Age-specific associations between systolic blood pressure and cardiovascular mortality

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ABSTRACT

Objective We aimed to identify the following in all age groups among individuals without known hypertension and CVD: (1) Whether a systolic blood pressure (SBP) of 130–139 mm Hg elevates cardiovascular disease (CVD) mortality. (2) Whether SBP shows a linear association with cause-specific CVD mortality.

Methods We used the Korean National Health Insurance sample data (n=429,220). Participants were categorised into three groups by age (40–59 years, 60–69 years and 70–80 years).

Results During 10.4 years of follow-up, 4319 cardiovascular deaths occurred. A positive and graded association was generally observed between SBP and overall and cause-specific CVD mortality regardless of age, except for ischaemic heart disease (IHD) mortality in those aged 70–80 years. Among those aged 70–80 years, the HRs (95% CIs) for overall CVD mortality were 1.08 (0.92–1.28), 1.14 (0.97–1.34) and 1.34 (1.14–1.58) for SBP values of 120–129 mm Hg, 130–139 mm Hg and 140–149 mm Hg, respectively, compared with SBP <120 mm Hg. For total stroke mortality, the corresponding HRs were 1.29 (1.02–1.64), 1.37 (1.09–1.72) and 1.52 (1.20–1.93), while for IHD mortality, the corresponding HRs were 0.90 (0.64–1.26), 0.86 (0.62–1.19) and 1.29 (0.93–1.78), respectively. Non-linear associations were significant for IHD.

Conclusions In the elderly Korean population, SBPs of 130–139 mm Hg elevated total stroke mortality, but not IHD mortality, compared with normal blood pressure, and a linear association was not observed for IHD mortality in the range <140 mm Hg.

INTRODUCTION

Elevated blood pressure (BP) remains among the top causes of disease burden worldwide.1 2 The recent US guidelines for hypertension have lowered the diagnostic cut-off to 130/80 mm Hg, including the elderly population.1 However, uncertainties remain regarding the effect of BP on various cardiovascular outcomes in different age groups. Indeed, the relative risks for BP on cardiovascular outcomes decrease with age,2 and not all cardiovascular disease (CVD) subtypes exhibit linear relationships with BP.3 4 Moreover, it is not clear whether a systolic blood pressure (SBP) of 130–139 mm Hg elevates risk compared with normal BP (SBP <120 mm Hg) for each subtype of cardiovascular outcomes in the elderly. A detailed analysis of the age-specific effects of BP on various cardiovascular outcomes would help establish individualised treatment recommendations in this era of a rapidly ageing society.

Although several large-scale epidemiological studies have addressed the age-specific relationships between BP and cardiovascular outcomes, most studies included hypertensive patients already taking medications and were largely based on data from Western populations.5–8 To establish an effective preventive strategy in Asian populations, prospective observational studies reflecting Asian-specific characteristics are needed. However, limited and even conflicting reports exist in studies on elderly Asians.10–13 The recent Chinese Multi-provincial Cohort Study found that no risk elevation was associated with an SBP of 130–139 mm Hg compared with normal BP in those aged ≥60 years.12 In the current study, we aimed to clarify whether SBP shows a linear association with cause-specific CVD mortality in all age groups and to identify whether an SBP of 130–139 mm Hg elevates CVD mortality in elderly individuals without known hypertension or CVD at baseline. For this analysis, we used a nationwide prospective cohort from Korea, and we confined the focus of our analysis to SBP, which has been reported to be a better predictor of cardiovascular outcomes than other BP parameters.8 14

