

BMJ Open Association between control status of blood pressure and frailty among middle-aged and older adults with hypertension in China: a longitudinal study

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ABSTRACT

Objective To assess the association between blood pressure (BP) control and frailty among middle-aged and older populations with hypertension in China from 2013 to 2018.

Design Prospective longitudinal study.

Setting This study analysed data from the China Health and Retirement Longitudinal Study, a nationally representative survey administered in 28 provinces of China.

Participants A total of 3254 participants diagnosed with hypertension previous to 2013 were taken into analysis. 1932 participants who were not frail in 2013 were enrolled to calculate relative risk.

Outcome measures The frailty score was constructed following Rookwood's Cumulative deficit frailty index, with a score >0.25 defined as frailty (outcome variable). The self-reported status of BP control (exposure variable) represented the general status of the participant's BP level. A fixed-effects model was used to analyse the association between BP control and frailty. A Cox proportional hazard model was further used to further calculate the relative risk of frailty for different BP control levels.

Results The fixed-effects model showed that compared with well-controlled BP, poorly controlled BP exhibited a positive association with frailty score ($\beta=0.015$; 95% CI 0.011 to 0.019; $p<0.001$). The Cox proportional hazard model also revealed a higher risk of frailty in the poorly controlled group (HR=1.96; 95% CI 1.49 to 2.56; $p<0.001$). Based on subgroup analyses, poorly controlled BP was positively associated with frailty in respondents aged <60 years old (fix-effects model: $\beta=0.015$, $p=0.021$; Cox model: HR=2.25, $p<0.001$), but not significant among those aged ≥ 75 years old.

Conclusions We provide new evidence of a negative association between BP control and frailty risk, but the findings differ among different age groups. Individualised strategies for BP management should be developed, especially for older hypertension patients.

INTRODUCTION

Frailty is an irreversible consequence of population ageing and is a condition characterised by a loss or reduction in physiological reserve resulting in increased clinical vulnerability.¹ Components of frailty include impaired

Strengths and limitations of this study

- This study uses a nationwide representative database (China Health and Retirement Longitudinal Study) in accordance with internationally accepted standards.
- This is the first study to assess the association between blood pressure (BP) control and frailty among middle-aged and older hypertensive adults with longitudinal data over 6 years based on a fixed-effect model and a Cox proportional hazard model.
- Recall bias existed in this study. Definitive validation in prospective studies is needed.
- Absolute BP values could not be obtained, and self-reported controlling status of BP may be overestimated.

cognition, depressive symptoms, exhaustion, limited mobility and a history of falls.² Measures to reduce or slow down frailty are critical in the promotion of healthy ageing. For example, exercise, cognitive stimulation, improving sleep, nutrition and social interaction are part of a multidomain approach to reduce frailty and promote healthy ageing.³ China, with a population constituting 18% of the world population and characterised by the fastest ageing trend, has become an ageing society, and as it continues to age, the burden on family members and public healthcare systems will continue to be exacerbated.^{4,5} Therefore, in-depth study associated with frailty in China is urgent.

Populations with chronic diseases have a high risk of frailty, with the two concepts presenting a certain amount of overlap.⁶ Hypertension is one the most widespread chronic diseases in China and has brought great challenges to the health system due to the associated cardiovascular diseases. In a study enrolling 1 738 886 participants aged 35–75 years, the prevalence of hypertension reached nearly half of the population



(44.7%).⁷ Frailty and hypertension often coexist, with intense and complex physiological connections between them.⁸ For hypertensive patients, controlling status of blood pressure (BP) is one of the most essential indicators for their health management level. The decline in homeostatic mechanisms among the frail individuals tend to be more physiologically dysregulated in achieving a stable BP control.⁹ Exaggerated BP variability representing a decline in homeostatic regulation of BP may indicate a frail state among the older population.¹⁰ A recent study from China evaluated the association between 24-hour ambulatory BP variability and frailty among older hypertensive patients, and indicated that the greater BP variability of systolic BP (SBP), particular the average real variability and the coefficient of variation, were independent risk factors associated with higher-order frailty status.⁸ Woo *et al*¹⁰ conducted a longitudinal cohort study on 1156 older community dwellers in Hong Kong, with repeated BP measured three times a week during 1 year, and the results also indicated that high BP variability increased the risk of frailty (OR: 1.57; 95% CI 1.05 to 2.37). More concretely, many studies explored the association between BP control of hypertensive patients and specific aspects of frailty, such as depression and anxiety,^{11 12} brain function and cognition¹³ and physical functions.¹⁴ A preponderance of evidence has emerged that indicates that the association between BP and events is attenuated or inverted among frail older adults or those with poor functional status.¹⁵ However, evidence of the relationship between BP control and frailty among the older adults remains controversial and limited in China, especially that assesses the impact of the BP control status over a relatively long period.

