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Which blood pressure measurement, systolic or diastolic, better predicts future hypertension in normotensive young adults?

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The impact of age-related differences in blood pressure (BP) components on new-onset hypertension is not known. A follow-up examination of 93 303 normotensive individuals (mean age 41.1 years) who underwent a health checkup in 2005 was conducted every year for 8 years. The primary end point was new-onset hypertension (systolic BP [SBP]/diastolic BP [DBP] ≥140/90 mm Hg and/or the initiation of antihypertensive medications with self-reported hypertension). During the mean 4.9 years of follow-up, 14 590 subjects developed hypertension. The impact of DBP on the risk of developing hypertension compared with optimal BP (SBP <120 mm Hg and DBP <80 mm Hg) was significantly greater than that of SBP in subjects younger than 50 years (hazard ratios, 17.5 for isolated diastolic high-normal vs 10.5 for isolated systolic high-normal [*P*<.001]; 8.0 for isolated diastolic normal vs 4.1 for isolated systolic normal [*P*<.001]). Among the subjects 50 years and older, the corresponding effects of DBP and SBP were similar. Regarding the risk of new-onset hypertension, high DBP is more important than SBP in younger adults (<50 years) with normal or high-normal BP.

1 | INTRODUCTION

The worldwide prevalence of hypertension in 2008 was 40% of adults 25 years and older.[1] Hypertension is estimated to cause approximately 13% of all annual deaths.[2] In light of the world's population growth and aging, hypertension is a global public health issue.[3] The prevalence of prehypertension including normal and high-normal blood pressure (BP) has varied from 15% to 59% in previous studies.[4–11] Prehypertension is associated with a higher risk of the future development of hypertension[12–17] and cardiovascular disease (CVD)[18–22] compared with optimal BP in the general population. The reported rates of progression to hypertension during 2 to 4 years of follow-up were 5% to 7% for individuals with optimal BP, 15% to 21% for those with normal BP, and 31% to 43% for people with high-normal BP.[13-15]

Predictors of hypertension subtypes are young age and male sex for isolated diastolic hypertension (IDH) and old age and female sex for isolated systolic hypertension (ISH).[23] A 2015 study in younger and middle-aged adults reported that the relative risk for CVD mortality compared with optimal-normal BP among men was highest for the subjects with systolic diastolic hypertension (SDH), followed by IDH, high-normal BP, and ISH, whereas in women, the risk was highest for those with SDH, followed by ISH.[24] In addition, the impact of slightly higher systolic BP (SBP) in comparison with diastolic BP (DBP) for developing future hypertension, which may result in future CVD, may be different even among individuals with normal BP or high-normal BPs. To our knowledge, however, no study has examined whether SBP or DBP is associated with the risk for the new onset of hypertension by age in subjects with prehypertension (separately for normal BP and high normal BP).

We conducted the present study to assess both the progression rate to hypertension at an 8-year follow-up and the impacts of sex- and age-related differences in BP components on the rate of progression

to hypertension among normotensive subjects who underwent an annual health checkup.

2 | METHODS

2.1 | Study population

In Japan, the Industrial Safety and Health Law requires employers to provide annual health checkups to their employees. We obtained the data of 67% (n=93 303, aged 18–88 years) of the 140 041 Japanese subjects who underwent a health checkup in 2005 (at baseline) at the Genki Plaza Medical Center for Health Care in Tokyo, Japan. The subjects were comprised of members of organizations and employees of companies in Tokyo. Individuals younger than 18 years (n=33), those with no measurement of BP (n=2216), those with hypertension (defined as SBP/DBP ≥140/90 mm Hg and/or the use of antihypertensive medication and/or self-reported hypertension, n=21 870), and those with self-reported cardiac or cerebrovascular disease (n=2132) were excluded from the baseline data. We also excluded the subjects (n=20 487) who did not undergo a further health checkup during the period from 2006 to 2013 (ie, as a follow-up). Figure 1 shows the flow chart of the study subjects. The study was conducted according to the principles of the Declaration of Helsinki.

