showed that the participants who achieved remission of hypertension were more likely to be those who had a higher educational level, were non-smokers, had comorbidity and emotional problems, and were on anti-diabetic medications at baseline. Furthermore, quitting alcohol drinking, returning to a normal BMI, and starting anti-diabetic and lipid-lowering drug treatments during the follow-up were also associated with a higher likelihood of hypertension remission. In the multivariable regression analysis which included only 323 participants with complete data on all the variables, "starting lipid-lowering drug treatment during follow-up" and "returning to normal BMI during follow-up" were statistically significantly associated with remission of hypertension. However, results of these comparisons should be interpreted cautiously because of the limited amount of data.

Supplementary analysis on remission rate of hypertension

The remission rate of hypertension was similar when "BP_{end}" and "baseline BP" were defined differently (Supplementary Tables S3 & S4). In the supplementary analysis that additionally included the participants who self-reported hypertension but had normal BP in the baseline measurement, 1647 (47.51%) had normal BP level in the last measurement. In the supplementary analyses that additionally included the participants who took antihypertensive drugs at the baseline wave or during the follow-up, remission rate was similar to that in the main analyses after correcting for the effects of drugs (Supplementary Table S5).

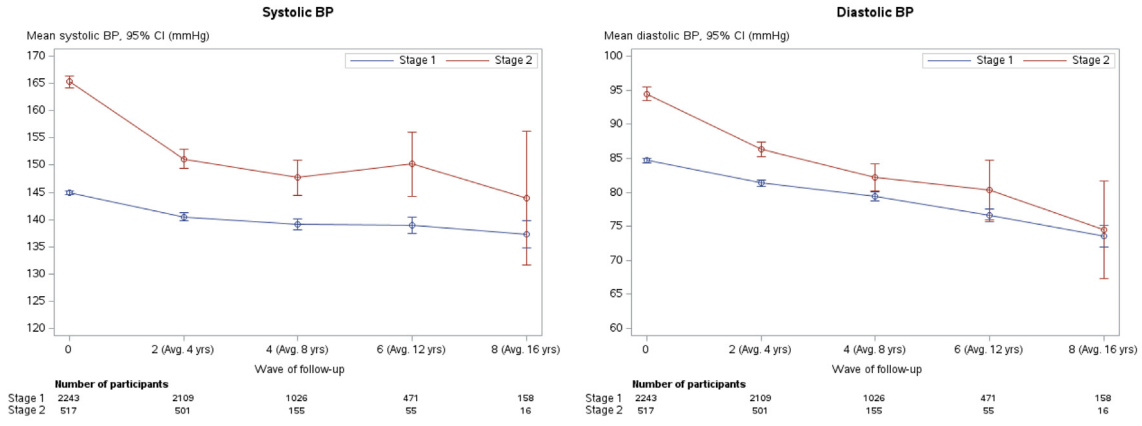

Fig. 3: Change of blood pressure over time stratified by baseline blood pressure levels.

Baseline blood pressure	Number of participants with different levels of change in systolic blood pressure				Mean change of systolic blood pressure (mmHg)	Number of participants with different levels of change in diastolic blood pressure				Mean change of diastolic blood pressure (mmHg)
	Decrease ≥6 mmHg	Decrease <6 mmHg	Increase <6 mmHg	Increase ≥6 mmHg		Decrease ≥3 mmHg	Decrease <3 mmHg	Increase <3 mmHg	Increase ≥3 mmHg	
Hypertension (n = 2760)	1439 (52.14)	377 (13.66)	253 (9.17)	691 (25.04)	−6.06[a]	1659 (60.11)	271 (9.82)	167 (6.05)	663 (24.02)	−5.43[a]
Stage 1 (n = 2243)	1095 (48.82)	313 (13.95)	227 (10.12)	608 (27.11)	−4.24[a]	1299 (57.91)	229 (10.21)	146 (6.51)	569 (25.37)	−4.61[a]
Stage 2 (n = 517)	344 (66.54)	64 (12.38)	26 (5.03)	83 (16.05)	−13.97[a]	360 (69.63)	42 (8.12)	21 (4.06)	94 (18.18)	−8.97[a]

[a]P < 0.001 (paired t-test).

Table 2: **Change of blood pressure from baseline to the end of follow-up.**

Baseline blood pressure	Blood pressure at the end of follow-up				Total, n (%)
	Optimal, n (%)	Prehypertension, n (%)	Stage 1 Hypertension, n (%)	Stage 2 Hypertension, n (%)	
Stage 1 Hypertension	226 (10.08)	810 (36.11)	867 (38.65)	340 (15.16)	2243 (100.0%)
Stage 2 Hypertension	26 (5.03)	109 (21.08)	190 (36.75)	192 (37.14)	517 (100.0%)

Table 3: **Transition of blood pressure level from baseline to the end of follow-up.**

Number of blood pressure measurements (including baseline measurement)	Normal at the last two follow-up measurements (mean span: 4 years)	Normal at the last three follow-up measurements (mean span: 8 years)	Normal at the last four follow-up measurements (mean span: 12 years)
Two only (n = 616)	–	–	–
Three only (n = 312)	208 (66.67)	–	–
Four only (n = 157)	106 (67.52)	67 (42.68)	–
Five only (n = 86)	56 (65.12)	37 (43.02)	25 (29.07)
Total (n = 1171)	370 (66.67)[a]	104 (42.80)[b]	25 (29.07)[c]

– Not applicable. [a]The denominator was 555 (=312 + 157 + 86). [b]The denominator was 243 (=157 + 86). [c]The denominator was 86.