Assessing the association of frailty and BP control may be the first step in understanding their complex interplay and might ultimately lead to the optimisation of the treatment and management of hypertension. Therefore, we used a longitudinal database from China to provide clear evidence of the association between BP control and frailty among the middle-aged and older adults diagnosed with hypertension. The hypothesis of this study was that poorly controlled BP is positively associated with a higher risk of frailty.

METHODS

Sample and data

Data used for this study were derived from the China Health and Retirement Longitudinal Study (CHARLS) database (<http://charls.pku.edu.cn>) with open access, which was conducted by the National School of Development of Peking University in 2011, 2013, 2015 and 2018.¹⁶ The survey collects high-quality micro-data from middle-aged and older individuals aged 45 years and above covering 28 provinces and 150 districts/counties in China. The total sample size of the CHARLS baseline survey in 2011 was 17 708 respondents (response rate is 80.5%), selected through multistage stratified

probability-proportionate-to-size sampling method. These participants were followed up once every 2–3 years to repeat the survey. The data included individual weighting variables to ensure that the survey sample was nationally representative. A more detailed description of the objectives and methods of CHARLS has been reported elsewhere.¹⁷

Data from 2013 to 2018 were used for this study because whether BP was controlled was not included in the survey in 2011. Respondents were asked whether they ever diagnosed with hypertension by doctors. Those diagnosed with hypertension before the 2013 survey, who participated in any follow-up waves were enrolled in the analysis. Considering the accuracy of frailty index, participants with answered frailty-related items fewer than 45 (80% out of the total 56 items) were excluded. Finally, 3254 respondents were enrolled at baseline (2013), while 2991 and 2639 individuals responded in 2015 and 2018, respectively.

Variables

Outcome variable

Frailty was the outcome measure in this study. A frailty score was constructed following Rookwood's Cumulative deficit frailty index, which is a well-known and validated index and is very useful in prospective analysis. It was developed as part of the CSHA study, with 92 baseline variables of symptoms (eg, low mood), signs (eg, tremor) and abnormal laboratory values, disease states and disabilities (collectively referred to as deficits) used to define frailty.^{18 19} According to the scale of CHARLS, except for the item 'ever diagnosed with hypertension', 56 items associated with physical, psychological and social deficits (shown in online supplemental table S1) were enrolled in the construction of frailty index in this study. All items were coded as 0 or 1, with 1 indicating difficulty. The frailty index was calculated by summing the values and dividing by the total number of possible difficulties. Then, a frailty index with a potential range from 0 to 1 was generated, with a higher score indicating more serious frailty. When analysing the risk of frailty according to HR, frailty was categorised using a score of 0.25 based on previous studies,^{19 20} with individuals with frailty scores <0.25 included in the non-frailty group and those with scores ≥0.25–1.00 included in the frailty group.

Exposure variable

The status of BP control was the exposure variable of this study. Some previous studies categorised patients with mean clinic SBP ≥140 mm Hg and/or diastolic BP (DBP) ≥90 mm Hg over the last 6 months,^{21 22} or 12 months,²⁴ into the poorly controlled group. In CHARLS survey, the respondents' BP were measured three times on the patient's right upper arm after 5 min of seated rest using an electronic BP monitor on the day of the interview.¹⁷ Furthermore, the respondents diagnosed with hypertension were asked whether their BP was generally under control. With restrictions to the unpublished 2018 physical examination

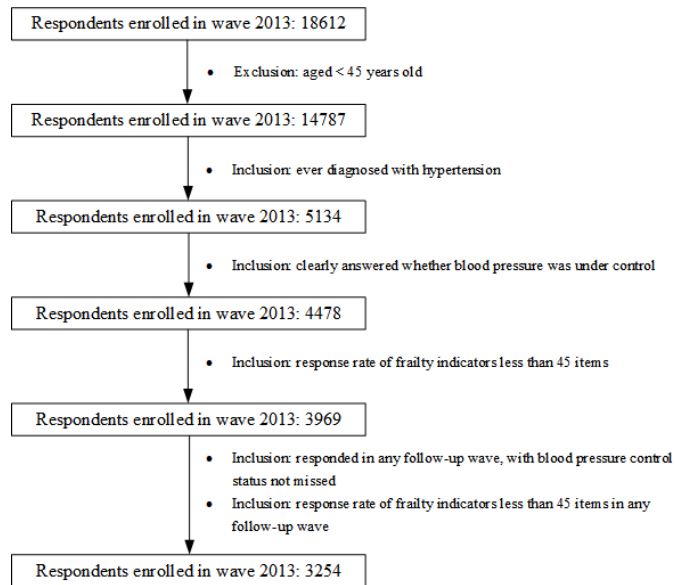


Figure 1 Flowchart of sample selection.

data, and considering that this was a prospective longitudinal study, rather than a cross-sectional study, we used the self-reported status of BP control as exposure variable to represent the general status of the participants, which reflected the dynamic change of the BP over the past 1–3 years, with 1 indicating ‘poorly controlled’ and 0 indicating ‘well controlled’.