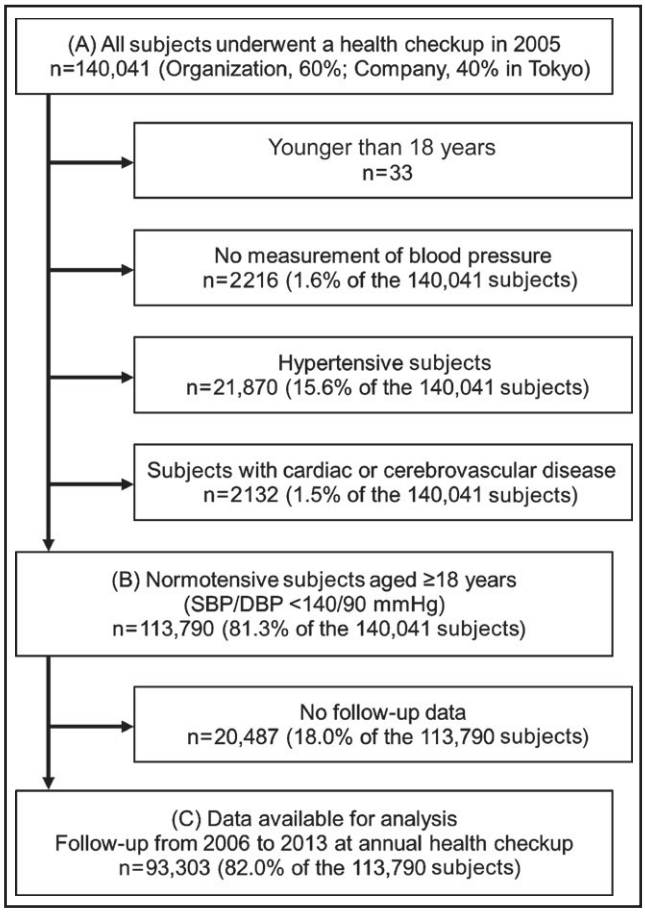

FIGURE 1 Flow chart of study subjects. DBP indicates diastolic blood pressure; SBP, systolic blood pressure

2.2 | Baseline and follow-up measurement

The BP of each subject was measured once by medical staff using a standard mercury sphygmomanometer after the subject had rested for 5 minutes in a seated position. When the SBP was ≥140 mm Hg or the DBP was ≥90 mm Hg, the BP was measured again after the subject took several deep breaths. After this second measurement, the lower BP values were used. We defined the initiation of antihypertensive medications as an answer "yes" to the question "Do you take an antihypertensive drug?" Self-reported hypertension was defined as the subject stating that he or she had been told by a physician that he or she had hypertension. The measured BP was classified as optimal (SBP <120 and DBP <80 mm Hg), normal (SBP 120–129 and/or DBP 80–84 mm Hg), high-normal (SBP 130–139 and/or DBP 85–89 mm Hg), or hypertension (SBP/DBP ≥140/90 mm Hg and/or the use of antihypertensive medications with self-reported hypertension), based on the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2014) criteria.[25]

For the examination of the association between the BP components and the development of hypertension, we reclassified the subjects' BP measurements into the following seven groups: optimal (SBP <120 mm Hg and DBP <80 mm Hg), isolated systolic normal (ISN; SBP 120–129 mm Hg and DBP <80 mm Hg), isolated diastolic normal (IDN; SBP <120 mm Hg and DBP 80–84 mm Hg), systolic diastolic normal (SBP 120–129 mm Hg and DBP 80–84 mm Hg), isolated systolic high-normal (ISHN; SBP 130–139 mm Hg and DBP <85 mm Hg), isolated diastolic high-normal (IDHN; SBP <130 mm Hg and DBP 85–89 mm Hg), and systolic diastolic high-normal (SBP 130–139 mm Hg and DBP 85–89 mm Hg).