METHODS

Study population and follow-up

The National Health Insurance Service (NHIS) provides compulsory health insurance that covers 97% of the Korean population. The study cohort (n=514,795) was a 10% random sample of 5.1 million NHIS health screening participants during 2002–2003 who were aged 40–79 years in 2002.15 We excluded 85,575 individuals due to missing information (n=1595) on body mass index (BMI), serum fasting glucose, total cholesterol and SBP; known heart disease or stroke (n=9695); or known prevalent hypertension (n=74,285) at baseline as assessed by the NHIS claim database. For the remaining 429,220 people, follow-up for causes of death was carried out until 31 December 2013 through national death records using unique personal identification numbers. The International Classification of Diseases-10th Revision was used to identify cases of death from CVD (100–199), and the subtypes of CVD mortality were classified into ischaemic heart disease (IHD: I20-I25), acute myocardial infarction (MI; I21), total stroke (I60–I69), haemorrhagic stroke (I60–I62), subarachnoid haemorrhage (SAH; I60), intracerebral haemorrhage (ICH; I61–I62) and ischaemic stroke (I63). In accordance with the conditions stipulated in Korean laws, health examination data can be provided for

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research without specific informed consent from the participants. Anonymised data were provided to the authors by NHIS.

Data collection
Weight and height were measured to the nearest kilogram and centimetre, respectively, while participants wore light clothing without shoes. BMI was calculated as weight in kilograms divided by the square of height in metres. BP was measured by a trained staff or a nurse in a seated position after resting for at least 5 min. Fasting serum glucose was assayed using enzymatic methods. Smoking history, alcohol use, physical activity, and history of heart disease, stroke and cancer were reported via a questionnaire. Health examination and data collection followed a standard protocol officially documented by the Ministry of Health and Welfare. The external quality validation process for clinical chemistry in participating hospitals was supervised by the Korean Association of Quality Assurance for Clinical Laboratories, and quality assessment was performed regularly. We considered individuals to have prevalent hypertension at baseline if they visited a medical institution for hypertension (I10-I15) at least once within 6 months before or 2 months after the baseline health examination date.

Statistical analysis
Baseline was defined as the time of the health examination. To identify age-specific effects, participants were categorised into three groups based on age at baseline (40–59 years, 60–69 years and 70–80 years). SBP values were categorised into six categories (<120 mm Hg (reference), 120–129 mm Hg, 130–139 mm Hg, 140–149 mm Hg, 150–159 mm Hg and ≥160 mm Hg). SBP was also analysed as a continuous variable, assuming a linear association. Non-linear associations were evaluated using a restricted cubic spline transformation of SBP with three knots (predefined at the 5th, 50th and 95th centiles in each analysis).

The HRs and CIs for CVD deaths were calculated using Cox proportional hazards models in each age group, further stratified by age (years) at baseline (40–44 years, 45–54 years, 55–64 years, 65–74 years and 75–80 years) after adjusting for age at baseline (continuous variable; within each age group), sex, smoking status (current smoker, former smoker, never smoker and missing information), alcohol consumption (none, <10 g ethanol/day, 10–39 g ethanol/day, ≥40 g ethanol/day and missing information), physical activity (at least once per week; yes and no), beneficiary income status (deciles; below 4 (low income), 4–7, 8–10 (high income)), BMI (continuous variable), total cholesterol (continuous variable) and fasting glucose (continuous variable). In the Cox models, the cause-specific hazard method was used for dealing with competing risks; individuals who experienced a competing event (other causes of death) or reached the end of the follow-up were treated as censored.16 Subgroup analyses were performed to examine differences in the associations according to age and sex. Cochran’s Q statistic was used as the interaction test to examine the difference in the effect size of SBP between age groups. The proportional hazards assumption was examined by using Schoenfeld residuals.17 No evidence was found of violation of the proportional hazards assumption for each continuous and dummy variable of SBP for IHD mortality. A sensitivity analysis that excluded those who died within the first 3 years of follow-up was conducted, and subgroup analyses were also used for sensitivity testing. All p values were two-sided. All analyses were conducted using SAS V9.4 software (SAS Institute, Cary, North Carolina, USA).