Covariates

The covariates in this study were selected based on the existing studies that proved their associations associated with BP control, including age, gender, marital status, hukou status (which is a special identifier in China and originally indicates the respondent’s or their family’s farmer or non-farmer status), education level, living area, public health insurance coverage, current work status, alcohol intake, smoking status, household per capita consumption, antihypertensive treatment and comorbidities. The definitions of all the covariates are presented in online supplemental table S2.

Statistical analysis

Smooth curve fitting for the dynamic change of frailty score across the survey waves in the well-controlled BP and poorly controlled BP groups were constructed on the basis of generalised additive models with all the covariates adjusted, which could reveal the non-linear effect of the variables with non-parametric smooth function.²³ In addition, we separately constructed smooth curves for the respondents who were categorised into the frail group and the non-frail group at baseline to observe the different trajectories.

The association between BP control and frailty score across the three waves was estimated by a fixed-effects model. An F-test between the pooled ordinary least squares and fixed-effects model ($p < 0.001$) and a Hausman specification test between the fixed-effects model and random-effects model

($p < 0.001$) were performed, and a fixed-effects model was chosen as the final model. The fixed-effects model treats each individual as their own control and has the advantage of reducing biases brought about by between-individual and hard-to-observe factors.²⁴

We further estimated the relative risk of frailty for different levels of BP control through Kaplan-Meier and Cox proportional hazard models. The endpoint was set as frailty (frailty score > 0.25), with the survey wave as the timescale. HRs with 95% CIs were calculated. Respondents classified as frail at baseline (1522 respondents) were excluded from the analysis, 1932 respondents were taken into analysis, and those who remained non-frail in 2018 were censored.

To validate the association between BP control and frailty, we performed four sensitivity analyses: (1) multiple imputation (MI) was performed to avoid statistical test performance reduction and bias caused by the direct exclusion of missing values. All the covariates were used for imputation through the R package ‘mice’. Based on five replications and a chained equation approach, five sets of databases were generated, and a pooled regression coefficient was calculated.²⁵ The number of missing values and the MI evaluation are shown in online supplemental table S3. (2) Considering the sample representativeness and selection bias, we included participants with answered frailty-related indicators fewer than 45 items and repeated the analysis. There were 3349 respondents in 2013, 3121 in 2015 and 2868 in 2018. For the Cox regression, 2010 respondents were included in the analysis. (3) Because antihypertensive treatment is essential in hypertension management and comorbidities are significantly associated with both BP control and frailty,^{26–28} we treated these two variables as time-varying confounders and created a marginal structural model (MSM) to further prove the association between BP control and frailty. In the MSM, the inverse probability of treatment weighting was used, with the weight in each time point not only decided by the previous level of the confounder but also by the current level. An MSM is highly effective in controlling time-dependent confounding factors in observational studies.²⁹ (4) As individuals can experience both worsening and improvement in their frailty state over time, we identified the respondents who were categorised into the frailty group at baseline (2013) and set frailty improvement as the outcome variable to explore the association between frailty improvement and BP control.

In addition, many studies have proven that the control rate of BP varies among different age groups, between rural and urban areas, as well as between men and women in China.^{14,30} Therefore, we performed three subgroup analyses to identify the association between BP control and frailty among specific respondents, including (1) respondents aged ≥ 75 years, respondents aged ≥ 60 and < 75 years and respondents aged < 60 years; (2) males versus females and (3) rural participants versus urban participants.

Mean \pm SD and number (percentage) are used for the initial description of the respondents’ characteristics.

**Table 1** Baseline description of the sample, 2013*

	All (N=3254)	Well-controlled (N=2600)	Poorly controlled (N=654)	P value
Age	61.9±8.8	62.0±8.7	61.3±8.8	0.023
Gender				0.244
Male	1484 (45.6%)	1199 (46.1%)	285 (43.6%)	
Female	1770 (54.4%)	1401 (53.9%)	369 (56.4%)	
Education levels				0.001
Less than lower secondary	2852 (87.6%)	2253 (86.7%)	599 (91.6%)	
Upper secondary and vocational training	329 (10.1%)	280 (10.8%)	49 (7.5%)	
Tertiary	73 (2.2%)	67 (2.6%)	6 (0.9%)	
Marital status				0.398
Married	459 (14.1%)	360 (13.9%)	99 (15.1%)	
Divorced or widowed	2794 (85.9%)	2239 (86.1%)	555 (84.9%)	
Living areas				<0.001
Rural	1851 (56.9%)	1427 (54.9%)	424 (64.8%)	
Urban	1403 (43.1%)	1173 (45.1%)	230 (35.2%)	
Hukou status†				<0.001
Agricultural	2349 (72.3%)	1821 (70.2%)	528 (81.0%)	
Non-agricultural	858 (26.4%)	739 (28.5%)	119 (18.3%)	
Unified residence or do not have	40 (1.2%)	35 (1.3%)	5 (0.8%)	
Public health insurance coverage				0.072
Not covered	103 (3.2%)	75 (2.9%)	28 (4.3%)	
Covered	3121 (96.8%)	2498 (97.1%)	623 (95.7%)	
Current work status				0.169
Not working	1356 (42.0%)	1098 (42.6%)	258 (39.6%)	
Working	1872 (58.0%)	1479 (57.4%)	393 (60.4%)	
Alcohol intake				0.783
Do not drink	2278 (70.0%)	1817 (69.9%)	461 (70.5%)	
Drink	974 (30.0%)	781 (30.1%)	193 (29.5%)	
Smoke				0.239
Never	1936 (74.4%)	1552 (74.6%)	384 (73.6%)	
Quit now	291 (11.2%)	239 (11.5%)	52 (10.0%)	
Smoke	375 (14.4%)	289 (13.9%)	86 (16.5%)	
Household per capita consumption	11828.7±15377.2	12083.4±15924.9	10805.9±12912.1	0.004
Comorbidity				0.128
No	667 (20.5%)	547 (21.0%)	120 (18.3%)	
Yes	2587 (79.5%)	2053 (79.0%)	534 (81.7%)	
Antihypertensive treatment				0.005
No	624 (19.2%)	473 (18.2%)	151 (23.1%)	
Yes	2624 (80.8%)	2122 (81.8%)	502 (76.9%)	