The annual health checkup included the subject's medical history, anthropometric measurements, and biochemical measurements. The medical history was self-reported in a questionnaire. Body weight with light clothing and height without shoes were measured by trained staff, and body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). Pulse rate was measured by medical staff after the subjects rested for 5 minutes. Blood samples were collected after overnight fasting and then assayed within 24 hours with an automatic clinical chemical analyzer at a central laboratory. Serum levels of total cholesterol, triglyceride, high-density lipoprotein cholesterol, glycated hemoglobin A_{1c}, and creatinine were measured. For each subjects, a urine sample was collected in the early morning after overnight fasting and was performed by the dipstick method. The urine dipstick results were interpreted by medical staff, and proteinuria was defined as a dipstick test result of 1+ or more.

2.3 | Follow-up and outcomes

In accordance with the Industrial Safety and Health Law in Japan, the subjects underwent annual health checkups from 2006 to 2013 at the Genki Plaza Medical Center for Health Care. The primary end point was new-onset hypertension (SBP/DBP ≥140/90 mm Hg and/or the initiation of antihypertensive medication with self-reported hypertension). The BP measurement procedures were the same as those

used at baseline. The subjects without hypertension at baseline who met any of these conditions in the 2006–2013 follow-up period were considered to have new-onset hypertension. The subjects who were lost to follow-up or who completed the follow-up were treated as censored.

2.4 | Statistical analyses

Values are expressed as the mean±standard deviation or percentages. We tested the statistical differences in the characteristics of the subjects classified by BP category with the *t* test for the slope in linear regression models of the mean values for continuous variables and with the Cochran-Armitage test for trends for categorical variables. First, we estimated the cumulative incidence of hypertension at the 8-year follow-up by the Kaplan-Meier method among the overall subjects (n=93 303). We then estimated the hazard ratios (HRs) and 95% confidence intervals (CIs) of the risk of developing hypertension at the 8-year follow-up by using multiple Cox proportional hazards models adjusted for BP category at baseline and covariates among the subjects (n=57 725; sample sizes reduced due to missing data). The sex- and age-stratified analysis (age <50 vs ≥50 years) was conducted separately. All statistical analyses were performed with SAS version 9.3 software (SAS Institute Inc, Cary, NC, USA). All reported *P* values were two-tailed, and those <.05 were considered significant.

3 | RESULTS

3.1 | Baseline characteristics

There were 93 303 subjects (48 773 men, 44 530 women; mean age 41.1 years) in the present study. A higher prevalence of men; older age; greater BMI and pulse rate values; higher levels of total cholesterol, triglyceride, low-density lipoprotein cholesterol, and hemoglobin A_{1c}; lower levels of high-density lipoprotein cholesterol and estimated glomerular filtration rate; and a higher prevalence of proteinuria were apparent with increases in BP category (Tables S1 to S3).

3.2 | Incidence of hypertension during 8 years of follow-up

During the 8-year follow-up representing 457 396 person-years, 14 590 subjects (10 123 men [10.9% of the overall population] and 4467 women [4.8% of the overall population]) developed hypertension, and the cumulative incidence of hypertension was 22% for the overall subject population. Figure 2 shows the incidence of various forms of developing hypertension by age. The incidence of hypertension was progressively higher with the increase in age (Figure 2). IDH was the most common hypertension subtype in the subjects younger than 50 years (Figure 2). Conversely, ISH was the most common hypertension subtype in the older age groups (Figure 2).

Figure 3 shows the cumulative incidence of hypertension by BP category at baseline. The incidence of hypertension increased with the BP category at baseline (Figure 3A). The incidence of hypertension in the subjects with IDHN was significantly higher than that in the subjects with ISHN (*P*<.001), and the incidence in the subjects with IDN was significantly higher than that in the subjects with ISN (*P*<.001; Figure 3B).

