Control of Late-life Systolic Blood Pressure and All-cause Mortality Among Oldest-old People in China: The Chinese Longitudinal Healthy Longevity Survey

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Abstract

Background: Blood pressure targets for oldest-old people have been long debated due to the concern that more stringent targets are associated with increased mortality. We aimed to investigate the association between late-life systolic blood pressure control (mean SBP) and variability (SBPV) and mortality in oldest-old people.

Methods: Based on the community-based Chinese Longitudinal Healthy Longevity Survey with follow-up conducted in the 3-year interval, we assembled a retrospective cohort of 5951 participants ≥80 years with available blood pressure measurements at baseline and second wave. The primary exposures were mean SBP and SBPV (defined as the annual difference in SBP divided by mean SBP) measured between baseline and second wave. The primary outcome was 3-year all-cause mortality assessed between the second and third waves.

Results: During 21733.9 person-years of follow-up, 4290 death was recorded. U-shaped associations of mortality with mean SBP and SBPV were identified; the value of 137 mmHg and 2.3 %/year conferred the minimum mortality risk, respectively. The associations of a larger SBPV with an increased mortality risk were observed for both rises and large falls in SBP. The hazard ratio was 1.16 (comparing lowest versus middle quintile; 95% CI: 1.06, 1.28) with large falls in SBPV and 1.10 (comparing highest versus middle quintile; 95% CI: 1.00, 1.21) with large rises in SBPV.

Conclusions: U-shaped associations between late-life SBP and SBPV and all-cause mortality were found. Our study suggests that a stable SBP level in the middle range decreases the risk of mortality in the oldest-old people.

Background

Hypertension is the leading determinant of major cardiovascular disease events and mortality, affecting over half of elderly people worldwide [1]. Its management is still far from ideal, especially in developing countries [2]. A key challenge for clinicians to enhance hypertension management in older people is the uncertainty about the most appropriate blood pressure targets in terms of benefits and risks. The latest available guidelines for hypertension management in the elderly were mainly based on the same body of evidence but differ significantly in target systolic blood pressure (SBP) values [3, 4]. Together with the controversial association of lowering SBP with all-cause mortality among oldest-old (older than 80 years) [5, 6], these factors have further fueled debate. A better understanding of the risks conferred by SBP control is needed to direct clinical decisions and to prevent either excess or inadequate use of antihypertensive treatments in the elderly population [7].

Besides, blood pressure variability was identified as a potential risk factor for adverse outcomes. For example, in a meta-analysis reported in 2016, long-term SBP variability (SBPV) is associated with cardiovascular and mortality outcomes, over and above the effect of mean SBP [8]. However, to our

knowledge, the link between SBPV and mortality has not previously been specifically investigated in elderly people, especially among octogenarians or nonagenarians.

Using data from the Chinese Longitudinal Healthy Longevity Survey, we aimed to investigate the association between both mean SBP and SBPV and 3-year all-cause mortality in Chinese oldest-old.

Methods

Data source and study population

This study is embedded in the Chinese Longitudinal Healthy Longevity Survey (CLHLS), which is a national cohort focusing on older Chinese people and is the largest cohort of centenarians in the world. A detailed study design of CLHLS has been published elsewhere [9]. Briefly, a multistage cluster sampling approach was used to ensure its representative of the general elderly Chinese population. After randomly selecting half the total number of countries and cities from 22 provinces, all centenarians living in the sampled area were invited to the participant and the response rate was 97.7%. For each participating centenarian, one octogenarian and one nonagenarian living in the same community or village were randomly sampled. According to systematic assessments of the randomness of attrition, credibility and validity of the measurement scale, and accuracy of reported age, the quality of the data for CLHLS was high. The CLHLS study was approved by the Research Ethics Committee of Peking University (IRB00001052-13074), and all participants or their proxy respondents provided written informed consent.

The baseline survey of the current study was conducted in 2005, with follow-up waves conducted in 2008, 2011, 2014, and 2018. A further extension of the cohort was initiated in the 2008 and 2011 waves following the same study protocol. An overview of the study population is shown in **e-Figure 1**.