*Mean±SD was used to describe continuous variable and number (constituent ratio (%)) was used to describe categorical variable.

†Hukou status indicates the respondent's hukou place and is a special identifier in China. Hukou status affects many aspects of life in China such as buying a house, buying a car, children's school enrolment and other welfare.

Ordinal χ^2 tests for categorical variables and Kruskal-Wallis one-way analysis of variance were used for numerical variables. The p values were two-sided, and an alpha level of 0.05 was used to define statistical significance. Data were analysed using Stata (V.15) and R V.3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). We wrote the manuscript according to the Strengthening

the Reporting of Observational Studies in Epidemiology guideline (online supplemental table S4).³¹

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Table 2 Distribution of frailty scores and prevalence of frailty in the well-controlled and poorly controlled blood pressure groups across the survey waves*

	2013 (n=3254)		2015 (n=2991)		2018 (n=2639)	
	Mean±SD	N (%)	Mean±SD	N (%)	Mean±SD	N (%)
Well controlled	0.23±0.12	976 (37.5)	0.25±0.14	1088 (45.1)	0.28±0.13	1180 (52.4)
Poorly controlled	0.28±0.14	346 (52.9)	0.33±0.15	368 (63.7)	0.38±0.15	305 (80.3)
Total	0.24±0.13	1322 (40.6)	0.27±0.15	1456 (48.7)	0.29±0.14	1485 (56.3)

*Mean±SD was used to describe the distribution of frailty score; N (%) was used to describe the prevalence of frailty, which means frailty score >0.25.

RESULTS

Figure 1 reveals the process of sample selection, 3254 respondents diagnosed with hypertension were taken into analysis. Table 1 describes the baseline characteristics of the sample: 2600 (79.9%) respondents with well-controlled BP and 654 (20.1%) respondents with poorly controlled BP. In the follow-up surveys, the control rates of BP were 80.7% and 85.6% in 2015 and 2018, respectively. The age in the well-controlled group was older than that in the poorly controlled group ($p=0.023$). The proportions of individuals with education levels less than lower secondary (91.6%), living in urban areas (35.2%) and with agricultural hukou status (81.0%) in the poorly controlled group were relatively higher than those in the well-controlled group (86.7%, 45.1% and 70.2%, respectively). Well-controlled respondents had higher household per capita consumption. The percentage of antihypertensive treatment is higher in the well-controlled group (81.8%) than the poorly controlled group (76.9%).

Table 2 shows the distribution of frailty scores and proportions of frailty in the well-controlled and poorly controlled groups across the three survey waves. The mean frailty score increased from 0.24 in 2013 to 0.28 in 2018 for the whole sample, from 0.23 in 2013 to 0.28 in 2018 in the well-controlled group, and from 0.28 in 2013 to 0.38 in 2018 in the poorly controlled group. The

mean score in the poorly controlled group was higher than that in the well-controlled group in each wave. The proportion of frailty in the whole sample was 40.6% in 2013, which increased to 56.3% in 2018. The proportions in well-controlled group and poorly controlled group were 37.5%, 45.1%, 52.4% versus 52.9%, 63.7%, 80.3% in 2011, 2013 and 2018, respectively.

Figure 2 shows the change of frail status with baseline frail group and non-frail group, respectively. Interestingly, there are 1322 respondents categorised into the frailty group at baseline, among which 206 respondents experienced improvement in their frailty state (from frail to non-frail) in wave 2 (2015), and 73 respondents remained non-frail in wave 3 (2018). Figure 3 reveals the smooth curve fitting for the frailty scores across three waves in the two groups, which clearly indicated higher frailty scores in the poorly controlled BP group than in the well-controlled group for the whole sample, as well as those who were frail and not frail in the baseline. Intriguingly, for non-frail respondents in 2013, the adjusted mean frailty score decreased in 2015 and increased in 2018 in the well-controlled BP group, and continued to increase in the poorly controlled BP group, with a descending slope from 2015 to 2018.