The age-specific cumulative incidence of hypertension by BP category at baseline is shown in Figure 4. The incidence of hypertension for all BP categories at baseline was significantly higher in the subjects 50 years and older compared with those younger than 50 years (all *P*<.005; Figure 4). Among the subjects younger than 50 years, the incidence of hypertension in subjects with IDHN was significantly

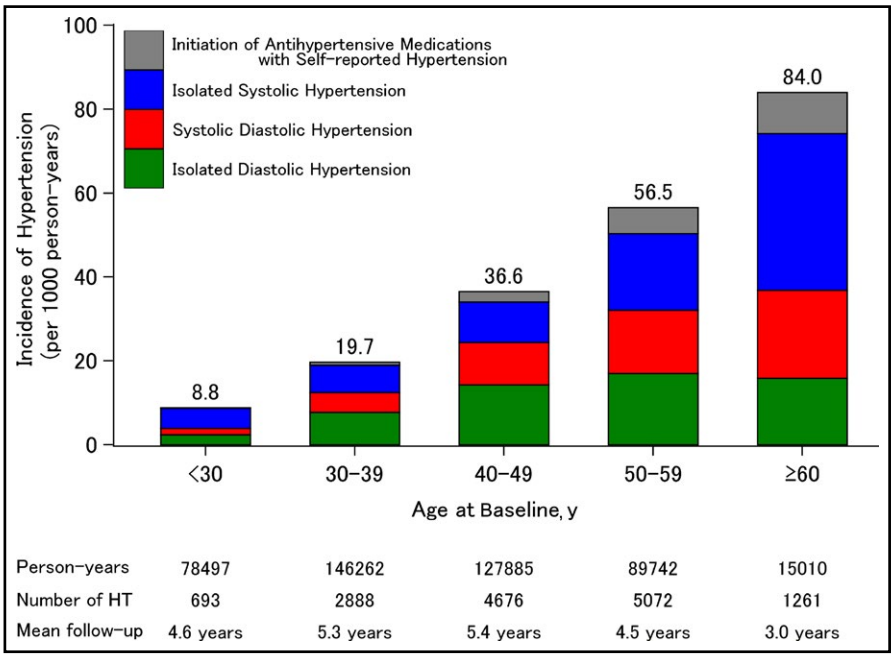

FIGURE 2 Incidence of new-onset hypertension (HT) by age group at baseline and by HT subtype. The number on top of each bar is the incidence of new-onset HT