Table 4: **Number and percentage of participants with normal blood pressure at the last two, three, or four follow-up measurements among those who achieved remission of hypertension.**

Exploratory analysis on CVD risk associated with remission of hypertension

1785 participants were included for this analysis. In the group that achieved remission, 66 participants developed CVD during 8214 person-years of follow-up. In the group that remained hypertensive, 100 participants developed CVD during 8773 person-years of follow-up. Compared with the latter group, the former group had a one-third lower CVD risk (adjusted HR 0.66, 95% CI 0.47–0.92, Supplementary Table S6).

Discussion

This study included 2760 individuals who were hypertensive at baseline and did not take antihypertensive drugs at baseline and during follow-up. Over a median follow-up of 6 years, BP decreased on average by 6.06/5.43 mmHg and returned to normal level in 42% of the participants. For those with available data, the magnitude of BP reduction became more pronounced at the 4th, 6th, and 8th waves (corresponding to a median follow-up of 8, 12, and 16 years). These findings were robust in various analyses. Exploratory analyses showed that the participants whose BP returned to normal level had a 34% lower CVD risk than those who remained hypertensive.

Possible explanations for the BP reduction we observed include "regression to the mean", which was observed in previous studies as well,[32] lifestyle modifications (e.g., weight reduction), and treatments for comorbidities (e.g., lipid-lowering drugs) as indicated by our exploratory analysis (see Supplementary Tables S1 & S2). The decrease in BP may also reflect an increased level of frailty in older adults. Delgado et al.[33] reported decreases in systolic BP from 10 to 3 years before death in individuals not treated with antihypertensive medications, and some other studies showed an association between low BP and frailty in older adults.[34–36] No matter which of the above factors was the predominant reason, however, it was clear that the BP reduction in nearly 70% and hypertension remission in 40% of the participants had been achieved in the absence of antihypertensive drug treatment. This finding challenges the commonly held view that hypertension is a lifelong

condition and may have important implications for the management of hypertension. For example, the 2017 ACC/AHA guideline[3] recommends all patients with a BP of 140/90 mmHg or higher receive antihypertensive drug treatment, while according to this study, a less aggressive strategy of management may be suitable for some patients as they could return to a normotensive state without the aid of drug treatment, at least in the first few years after diagnosis.

It is tempting to think that the BP reduction we observed was attributed to the so-called Hawthorne effect and white-coat effect. However, we would argue that this is unlikely, for several reasons. First, this study is a retrospective analysis of data from ELSA and HRS which were not specifically established for hypertension research. The participants were unaware of any specific research hypothesis at baseline and during the follow-up, hence a small chance of Hawthorne effect. If the Hawthorne effect were to be considered a significant issue in this study, then all health outcomes that are subject to behavioral and/or psychological changes in ELSA and HRS as well as in the numerous other cohorts across the world would be inherently untrustworthy. Second, while recognizing that the white-coat effect could not be totally avoided unless ambulatory BP monitoring data was used for analysis, we would like to emphasize that the approach to BP measurement did not differ among the participants included in this study and did not differ from the approach adopted by most cohort studies and clinical trials such as the Framingham Heart Study[37] and Heart Outcomes Prevention Evaluation trial.[38] If the white-coat effect were to be considered as a major issue, it would cast doubts on the reliability of the diagnosis of hypertension and the observed change in BP (whether it be increase or decrease) in all cohorts and trials that employed similar BP measurement methods. Third, if the change of BP were mainly caused by the Hawthorne effect and white-coat effect, it would be hard to explain why BP increased in 25% of the participants and why participants who achieved remission of hypertension had a much lower CVD risk.

People may question the definition of hypertension remission in this study and argue that the remission we observed could have resulted from chance or measurement error. Indeed, neither current clinical guidelines nor previous studies have provided a universal definition for the remission of hypertension.[9,39,40] For example, the remission of hypertension was defined as achieving a normal BP (<140/90 mmHg) through drug treatment and maintaining the normal state in the absence of drug treatment for at least two years in an early report of Framingham Heart Study,[9] while other studies defined remission of hypertension as having a normal BP at follow-up measurement, regardless of the treatment status at baseline and without requirement for how long the normal state should be maintained.[29,40,41] However, the multiple supplementary analyses we conducted (Table 4 and Supplementary Tables S3 & S4), which were essentially using different approaches to define BP change and remission showed that our results could not be explained by chance alone.