The fixed-effects model showed that compared with the well-controlled group, the poorly controlled group exhibited a positive association with frailty score ($\beta=0.015$; 95% CI 0.011 to 0.019; $p<0.001$) after covariates were controlled (table 3). We further estimated the relative risk through a Cox proportional hazard model, with 1932 respondents who were not frail in 2013 included in the analysis (baseline characteristics were shown in online supplemental table S5). The risk of frailty in the poorly controlled group (HR=1.96; 95% CI 1.49 to 2.56; $p<0.001$) was significantly higher than that in the well-controlled group (table 3 and figure 4).

We performed four sensitivity analyses (table 4). First, MI was used, and both the fixed-effects model ($\beta=0.013$; 95% CI 0.008 to 0.018; $p<0.001$) and Cox proportional hazard model (HR=1.95; 95% CI 1.61 to 2.36; $p<0.001$) showed consistent results before imputation. Second, we included participants answering fewer than 45 items (of frailty indicators) and repeated the analysis, and the results were consistent (fixed-effects model: $\beta=0.019$, $p<0.001$; Cox proportional hazard model: HR=1.91,

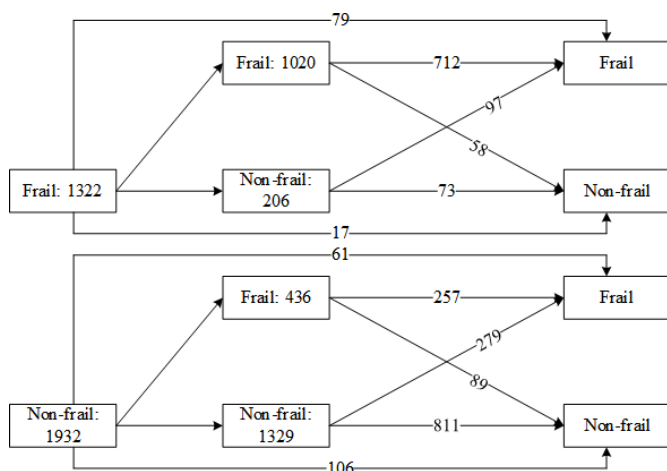


Figure 2 The change of frailty status in the baseline frail group and non-frail group. The respondents loss to follow-up are not presented.

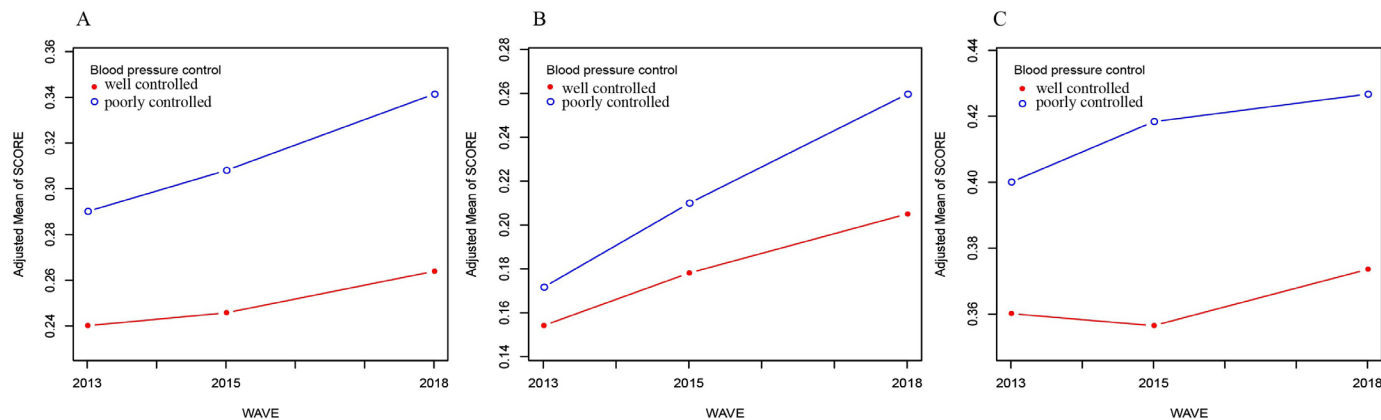


Figure 3 Smooth curves fitting for the dynamic change of frailty scores in different blood pressure controlled groups based on generalised additive models with all the covariates adjusted. (A) The whole sample; (B) respondents frail in the baseline; (C) respondents not frail in the baseline.