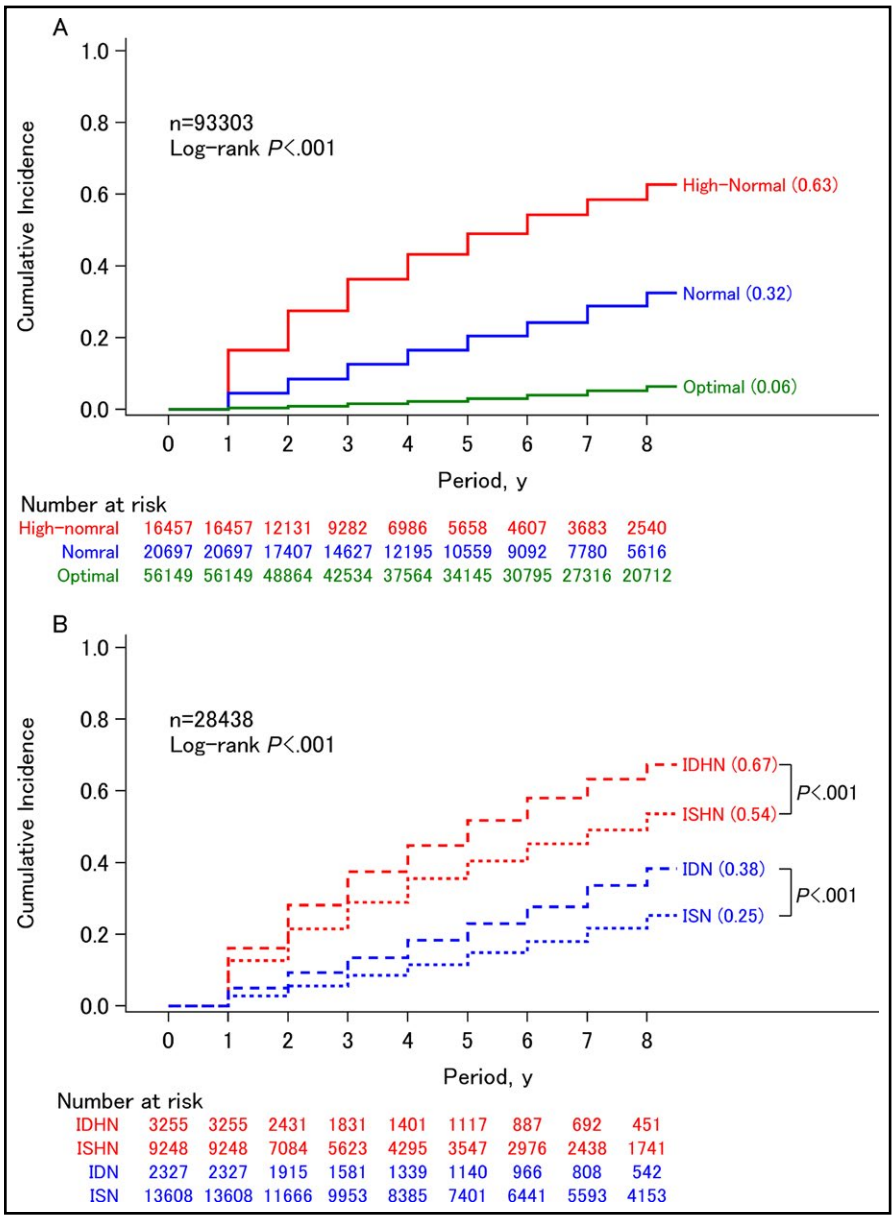

FIGURE 3 Cumulative incidence of hypertension for each normotensive group at baseline. (A) Optimal, normal, and high-normal blood pressure (BP) at baseline. (B) Isolated components with normal and high-normal BP at baseline. The label of each line is the BP category and (in parentheses) the cumulative incidence of hypertension. The log-rank test was used to calculate *P* values. IDHN indicates isolated diastolic high-normal BP; IDN, isolated diastolic normal BP; ISHN, isolated systolic high-normal BP; ISN, isolated systolic normal BP

higher than in those with ISHN (*P*<.001), and the incidence in the IDN subjects was significantly higher than that in the subjects with ISN (*P*<.001; Figure 4A,B).

Among the subjects 50 years and older, the incidence of hypertension in those with IDHN was similar to that in the subjects with ISHN (*P*=.018), and the incidence in the IDN group was similar to that in the ISN group (*P*=.031), although there were statistically but not clinically significant differences (Figure 4C,D). There were no essential sex differences in these associations (data not shown).

3.3 | Risk of developing hypertension

The HRs and 95% CI values for developing hypertension according to BP category at baseline and obtained using a Cox proportional hazards model are plotted in Figure 5 and summarized in Table S4. In the overall analysis adjusted for age, sex, BMI, pulse rate, total cholesterol, high- and low-density lipoprotein cholesterol, and proteinuria, the BP category at baseline compared with optimal BP was significantly associated with the development of hypertension (*P* for trend <.001). In the age-stratified analysis adjusted for sex, BMI, pulse rate, total cholesterol, high- and low-density lipoprotein cholesterol, and proteinuria, the HR for developing hypertension by BP category at baseline compared with optimal BP was significantly greater in the subjects younger than 50 years compared with those 50 years and older (BP category by age interaction *P*<.01).