RESULTS
Baseline demographic findings
Among the 429220 participants, 237738 (55.4%) were men. Their mean age was 51.8 (SD 9.3) years and their mean SBP was 124.7 (SD 16.9) mm Hg. Overall, 92,572 (21.6%) participants had an SBP ≥140 mm Hg (table 1). Clinical profiles classified by SBP category are provided in online supplementary table 1. During 10.4 years of follow-up, a total of 4319 cardiovascular deaths occurred.

Associations between SBP and overall/individual CVD mortality in the overall population
In the overall population, every 20 mm Hg elevation in SBP was associated with a 40% elevated risk of overall cardiovascular death (HR 1.40 (1.36–1.44)). The association with total stroke mortality was stronger than the association with IHD mortality (HRs were 1.51 (1.45–1.58) for total stroke and 1.31 (1.23–1.40) for IHD). For stroke subtypes, haemorrhagic stroke (HR 1.65 (1.49–1.57)) exhibited a stronger association with SBP than ischaemic stroke (HR 1.27 (1.11–1.45), online supplementary table 2).

Age-specific associations of SBP with overall/individual CVD mortality
When stratified by age, assuming a linear association, the strength of association weakened according to ageing (p for interaction <0.001 for overall CVD mortality), but remained significant even in the elderly group for various causes of CVD mortality (figure 1, online supplementary table 3). In detail, each 20 mm Hg elevation in SBP was associated with 1.67-fold (95% CI 1.57 to 1.78) elevated risk for overall CVD mortality in those aged 40–59 years, 1.40-fold increase (95% CI 1.33 to 1.48) in those aged 60–69 years and 1.22-fold increase (95% CI 1.16 to 1.29) in those aged 70–80 years.

In the categorical analyses, a positive and graded association was generally observed between SBP and both overall and cause-specific CVD mortality regardless of age, except for IHD mortality in those aged 70–80 years (figure 2, online supplementary tables 4 and 5). In persons aged 70–80 years, for overall CVD mortality, the HRs (95% CI) were 1.08 (0.92–1.28) for SBP of 120–129 mm Hg, 1.14 (0.97–1.34) for SBP of 130–139 mm Hg, 1.34 (1.14–1.58) for SBP of 140–149 mm Hg, 1.56 (1.31–1.86) for SBP of 150–159 mm Hg and 1.81 (1.52–2.17) for SBP ≥160 mm Hg when compared with SBP <120 mm Hg. For IHD mortality, the corresponding HRs (95% CI) were 0.90 (0.64–1.26), 0.86 (0.62–1.19), 1.29 (0.93–1.78), 1.44 (1.02–2.04) and 1.58 (1.11–2.27), respectively. For acute MI, a similar pattern was observed.

The subgroup analysis by sex revealed similar results to those of the main analysis (online supplementary tables 6 and 7 and supplementary figures 1 and 2). The sensitivity analysis excluding those who died within the first 3 years of follow-up also yielded similar results (online supplementary table 8 and figure 3).

When the shape of the association was explored using a restricted cubic spline model (figure 3), the results were similar to those obtained from the categorical analysis. The slope of the association was steeper for mortality from stroke than for mortality from IHD in each age group, and the relationship was generally stronger in the younger population. Non-linear associations were significant for IHD (including acute MI) mortality in people aged 70–80 years. The risk for IHD (including acute MI) mortality was lowest around an SBP of 120–130 mm Hg in the elderly.

DISCUSSION

Association of SBP with CVD mortality: a focus on the age-specific effect

Currently, the suggested thresholds for hypertension in the elderly differ between the European (SBP ≥140/90 mm Hg) and US (SBP ≥130 mm Hg) guidelines. Unfortunately, scant data support the establishment of an appropriate cut-off for hypertension in Asian populations. In this prospective cohort involving over 0.4 million Korean adults who initially had no known hypertension or CVD, we found that, unlike other age groups, those aged 70–80 years demonstrated a non-linear association between SBP and IHD mortality. An SBP of 130–139 mm Hg was not associated with increased IHD mortality compared with normal BP (SBP <120 mm Hg). Although an SBP of 130–139 mm Hg was associated with elevated stroke mortality, the overall CVD mortality for an SBP of 130–139 mm Hg increased by only 14%. Furthermore, the association was non-significant in those aged 70–80 years, casting doubt on the appropriateness of incorporating an SBP of 130–139 mm Hg into the definition of hypertension in elderly Koreans.