$p < 0.001$). Third, we created an MSM to adjust for time-varying confounders, including comorbidity and anti-hypertensive treatment. The Cox model also showed a higher risk of frailty in the poorly controlled BP group (HR=1.65; 95% CI 1.26 to 2.15; $p < 0.001$). These sensitivity analyses validated the conclusions and indicated that a higher risk of frailty would be caused by poorly controlled BP in the whole sample. In the respondents who were frail at baseline, the fixed-effects model still indicated that poorly controlled BP was associated with an increasing frailty score ($\beta = 0.015$, 95% CI 0.004 to 0.027; $p = 0.009$). Cox regression, with frailty improvement as the outcome, indicated a negative association between poorly controlled BP and frailty improvement (HR=0.61; 95% CI 0.041 to 0.93; $p = 0.020$). These results further validated our main conclusion.

Before subgroup analysis, we compared the baseline frailty status between different subgroups (online supplemental table S6). The proportion of frailty increased with age, and was higher in females and rural areas than in males and urban areas, respectively, in both well-controlled and poorly controlled group. The subgroup analysis (table 5) further identified populations with a high risk of frailty. For respondents aged < 60 years old, poorly controlled BP was positively associated with frailty in both the fixed-effects model ($\beta = 0.015$; 95% CI 0.002 to 0.028; $p = 0.021$) and the Cox model (HR=2.25; 95% CI 1.48 to 3.43; $p < 0.001$); nevertheless, these impacts were not significant in those aged ≥ 75 years old. For those aged ≥ 60 and < 75 years old, the impact was significant through Cox model, and not significant through fixed-effects model. Moreover, the positive association between poorly controlled BP and frailty was existed in subgroups of males, females, rural respondents and urban respondents, with consistent significance analysed by both fixed-effects models and Cox models.

DISCUSSION

Using longitudinal data of a middle-aged and older population across 6 years and cohort analysis, with fixed-effect

models, Cox proportional hazard models and strict sensitivity analysis, this study provides clear evidence on the association between BP control and frailty among middle-aged and older populations with hypertension. We found that poorly controlled BP was positively associated with frailty among the respondents with hypertension in the whole sample. Based on subgroup analysis, a significantly higher risk existed in respondents aged under 60 years old. The risk disparities between males and females, as well as rural and urban areas were not significant.

The proportion of frailty ranges from 40.6% (2013) to 56.3% (2018) in this study. As reviewed by Vetrano *et al*, frailty incidence measured by frailty index ranged from 16% to 68% among the older population (containing not just hypertensive population).³² Therefore, we considered the proportion of frailty in this study to be within the acceptable range. In addition, the rate of well-controlled BP ranged from 79.9% to 85.6% in this study. In a recent review, the ranges of hypertension control rate among hypertensive patients in China were 4.2%–30.1%,³³ which is much lower than that found in our study. This could be explained by the awareness and treatment rate of the respondents. The awareness and treatment rates in that review ranged from 23.6% to 56.2% and from 14.2% to 48.5%, respectively. However, in our analysis, only the respondents ever clearly diagnosed with hypertension by doctors were included, who were proven to have higher awareness associated with better BP control effectiveness.³⁴ In addition, the treatment rate in our study exceeded 80%, which is much higher than the review, and consequently brings about higher control rate. Another study, which also used the CHARLS (2015) to evaluate the BP control rate, with SBP under 140 mm Hg and DBP under 90 mm Hg defined as well-controlled, presented a control rate of 57.4%.³⁵ Nevertheless, we could not rule out the possibility that the participants overestimated the effectiveness of their BP control.

Many studies have demonstrated that frailty is associated with an increased risk of falls, delirium, disability and mortality. Hypertensive respondents constituted nearly

Table 3 Association between blood pressure control and frailty score based on a fixed-effects model and Cox proportional hazard model

	Fixed-effects model (n=3254)		Cox proportional hazard model (n=1932)	
	β (95% CI)*	P value	HR (95% CI)	P value
Blood pressure control (ref. well controlled)				
Poorly controlled	0.015 (0.011 to 0.019)	<0.001	1.96 (1.49 to 2.56)	<0.001
Age	0.008 (0.008 to 0.008)	<0.001	1.03 (1.01 to 1.04)	<0.001
Gender (ref. male)†				
Female	–	–	1.79 (1.36 to 2.36)	<0.001
Education level (ref. less than lower secondary)				
Upper secondary and vocational training	–0.003 (–0.015 to 0.009)	0.79	0.61 (0.42 to 0.88)	0.009
Tertiary	–0.030 (–0.050 to –0.010)	0.131	0.46 (0.20 to 1.06)	0.069
Marital status (ref. divorced or widowed)				
Married	–0.007 (–0.016 to 0.002)	0.424	1.12 (0.80 to 1.58)	0.500
Hukou status (ref. agricultural)				
Non-agricultural	–0.027 (–0.038 to –0.016)	0.011	1.07 (0.79 to 1.44)	0.680
Unified residence or do not have hukou	–0.010 (–0.024 to 0.004)	0.482	0.88 (0.32 to 2.45)	0.805
Public health insurance coverage (ref. not covered)				
Covered	0.001 (–0.006 to 0.008)	0.855	1.05 (0.62 to 1.80)	0.845
Current work status (ref. not working)				
Working	–0.015 (–0.019 to –0.011)	<0.001	1.15 (0.90 to 1.47)	0.273
Drink (ref. do not drink)				
Drink	–0.008 (–0.012 to –0.004)	0.077	0.83 (0.64 to 1.07)	0.147
Smoke (ref. never)				
Quit now	0.018 (0.009 to 0.027)	0.042	1.20 (0.84 to 1.73)	0.318
Smoke now	0.007 (–0.005 to 0.019)	0.558	1.12 (0.79 to 1.60)	0.515
Residence (ref. rural)†				
Urban	–	–	0.6 (0.47 to 0.77)	<0.001
Household per capita consumption	0.000 (0.000 to 0.000)	0.147	1.00 (1.00 to 1.00)	0.931
Comorbidity (ref. no)				
Yes	0.024 (0.018 to 0.030)	<0.001	2.52 (1.93 to 3.28)	<0.001
Antihypertensive treatment (ref. no)				
Yes	0.014 (0.010 to 0.018)	0.002	1.19 (0.93 to 1.54)	0.168