Having said that, we must admit that our analysis on underlying factors of the remission of hypertension is far from adequate. For example, previous RCTs showed that salt substitution and healthy diet could lower BP by as much as 7.1/1.9 mmHg and 10.0/3.8 mmHg, respectively,[4,5] and herbal supplements has been shown effective in BP reduction.[42,43] Other factors such as potassium intake, mental stress, and chronic kidney disease could also potentially affect the BP.[44–46] However, the information on these factors was very limited or even not available from HRS and ELSA. Thus, the factors contributing to BP changes observed in this study warrant further investigation.

The unique strength of this study lies in that it was focused on hypertensive patients and that the treatment status was confirmed by multiple waves of interview asking the same questions repeatedly. This enabled us to sample the participants who were never treated with antihypertensive drugs, thereby precluding the effects of antihypertensive drugs on the observed BP. By contrast, in previous cohort studies of BP changes over time, there was either no separate analysis of hypertensive patients or a varying proportion of patients receiving drug treatment at baseline and/or during follow-up, making it impossible to disentangle natural change of BP from the effects of drug treatment. Furthermore, the supplementary analyses performed to examine the impact of various possible biases demonstrated that our results were robust.

This study has several limitations. First, as none of the participants included in the main analysis received antihypertensive drugs, one may question their representativeness of the overall hypertensive population and consequently the generalizability of our findings. Indeed, those who received drug treatments for whatever reasons had higher proportions of multiple CVD risk factors than those who did not (Supplementary Table S7). However, the results of supplementary analyses that included the treated people and corrected for the effects of drugs were similar to those of the main analyses (Supplementary Table S5), indicating that the selection bias did not constitute a major problem in this study.

Second, hypertension at baseline and that at the end of follow-up were both defined according to the mean BP readings obtained in a single occasion, which may not be accurate enough for the diagnosis of hypertension. However, our supplementary analyses using the mean BP of two or more waves of measurements as "baseline BP" or "BP_{end}" yielded similar results, suggesting that the measurement error if any did not influence our findings materially.

Third, the use of antihypertensive drugs and the CVD status were self-reported, which may raise concern about the accuracy of data. However, previous studies showed that the negative predicted value of self-reported use of antihypertensive drugs ranged from 99% to 100%,[47] meaning that almost all the participants who reported no use of antihypertensive drugs were truly untreated. Regarding the CVD events, the self-reported rate in ELSA was 11.02%, and the rate adjusted for potential over- or under-reporting was 12.50% (see Supplementary Methods for details), suggesting that its accuracy was little affected by self-report. As for HRS, the reported prevalence of CVD was similar to the estimate of a nationally representative survey,[48] suggesting a high level of accuracy. Overall, it can be seen that the potential misclassification caused by self-reporting would unlikely influence our main findings materially.

Fourth, the median follow-up for change of BP was only 6 years which was relatively short as compared with the average duration from diagnosis of hypertension to occurrence of hard outcomes such as CVD, although our analysis of those who were followed up for at least 8, 12 and 16 years showed that the reduction in BP could sustain for a much longer time. Indeed, it may be necessary for some participants who achieved remission to receive antihypertensive drugs later on. However, they can be exempt from drug treatments and all the related problems (e.g., adverse effects and out-of-pocket payment) for years by adopting a less aggressive strategy of management at the beginning.

Fifth, our analysis on the predictors of BP reduction in the absence of antihypertensive drugs was at best exploratory, mainly because some important covariates were not available in detail in the two cohorts and the sample size for multivariable regression analysis was small. For the same reason, the results of analysis on CVD risk associated with remission of hypertension might be imprecise and subject to residual confounding. Further studies with data on more variables and larger sample size are warranted to confirm these findings, identify those who are likely to return from hypertension to normal BP without receiving antihypertensive drugs, and ultimately improve management of hypertension towards the goal of "precise treatment".

Sixth, in the exploratory analysis of CVD risk, only the participants with at least two BP measurements before CVD occurred were included, meaning that the CVD could not occur during the interval between the baseline and the last measurement of BP, which may cause immortal time bias.[49] However, in our study, the average interval between baseline and the last measurements of BP was similar (7.86 and 7.17 years) in those who achieved remission of hypertension and those who remained hypertensive at the last measurement, suggesting low risk of immortal time bias.

In conclusion, in many of this study population, hypertension could be reversed without the intervention of drug treatment in the first few years after diagnosis. This finding may have important implications for more individualized management of hypertension. Further studies to identify the factors or algorithms predictive of such hypertension remission are warranted.

Contributors

ZYY, FS, and STW conceived the research question and designed the study. STW and LBT curated and analysed the data. STW wrote the first draft of the manuscript. JLT, FS, ZRY, and ZYY critically reviewed and revised the manuscript. ZYY and JLT obtained funding. ZYY supervised the study. All authors contributed to the interpretation of the results. STW and ZYY accessed and verified the data. ZYY had final responsibility for the decision to submit for publication.

Data sharing statement

English Longitudinal Study of Ageing data are freely available to researchers through the UK data service at https://beta.ukdataservice.ac.uk/datacatalogue/series/series?id=200011. Health and Retirement Study data are available upon registration with the University of Michigan at https://hrsdata.isr.umich.edu/data-products/public-survey-data.

Declaration of interests

The authors 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.eclinm.2024.102678.

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