Exposures and outcome

As shown in **e-Figure 2**, the primary exposures were mean SBP and SBPV, measured between baseline and second wave. The primary outcome was 3-year all-cause mortality, identified between second and third waves.

Mean SBP was assessed by calculating the updated arithmetic mean of SBP in the consecutive two waves from 2005 onwards ((Second wave-Baseline)/2). Within-individual SBPV between two sequential waves was defined as the difference in SBP between two waves divided by the mean ((Second wave-Baseline)/mean). To account for slightly different visit intervals, this measurement was further scaled to the average variation per year, assuming a constant rate of variation between the two waves [10].

Both exposure measurements (mean SBP and SBPV) were assessed as time-varying exposures, first assessed at the 2008 wave using SBP values from 2005 and 2008 waves, and then updated at the 2011 wave using SBP values from 2008 and 2011 waves, and so on.

Covariates

Information on covariates was collected at baseline using a structured questionnaire. One section included sociodemographic characteristics (age, sex, body mass index (BMI), educational level, economic income (high *vs* medium/low)), smoking status (current, past, or never smoker), and alcohol consumption (current *vs* former/never). Visual status was defined as "good" or "poor" according to whether participants could identify the break in the image of a circle held before them. Cognitive function was measured by the Chinese version of Mini-Mental State Examination (MMSE) and we defined mild cognitive impairment (MCI) based on both MMSE score and education level: <18 for those without formal education, < 21 for those with 1–6 years of education, < 25 for those with more than 6 years of education [11]. Restriction in daily living activities was defined as a participant being dependent on toileting, bathing, indoor activities, dressing, eating, or continence. Comorbidity was defined according to the number of the self-reported disease, including diabetes mellitus, cardiovascular disease, stroke, respiratory disease, and cancer.

Frailty was assessed by the adjusted osteoporotic fracture index [12, 13], which including three components: (1) underweight (BMI < 18.5 kg/m^2); (2) participants having trouble standing up from a chair without the assistance of arms; and (3) a positive response to the question "how many times suffering from serious illness in the past two years". We categorized frailty status into: frail (two or three components), pre-frail (one component), and robust (no component).

Statistical methods

Primary analyses. Our analysis focused on the association between control of SBP (mean SBP and SBPV), assessed over two sequential study waves, and 3-year all-cause mortality, among oldest-old. Person-time accumulated from the second wave (first assessment of mean SBP and SBPV) until the date of death, date of loss to follow-up, or end date of follow-up (the updated third wave), whichever came first.

We first investigated the association between continuous mean SBP and SBPV and 3-year all-cause mortality using Cox proportional hazards models with penalized splines, which examine the potential non-linear or irregular shape of the hazard functions. Other covariates, such as BMI, could also exert a non-linear effect here. Following the suggested procedure [14], we obtained the corresponding multivariable degree of freedom based on the corrected Akaike information criterion and biological plausibility. Then, we further stratified mean SBP and SBPV into quintile with the reference group defined as the middle quintile to facilitate understanding.

All Cox models were adjusted for baseline covariates, collecting from the updated baseline: age, sex, BMI, educational background, economic income, smoking status, alcohol consumption, visual status, MCI, restriction in activities of daily living, comorbidity, and cohort. The proportional hazard assumption was assessed by visual inspection of the scaled Schoenfeld residuals plot.

Secondary analyses. Given the previously reported terminal decline in SBP at the end-of-life [15], we also checked the potential impact of reverse causality by repeating the above analyses using 1-year and 2-

year lag periods, separately. Also, to identify the potential effect modification, we stratified the analyses by self-reported doctor-diagnosed hypertension and frailty status at baseline.

Sensitivity analyses. To test the robustness of the main findings, we performed the following analyses: (1) excluding participants who contributed to more than one cohort; (2) reporting the associations using multiple imputations to reduce potential selection bias caused by missing covariates; and (3) estimating how strong residual confounding would need to be to explain away the observed association using the E-value [16].