* β refers to the regression coefficient calculated by fixed-effects model.

†The variable ‘Gender’ and ‘Residence’ were omitted in the fixed-effects model because of collinearity.

30% of the sample, and it is of great significance to verify the association between their BP and frailty risk. Our results revealed that a higher risk of frailty was associated with poorly controlled BP among respondents with hypertension, consistent with studies of Zhu *et al*⁸ and Woo *et al*,¹⁰ which indicated the BP variability was risk factor associated with higher-order frailty status. Compared with those two studies, our study assessed the association of frailty risk with general control status of BP over a relative period, and further indicated that intensive control of BP could influence the trajectory of frailty according to both

longitudinal and cohort analyses. Poorly controlled BP can predict many advanced disease and adverse outcomes including cognitive decline, falls, morbidity (cardiovascular disease, strokes, heart failure and chronic kidney disease, etc) and so on.^{8 36–38} This can partly explain the negative association between poor BP control and higher frailty risk, as frail older individuals accumulate more deficits and undergo more adverse events as age increases. However, the pathophysiological mechanisms between them are complex and not fully understood and need to be determined through more prospective studies.

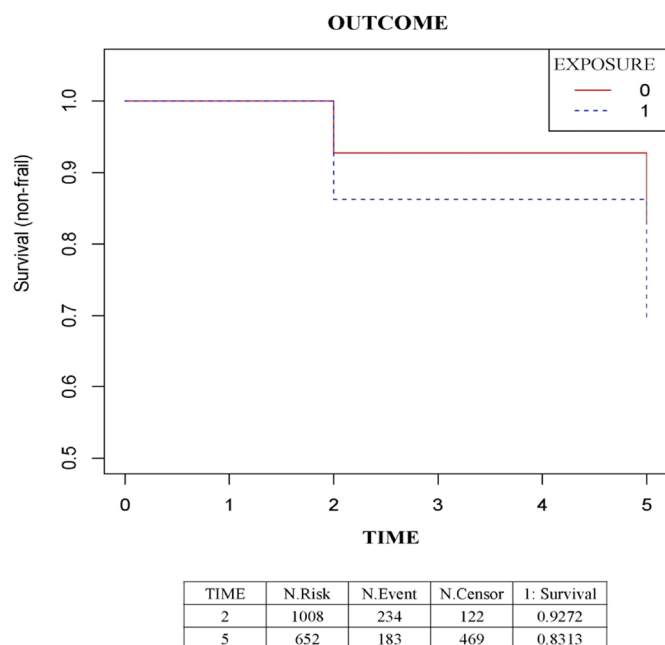


Figure 4 Kaplan-Meier analysis of adjusted frailty trajectories according to blood pressure control level using the proportional hazards model. 0=well controlled; 1=poorly controlled.

Intriguingly, there was heterogeneity, with different risks of frailty among different age groups. For the relatively younger respondents (<60 years old), the control of BP could significantly decrease the frailty risk, as well as many other adverse outcomes. However, for older individuals, especially those aged ≥ 75 years old, high BP was not significantly associated with frailty. This may be caused by individual heterogeneity, complexity of disease conditions, medication intake and greater vulnerability in physical and psychological status. In a recent study conducted in Japan, the association of SBP with physical frailty and cognitive function varied among different age groups,

with a lower SBP level being associated with a higher prevalence of physical frailty only among 80 years old taking antihypertensive medications, a higher SBP being associated with lower cognitive function among 70-year-old individuals, and a non-significant association among participants of all ages (≥ 69 years old) who did not use antihypertensive medication.¹⁴ Another cross-sectional study found that BP changed little in relation to age in all groups, except in individuals with untreated hypertension.³⁹ Many studies have reported a positive association between lower BP and frailty, cognitive impairment, and even mortality in the older population, but the mechanism is not yet clearly understood. Therefore, for older population with hypertension, it is important to note that BP control is challenging. The causal relationship should be clarified whether the frailty is caused by excessive reduction of BP in the further prospective study. What is certain is that treatment of hypertension in the older population is quite beneficial, but it is necessary to take into account some special characteristics of these patients, such as altered pharmacokinetics, comorbidity or polypharmacy. The BP control strategy for older hypertension patients should be individualised, with their quality of life, physical and psychological characteristics, and risk situations evaluated.