Regarding the effect of BP on CVD outcomes in the elderly without a previous history of CVD, there have been limited and conflicting results. In the current analysis, a reverse-L-shaped association, with risk elevation beginning at...
approximate an SBP of 140 mm Hg or higher, was observed in the elderly for IHD mortality. This finding differs from that of a previous study conducted by the Prospective Studies Collaboration that exhibited a linear association between BP and CVD (both IHD and stroke) mortality in the elderly. However, a more detailed examination of the data from that study indicates that the association between BP and mortality outcomes was not entirely linear, and that the slope seems to have been flattened in the lower BP range (below 140 mm Hg) in the elderly. Rapsonaniki et al reported non-significant risk elevation for each CVD subtype, including MI, except for stable angina, in the BP range of 115–140 mm Hg among the elderly. Yi et al previously reported that the nadir risk was near an SBP of 100 mm Hg, with increasing risk for higher BPs. However, that study defined the elderly population broadly (60–95 years), thereby including many individuals aged 60–69 years. In the Asia Pacific Cohort Studies Collaboration Study, the slope of the association between SBP and IHD risk seemed to be flattened in the range of baseline SBP <160 mm Hg in the elderly (aged ≥70 years), and the 95%CI of the risk associated with baseline SBP of 120–139 mm Hg and 140–159 mm Hg overlapped that of SBP <120 mm Hg. Additionally, the recent Chinese Multi-provincial Cohort Study exhibited no CVD (including both IHD and stroke) risk association for an SBP of 130–139 mm Hg, compared with normal BP, among the population aged ≥60 years. The results of the Hisayama Study among the Japanese elderly were similar to ours, as the risk of SBP of 130–139 mm Hg for IHD and overall CVD was not significant compared with the reference SBP (<120 mm Hg). Furthermore, our results correspond well with clinical trials among elderly Asians in which a strict BP control strategy failed to improve CVD outcomes.

### Possible mechanisms

It is plausible that compromised coronary autoregulation function coupled with advanced atherosclerosis and left ventricular hypertrophy, which are common findings in the elderly, might lead to hypoperfusion of the myocardium in the setting of low BP. An appropriate level of SBP (not too low) might be required to maintain coronary perfusion in the elderly. Furthermore, other risk factors, such as impaired glucose tolerance or dyslipidaemia, might strongly contribute to the pathology of coronary events in the elderly. In the Hisayama Study, BP was not associated with cardiovascular events when the SBP was <140 mm Hg in the elderly in the low-risk group; however, the concomitant CVD risk turned out to contribute strongly to adverse outcomes. However, it remains necessary to elucidate the precise mechanism underlying the non-linear association between BP and IHD and the less beneficial effect of strict BP control on IHD.
Figure 2  Risk for CVD mortality by SBP category in the overall population, stratified by age. CVD, cardiovascular disease; ICH, intracranial haemorrhage; IHD, ischaemic heart disease; MI, myocardial infarction; SAH, subarachnoid haemorrhage; SBP, systolic blood pressure.
outcomes, which has been found to be especially prominent in the elderly. The possibility of reverse causality may also be considered. However, we rigorously excluded patients with known CVD, and the participants in the current study represented a relatively healthy population capable of visiting a clinic. Furthermore, similar results were obtained after excluding subjects who died within the first 3 years of follow-up.

Other findings
Similar to previous studies, at younger age, the strength of the association between SBP and cause-specific CVD mortality was stronger, and an SBP of 130–139 mm Hg was associated with increased overall and individual CVD mortality. Additional interventional studies are needed to clarify the effect of early management of an SBP of 130–139 mm Hg in the young and middle-aged population in light of cardiovascular benefits, as well as cost-effectiveness and long-term medication use.