Results

Participant characteristics

Of the 5951 participants included, 3569 (60%) were women, and the mean (SD) age was 90.5 (7.0) years. Repeated involvement was allowed for eligible participants among the three cohorts (cohort 2005: 3255, cohort 2008: 4056, cohort 2011: 2450), Table 1 describes the characteristics for participants in a specific cohort. During a median follow-up of 2.4 years (from the second wave to the third wave, interquartile range 1.4-3.0), 4290 died among 9761 included participants (overall mortality rate 197.4 cases per 1000 person-years).

Table 1
Characteristics of the included participants.

	Total population (n = 5951)	Cohort 2005 (n = 3255)	Cohort 2008 (n = 4056)	Cohort 2011 (n = 2450)
Age, year	90.5 (7.0)	90.0 (6.7)	90.0 (7.0)	89.7 (7.2)
Sex, female	3569 (60)	1932 (59)	2373 (59)	1429 (58)
Body mass index, kg/m^2	19.5 (3.3)	18.9 (3.2)	20.1 (3.2)	21.0 (3.8)
Education, illiterate	4099 (69)	2187 (67)	2722 (67)	1622 (66)
Residence				
city	1106 (19)	729 (22)	694 (17)	364 (15)
town	1142 (19)	663 (20)	856 (21)	745 (30)
rural	3703 (62)	1863 (57)	2506 (62)	1341 (55)
Economic income				
median / low	4961 (83)	2672 (82)	3445 (85)	1943 (79)
high	990 (17)	583 (18)	611 (15)	507 (21)
Smoke				
current	942 (16)	549 (17)	636 (16)	390 (16)
past	806 (14)	508 (16)	587 (14)	369 (15)
never	4203 (71)	2198 (68)	2833 (70)	1691 (69)
Current drinker	1133 (19)	655 (20)	708 (17)	432 (18)
Mild cognitive impairment	1397 (23)	726 (22)	930 (23)	455 (19)
Restriction on activities of daily living	1076 (18)	652 (20)	533 (13)	496 (20)
Poor visual function	2199 (37)	1199 (37)	1470 (36)	892 (36)
Frailty status				
Robust	2086 (35)	1013 (31)	1654 (41)	1052 (44)
Pre-frailty	2574 (43)	1428 (44)	1678 (41)	971 (40)
Frailty	1276 (21)	813 (25)	724 (18)	385 (16)
Hypertension	931 (16)	482 (15)	648 (17)	614 (26)
Diabetes mellitus	88 (1)	47 (1)	76 (2)	68 (3)

	Total population (n = 5951)	Cohort 2005 (n = 3255)	Cohort 2008 (n = 4056)	Cohort 2011 (n = 2450)
Cardiovascular disease	422 (7)	240 (7)	295 (7)	267 (11)
Stroke and cerebrovascular disease	257 (4)	128 (4)	191 (5)	156 (6)
Respiratory disease	612 (10)	379 (12)	380 (9)	277 (11)
Cancer	14 (0)	7 (0)	8 (0)	12 (0)
Comorbidity				
0	4757 (80)	2579 (79)	3246 (80)	1817 (74)
≥ 1	1194 (20)	676 (21)	810 (20)	633 (26)
Interval (baseline ~ second), year	3.1 (0.3)	3.2 (0.1)	3.1 (0.2)	2.6 (0.4)
Baseline wave				
Systolic blood pressure, mmHg	134.9 (20.2)	131.0 (17.9)	138.0 (21.4)	137.8 (21.0)
Diastolic blood pressure, mmHg	80.6 (11.6)	82.1 (11.7)	78.4 (11.4)	79.5 (11.3)
Second wave				
Systolic blood pressure, mmHg	136.0 (21.9)	135.2 (21.4)	135.9 (21.8)	137.9 (21.7)
Diastolic blood pressure, mmHg	78.9 (12.3)	78.6 (12.3)	79.1 (12.2)	79.7 (11.5)

Note: Repeated involvement was allowed for eligible participants among different cohorts. Data are mean (standard deviation) for continuous variables, n (%) for categorized variables.