The strengths of this study include the use of a nationwide representative database, with longitudinal and high-quality micro-data among the middle-aged and older population with hypertension. However, there are several limitations in this study. First, recall bias existed, as all the information was self-reported. The self-rated level of BP control and frailty elements may be different from reality. Particularly, the control rate of BP control may be overestimated by the self-reported method. Therefore, the relationship between BP and frailty needs more definitive validation in prospective cohort studies and clinical trials. Second, this study only evaluated the impact of BP

Table 4 Sensitivity analyses to assess the association between frailty and blood pressure (BP) control

	Fixed-effects model		Cox proportional hazard model	
	β (95% CI)	P value	HR (95% CI)	P value
Main analysis	0.015 (0.011 to 0.019)	<0.001	1.96 (1.49 to 2.56)	<0.001
Multiple imputed†	0.013 (0.008 to 0.018)	<0.001	1.95 (1.61 to 2.36)	<0.001
With participants answering less than 45 items included‡	0.019 (0.011 to 0.026)	<0.001	1.91 (1.47 to 2.48)	<0.001
Marginal structural model§	–	–	1.65 (1.26 to 2.15)	<0.001
For the frail respondents in the baseline¶	0.015 (0.004 to 0.027)	0.009	0.61 (0.41 to 0.93)	0.020

*The reference group was the well-controlled BP group.

†The imputing method was from the posterior predictive distribution. Five sets of data were generated, and the regression coefficients were pooled.

‡We included participants who answered fewer than 45 items on the frailty-related index and repeated the analysis. There were 3349 respondents in 2013, 3121 in 2015 and 2868 in 2018. For the Cox regression, 2010 respondents were included in the analysis.

§Antihypertensive treatment and comorbidities were adjusted as time-varying confounders, and other covariates were adjusted as fixed confounders. Inverse probability of treatment weighting was used.

¶A total of 1322 respondents categorised into the frail group at baseline (2013) were included in this sensitivity analysis. In the Cox regression model, the improvement of the frailty state (from frail to non-frail) was set as the outcome.

Table 5 The association between frailty and blood pressure (BP) control among different ages, genders and living areas*

	Fixed-effects model		Cox proportional hazard model	
	β (95% CI)	P value	HR (95% CI)	P value
Age group†				
<60 years old	0.015 (0.002 to 0.028)	0.021	2.25 (1.48 to 3.43)	<0.001
≥60 and <75 years old	0.010 (−0.001 to 0.022)	0.071	1.72 (1.14 to 2.60)	0.009
≥75 years old	0.026 (−0.004 to 0.055)	0.089	0.56 (0.09 to 3.45)	0.540
Gender‡				
Male	0.020 (0.008 to 0.031)	0.001	2.63 (1.61 to 4.32)	<0.001
Female	0.012 (−0.002 to 0.021)	0.015	1.75 (1.25 to 2.44)	0.001
Living area§				
Rural	0.012 (0.003 to 0.022)	0.012	2.04 (1.48 to 2.83)	<0.001
Urban	0.018 (0.007 to 0.030)	0.001	1.85 (1.10 to 3.12)	0.021

*The reference group was the well-controlled BP group.

†The adjusted covariates include age, gender, marital status, hukou status, education level, living area, public health insurance coverage, current work status, alcohol intake, smoking status, household per capita consumption, antihypertensive treatment and comorbidities.

‡All the covariates were adjusted except for gender.

§All the covariates were adjusted except for living area.

control, which is a binary variable, rather than the absolute value of BP. The BP values through examination were not available in 2018. Third, limited by the scale of CHARLS, only parts of frailty-related indicators were used to calculate frailty scores, which may imperfectly accurate. For example, a comprehensive approach to obtain frailty needs also some physical evaluation, such as the Short Physical Performance Battery, which is not available. Finally, the types of hypertension could not be clarified, such as critical hypertension, mild hypertension, moderate hypertension or severe hypertension, and these may have different relationships with frailty. Fifth, the missing values in frailty index-related indicators lead to the loss of sample size, and consequently may have an impact on the representativeness of this study. Nevertheless, with several sensitivity analysis, accounting for different bias or confoundings, our results are robust.

CONCLUSIONS

To the best of our knowledge, this is the first study to assess the association between BP control and frailty among middle-aged and older hypertensive populations with longitudinal data over 6 years. We provide new evidence on the negative association between BP control and frailty risk. Furthermore, we identified the more sensitive populations that have a higher risk of frailty associated with poorly controlled BP. We appeal that a intensive management for BP among hypertension patients, especially for the older ones. Deeper research should be conducted to explore the influencing mechanism between BP and frailty and other adverse outcomes.

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