Among the subjects younger than 50 years, significant differences in the risk of developing hypertension were found between the IDHN and ISHN groups (*P*<.001) and between the IDN and ISN groups (*P*<.001; Figure 5). Among the older subjects (≥50 years), significant differences in the risk of developing hypertension were revealed between IDHN and ISHN (*P*=.013) and between IDN and ISN (*P*=.005), although these were statistically but not clinically significant

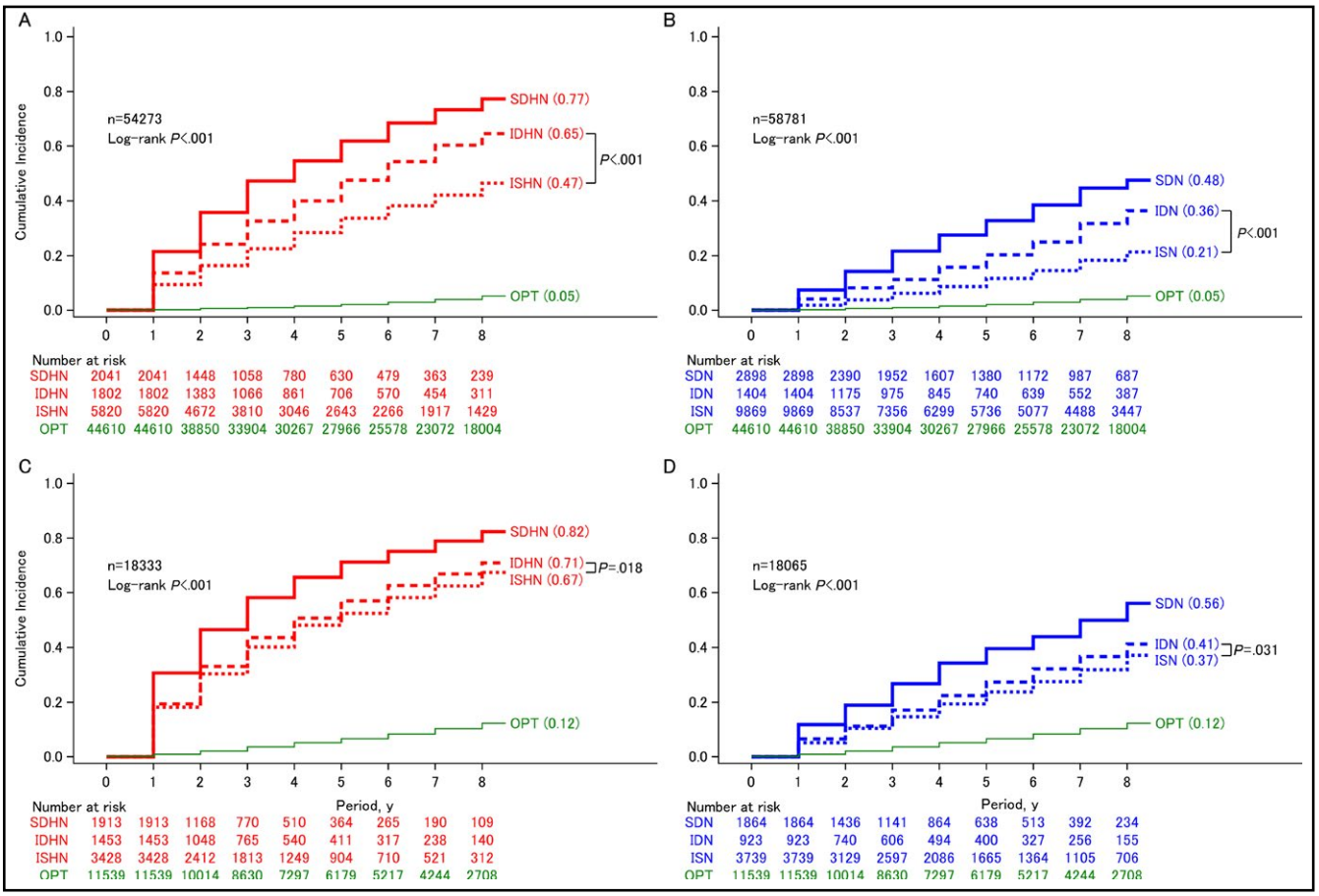

FIGURE 4 Cumulative incidence of hypertension for each normotensive and age group at baseline. (A) Optimal and high-normal blood pressure (BP) at baseline in subjects younger than 50 years. (B) Optimal and normal BP at baseline in subjects younger than 50 years. (C) Optimal and high-normal BP at baseline in subjects 50 years and older. (D) Optimal and normal BP at baseline in subjects 50 years and older. The label of each line is the BP category and (in parentheses) cumulative incidence of hypertension. The log-rank test was used to calculate *P* values. IDHN indicates isolated diastolic high-normal BP; IDN, isolated diastolic normal BP; ISHN, isolated systolic high-normal BP; ISN, isolated systolic normal BP; OPT, optimal BP; SDHN, systolic diastolic high-normal BP; SDN, systolic diastolic normal BP

differences (Figure 5). There was no essential sex difference in these associations (Figures S1 and S2).

The HRs and 95% CI values for developing SDH, IDH, and ISH according to BP category at baseline are shown in Figures S3 and S4. Increased DBP (IDHN and IDN) predicted new-onset IDH and increased SBP (ISHN and ISN) predicted new-onset ISH.