Control of systolic blood pressure and all-cause mortality

The results of the Cox proportional hazards model with penalized splines suggested a U-shaped association between mean SBP and all-cause mortality (Fig. 1). Over 3.0 (median) years, the mean SBP value that conferred the minimum mortality risk was 137 mmHg. Compared with participants with a mean SBP of 137 mmHg, those with a lower (< 122 mmHg) or higher (> 158 mmHg) value had a significantly higher risk of mortality. In contrast, in those with a mean SBP of 122 ~ 158 mmHg, no statistically significant association with death was observed. Table 2 **and** Fig. 2 show the hazard ratios (HRs) and 95% confident intervals (CIs) of mortality by quintiles of mean SBP with the middle quintile used as the reference. Compared to participants with mean SBP of 131 ~ 138 mmHg, those among the lowest (< 123 mmHg) or highest (> 148 mmHg) quintile had a higher risk of all-cause mortality, with HR 1.09 (95%CI: 1.00, 1.20), and 1.10 (95% CI: 1.00, 1.21), respectively.

Table 2
Associations of categorized mean systolic blood pressure (mean SBP) and systolic blood pressure variability (SBPV) and all-cause mortality, using different lag periods.

Variables	Lag periods (years)	Hazard ratios (95% CI) [a]				
		Q1 (< 123 mmHg)	Q2 (123 ~ 131 mmHg)	Q3 (131 ~ 138 mmHg)	Q4 (138 ~ 148 mmHg)	Q5 (> 148 mmHg)
Mean SBP	0	1.09 (1.00, 1.20)	1.02 (0.93, 1.12)	1.00 (reference)	0.95 (0.87, 1.05)	1.10 (1.00, 1.21)
	1	1.11 (0.99, 1.24)	1.04 (0.93, 1.17)	1.00 (reference)	1.00 (0.88, 1.12)	1.15 (1.03, 1.30)
	2	1.03 (0.87, 1.23)	1.10 (0.93, 1.30)	1.00 (reference)	1.03 (0.87, 1.22)	1.31 (1.11, 1.54)
		Q1 (<-5.1 %/year)	Q2 (-5.1~-1.5 %/year)	Q3 (-1.5 ~ 1.6 %/year)	Q4 (1.6 ~ 5.3 %/year)	Q5 (> 5.3 %/year)
SBPV	0	1.16 (1.06, 1.28)	1.11 (1.00, 1.22)	1.00 (reference)	1.06 (0.96, 1.16)	1.10 (1.00, 1.21)
	1	1.15 (1.02, 1.29)	1.11 (0.98, 1.24)	1.00 (reference)	1.01 (0.90, 1.14)	1.08 (0.96, 1.21)
	2	1.24 (1.04, 1.46)	1.15 (0.97, 1.36)	1.00 (reference)	1.04 (0.87, 1.24)	1.20 (1.02, 1.42)

[a] With adjustment for age, sex, body mass index, educational background, economic income, smoking status, alcohol consumption, visual status, mild cognitive impairment, restriction in activities of daily living, comorbidity, and cohort at updated baseline.

A stronger association between mean SBP and mortality was noted especially over a longer lag period (Fig. 2) and among those who had self-reported hypertension (Fig. 3). The HR associated with higher mean SBP (the highest quintile) increased from 1.10 (95%CI: 1.00, 1.21) for mortality risk with lag 0 year after the exposure measurement, 1.15 (95%CI: 1.03, 1.30) for risk with lag 1 year, to 1.31 (95%CI: 1.11, 1.54) with lag 2 years. A similar trend was found among different frailty statuses, but with limited significant association found which may due to the smaller sample size after stratifying.

Systolic blood pressure variability and all-cause mortality

Cox proportional hazards models with penalized splines shown a U-shaped association between SBPV and three-year all-cause mortality; the lowest mortality risk was found among participants with SBPV of 2.3%/year (Fig. 1). The associations of a larger SBP variation with an increased mortality risk were observed for both rises and large falls in SBP after categorizing SBPV by quintile (Table 2, Fig. 2). The HR

was 1.16 (comparing lowest versus middle quintile; 95% CI: 1.06, 1.28) with large falls in SBPV and 1.10 (comparing highest versus middle quintile; 95% CI: 1.00, 1.21) with large rises in SBPV.