Furthermore, our data showed the stroke-prone characteristics of Asian populations, as BP showed a stronger association with stroke than with IHD. Among stroke subtypes, haemorrhagic stroke showed a steeper slope of association than ischaemic stroke, similar to the findings of a study in the China

Figure 3  Shape of the association between SBP and CVD mortality using a restricted cubic spline model. CVD, cardiovascular disease; IHD, ischaemic heart disease; MI, myocardial infarction; SBP, systolic blood pressure.
Kadoorie Biobank population.\textsuperscript{11} However, the study of Lacey \textit{et al} did not distinguish between different subtypes of haemorrhagic stroke. Currently, limited data are available regarding the effects of BP on SAH. In our study, the relationship of SBP with SAH mortality was generally similar among different age groups. Conversely, in the study by Rapsomaniki \textit{et al}, the pattern of association between SBP and SAH was different in the elderly.\textsuperscript{9} It is also noteworthy that the steeper slope of the association for haemorrhagic stroke than for ischaemic stroke was more evident in elderly adults (aged 70–80 years).

**Clinical implications**

SBP is a vital CVD risk factor regardless of age; meanwhile, our research indicates that the ‘lower is better’ concept might not be directly applicable to elderly subjects with an SBP of 130–139 mm Hg, particularly for IHD mortality prevention. Furthermore, the number needed to treat to prevent one death per year from overall CVD, calculated by inverting the age-sex adjusted mortality difference, was high (2118) for a baseline SBP of 130–139 mm Hg, and was 2.5% (95% CI 0.4% to 5.4%) in those aged 70–80 years (online supplementary table 9). This observation raises the concern that it may be ineffective to define an SBP of 130–139 mm Hg as hypertension in elderly individuals with a relatively low risk of CVD from a cost-effectiveness perspective.

**Strengths and limitations**

The current study was a population-based study involving a large number of participants and substantial and complete follow-up, which enabled a thorough evaluation of the age-specific effects of SBP on cause-specific CVD. Our study could serve as a useful reference for identifying SBP-related risks in the general population. Further, the current study provided a detailed classification of the subtypes of stroke (ischaemic, ICH and SAH). Lastly, our results remained robust even after extensively controlling for possible confounders. Several limitations in the present study should be noted. First, the BP measurements could have been less than ideal, because health examination was performed in various centres and BP was evaluated only once at baseline. Thus, the relative risks associated with SBP might have been underestimated due to non-differential misclassification of BP and the regression dilution effect.\textsuperscript{27} Second, the cause of death on Korean death certificates might have been subject to misclassification. However, death certificates have been found to be reasonably valid in comparison with medical records.\textsuperscript{28} In patients with stroke, CT and MRI are routinely performed (>90%) in Korea.\textsuperscript{29} Third, we examined CVD mortality, but not non-fatal events. The associations between BP and mortality might have been different from those between BP and the incidence of non-fatal events. Fourth, our sample exclusively comprised Koreans, limiting the generalisability of our findings to other ethnicities. Lastly, the nature of an observational study limits causal inferences, and our findings therefore cannot directly indicate the most appropriate BP cut-off for initiating BP interventions. However, it could serve as a basis for designing future clinical trials or for setting individualised treatment strategies in the elderly.

**CONCLUSIONS**

In a Korean general population without a previous history of hypertension or CVD, we observed a non-linear relationship between SBP and IHD mortality in the elderly, while we demonstrated that elevated BP is a significant risk factor across all age groups. Furthermore, elderly adults with an SBP of 130–139 mm Hg did not show a significant elevation in mortality from IHD or overall CVD. Given the rapidly growing ageing population, subsequent interventional and/or epidemiological studies would be helpful to clarify whether the initiation of BP interventions at a lower threshold would lead to improvements in various cardiovascular outcomes across age and racial groups.
Cardiac risk factors and prevention