4 | DISCUSSION

4.1 | Major findings

In this 8-year follow-up study of 93 303 Japanese subjects aged 18 to 88 years with no hypertension at baseline, representing 457 396 person-years, the major findings were that the effect of DBP was greater than that of SBP on the risk of developing hypertension associated with normal and high-normal BP compared with optimal BP in the subjects younger than 50 years. The hypertension incidence in our overall population is consistent with prior reports.

4.2 | Prevalence of prehypertension and hypertension

In previous studies, the prevalence of prehypertension varied from 15% to 59%, and the prevalence of hypertension varied from 22% to 44%.[4–11] The prevalence of prehypertension in the present study (32%) was lower than that reported in Nigeria,[4] China,[5] and Iran,[6] which ranged from 52% to 59%, and it was higher than the 15% reported in Turkey.[7] In the other regions and countries, such as Asia[8–10] and the United States,[11] the prevalence of prehypertension ranged from 31% to 33%, which is comparable to our present finding. However, the prevalence of hypertension in the present study (16%) is lower than those of some previous studies.[4–11] Consistent with prior reports,[4,6,7–11] the present study's prehypertension group showed a higher proportion of men and higher values of age, BMI, total cholesterol, triglyceride, low-density lipoprotein cholesterol, and hemoglobin A_{1c}, and lower high-density lipoprotein cholesterol compared with the subjects with optimal BP. To our knowledge, however, no studies have compared the impact of baseline SBP <140 mm Hg vs