The magnitude of these associations increased with longer lag intervals, for example, the HR for a large variation was 1.24 (comparing lowest versus middle quintile; 95% CI: 1.04, 1.46) and 1.20 (comparing highest versus middle quintile; 95% CI: 1.02, 1.42) when 2 years lagged between the measurement of SBPV and mortality (Table 2, Fig. 2). After further stratifying participants by hypertension status, though similar trends were found in each subgroup, the magnitude of association with SBPV was somewhat larger among participants with self-reported hypertension, while lost significance for those without self-reported hypertension. Moreover, among participants with different frailty statuses, we also found that a large SBP variation related to a higher risk of all-cause mortality with borderline significance (Fig. 3).

Sensitivity analyses

Findings were consistent in the sensitivity analyses (see **e-Table 1** and **e-Figure 3–4**). The association estimates appeared to have a wider confidence interval after excluding individuals involving in more than one cohort but still suggested U-shaped. Results based on data from multiple imputations did not affect the main findings. They reported that a large SBP variation was associated with higher mortality risk and the magnitude increased with longer lag periods. The final sensitivity analysis using E-value shown that, to explain away mortality risk ≥ 2 years after the measurement of SBPV (HR with a fall in SBPV: 1.24 (1.04, 1.46)), the unmeasured confounding would need to be associated with both the SBPV and all-cause mortality by an HR of 1.16 each, above and beyond the measured confounders.

Discussion

Based on a large-scale community-based cohort, our results indicated a U-shaped association between late-life SBP and SBPV and risk of all-cause mortality, with mean SBP of 137 mmHg, SBPV of 2.3%/year, related to the lowest mortality risk. The associations of a larger SBP variation with an increased mortality risk were observed for both rises and large falls in SBP. The magnitude of these associations would increase with longer lag intervals.

Systolic blood pressure and mortality

The observed association between lower SBP values and increased risk of all-cause mortality among oldest-old is in line with previous concerns regarding the intensity of antihypertensive treatment in the elderly population [17]. Although low blood pressure may in itself cause harm, it is also likely to an indicator of poor health status. However, former studies also reported no evidence of an interaction between antihypertensive treatment and frailty status [18]. Low SBP was associated with mortality even in fit participants [15]. Results from the Berlin Initiative Study also found that control blood pressure values below 140/90 mmHg during antihypertensive treatment may be associated with an increased risk of mortality in participants ≥ 70 years [19]. In contrast, the link between higher SBP and mortality has been relatively consistent in later life with the only concerns regarding how high to go. Several guidelines

have been released to treat elevated blood pressure, mainly based on the same body of evidence but differ significantly in some aspects, such as the definition of ‘old’ patients, the definition of arterial hypertension, blood pressure target value in older patients [3]. A previous study which based on the same cohort also reported a U-shaped association of mortality with SBP, with lower risk among participants who have a middle range of SBP (107 ~ 154 mmHg) [13].

A U-shaped or J-shaped relationship between targeted SBP and risk of morbidity and mortality has long been suggested [4]. This hypothesis is based on a presumed SBP threshold for organ blood flow autoregulation, and the potential role of blood pressure as a compensatory mechanism for preserving organ function [20]. Considering the totality of evidence, less aggressive treatment would be an optimal approach in treating hypertension in older people, more individualized treatment plans should be designed when treating frail older adults [21].

Systolic blood pressure variability and mortality

Variability in blood pressure has been recognized as a potential risk factor, whereas no standard formula available for its calculation. Multiple measures, such as standard deviation, coefficient of variation, and root successive variance, hamper the understanding of blood pressure variability [8]. Some have not adjusted for mean blood pressure and confound high variability with high mean blood pressure [22], or with the mean adjusted but not fully consistent with the variability measure [23]. In our study, to adjust for mean blood pressure and account for different visit intervals, the blood pressure variability was calculated as the difference in SBP between two waves divided by the mean and further scaled into the average variation per year. Using the same measure, Yuan et al. reported that a large blood pressure variation over the years was associated with subclinical brain structural changes [24] and an increased long-term risk of dementia [10]. We found an elevated 3-year risk of all-cause mortality was observed with a large rise and fall in later-life SBPV among the oldest-old people.

Blood pressure variability, especially long-term, is associated with cardiovascular and mortality outcomes and shows additional prognostic value independent of mean blood pressure [8]. Although the underline mechanism has not been well understood, it could be partly explained by arterial stiffness [25] or the changes to antihypertensive drugs resulting from poor blood pressure control [26]. Certain lifestyle factors, such as behavioral, emotional, and cardiac rhythm, could also affect blood pressure variability in the relatively short term [27]. Future studies should explore this relationship in-depth to determine dynamic and individualized targets for older people.

Strengths and limitations

Our study has some unique and useful features. The most important feature is that based on the large-scale population-based cohort, we thoroughly investigated the association of late-life systolic blood pressure and variability with risk of mortality among the oldest-old, which filled in a certain knowledge gap about control of late-life blood pressure in the older population [28]. Also, given the previously raised concerns that a terminal decline of SBP in the final 2 years of life which cause reverse causality [15], we used different lag periods and found an even stronger magnitude among longer lag intervals. On the

other hand, there are still some limitations in our study. Firstly, the validated data of morbidity and cause-specific mortality was unavailable in this cohort, limiting our ability to check whether there is possible heterogeneity for different types of outcomes. Secondly, although we carefully adjusted many potential confounders, other unknown factors were still possible. Many factors, such as treatment of hypertension, blood glucose, were not collected in the CLHLS and therefore could not be analyzed. Finally, our study included only the Chinese elderly, limiting the generalizability of our findings to other populations.

Conclusions

Our findings suggest that SBP variability might be an important factor in understanding mortality risk in the oldest-old, affirming the need to develop better strategies for blood pressure management in this population. Although developing a strategy to more reliably achieve stable blood pressure control in older people might be important, further examination of the relationship between SBPV and clinical outcomes is required to inform appropriate treatment targets and models for blood pressure control.

Abbreviations

CLHLS: the Chinese Longitudinal Healthy Longevity Survey; SBP: systolic blood pressure; SBPV: systolic blood pressure variability; MMSE: Mini-Mental State Examination; MCI: mild cognitive impairment; BMI: body mass index; HR: hazards ratio.

Declarations

Ethics approval and consent to participate

The CLHLS study was approved by the Research Ethics Committee of Peking University (IRB00001052-13074), and all participants or their proxy respondents provided written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

The original CLHLS dataset are available at https://opendata.pku.edu.cn/dataverse/CHADS. The full dataset used in this analysis are available from the corresponding author upon reasonable request.

Competing interests

The authors report no potential conflicts of interest.

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None.

Authors' contributions

H.G. and K.W. are responsible for the study concept and design; K.W. composed the statistical dataset, performed the statistical analyses; H.G. wrote the manuscript; F.A., W.Z., Y.J., L.Z., Y.L., F.Z., J.G., J.Z. and Z.X. revised/edited the manuscript for intellectual content.

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Figures

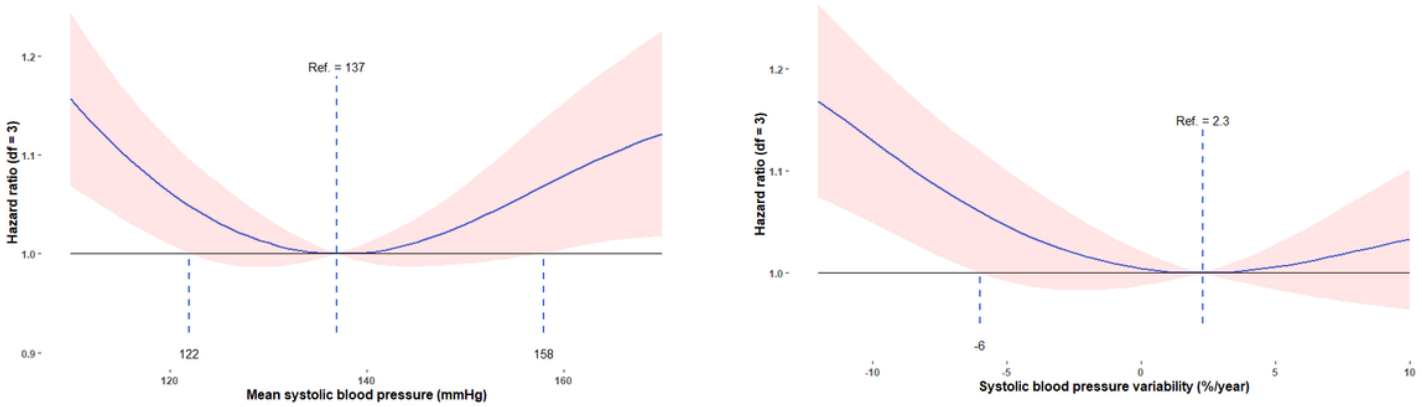

Figure 1

Associations of mean systolic blood pressure and systolic blood pressure variability and all-cause mortality.

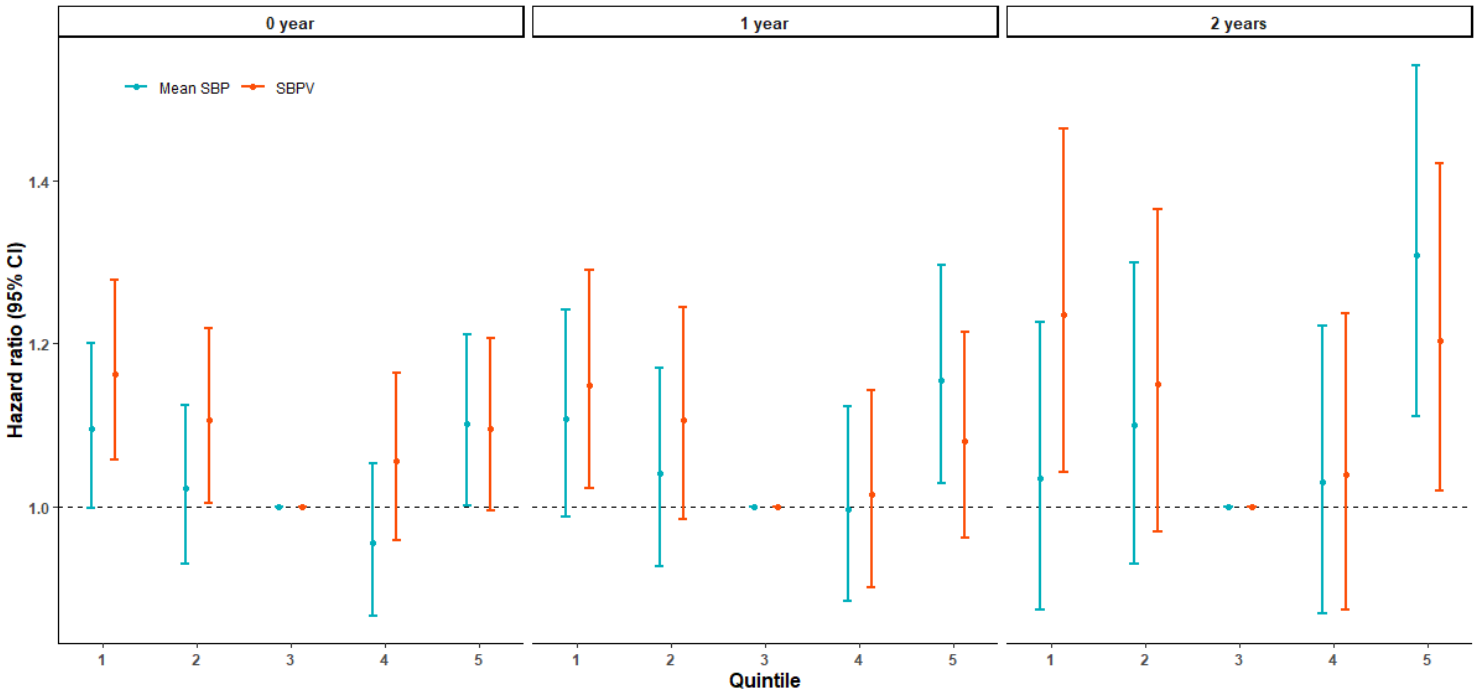

Figure 2

Associations of categorized mean systolic blood pressure (mean SBP) and systolic blood pressure variability (SBPV) and all-cause mortality, using different lag periods.

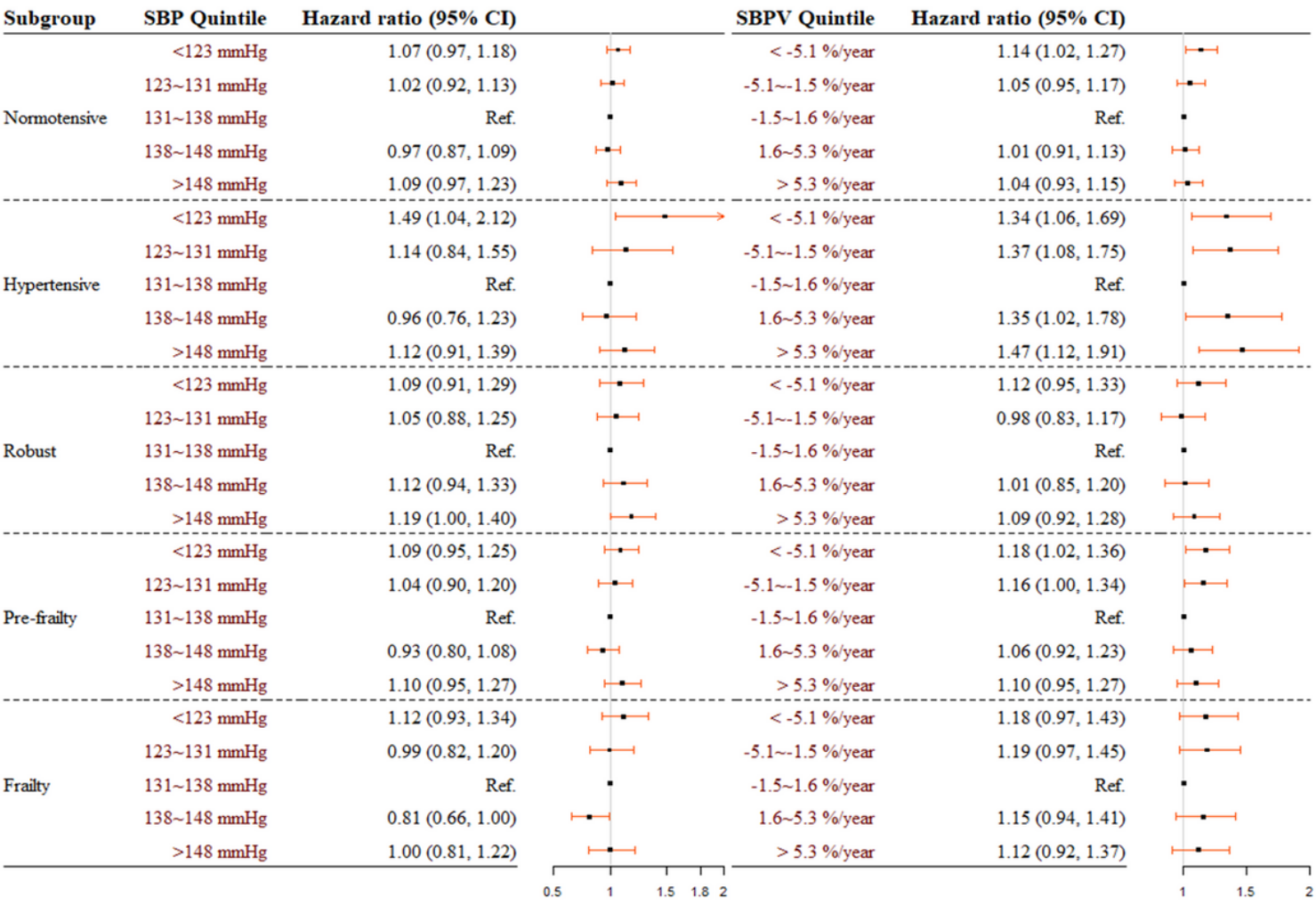

Figure 3

Associations of categorized mean systolic blood pressure (mean SBP) and systolic blood pressure variability (SBPV) and all-cause mortality among different subgroups.

Supplementary Files

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