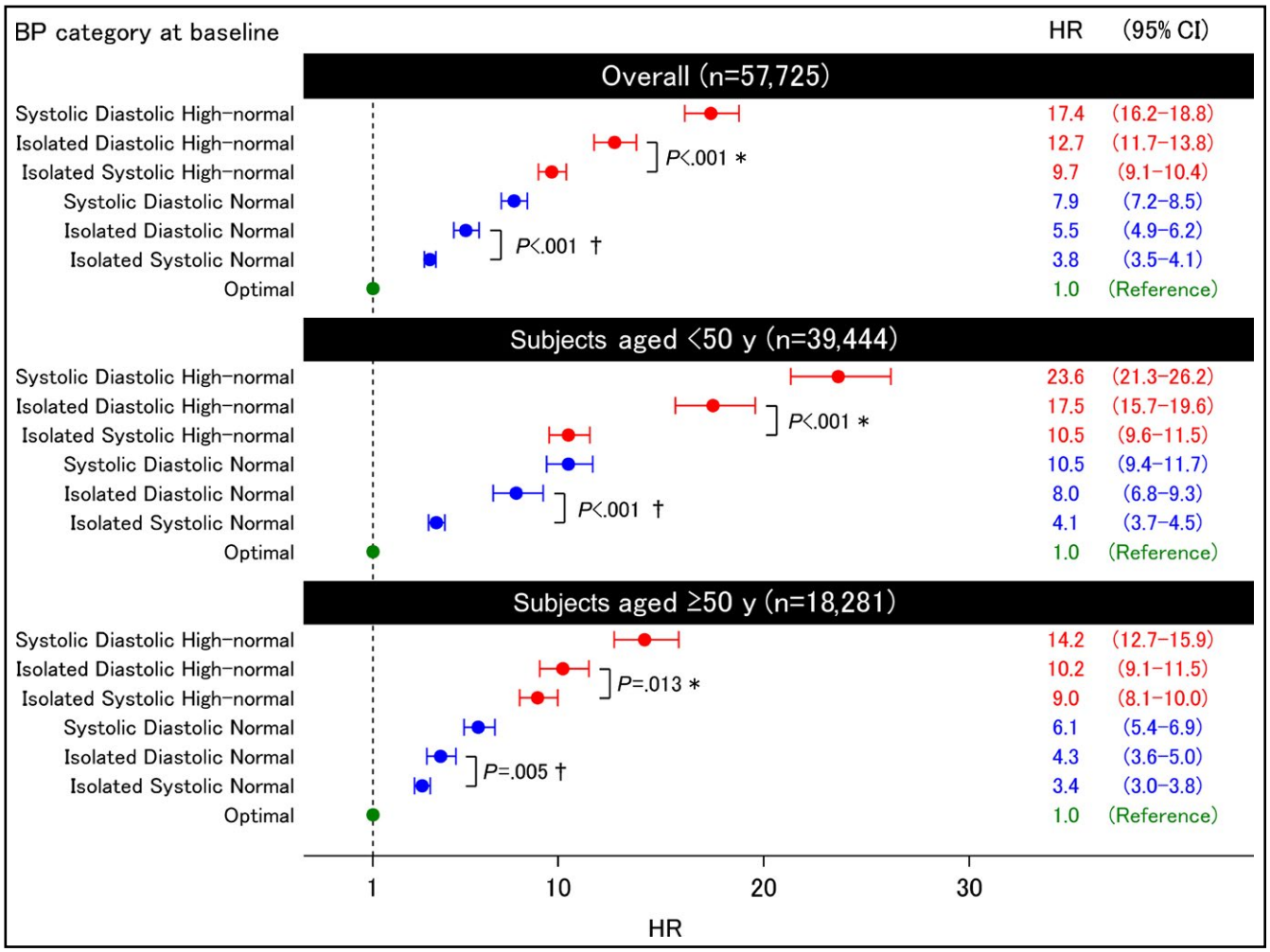

FIGURE 5 Hazard ratio (HR) and 95% confidence interval (CI) for new-onset hypertension by blood pressure (BP) category at baseline and by overall (adjusted for age, sex, body mass index, pulse rate, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and proteinuria), and age group (<50 or ≥50 years, adjusted for sex, body mass index, pulse rate, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and proteinuria). **P* values were calculated using isolated systolic high-normal BP as reference. †*P* values were calculated using isolated systolic normal BP as reference

that of DBP <90 mm Hg separately on the risk of new-onset hypertension in subjects with prehypertension.

4.3 | Rate of progression to hypertension by BP category

Longitudinal associations between baseline BP and the risk for hypertension have been suggested in previous studies.[12–15] Hansen and colleagues[12] reported that among 2357 Danes aged 30 to 60 years, the crude progression rates to hypertension from optimal, normal, and high-normal BP during a median of 10.9 years were 10%, 37%, and 58%, respectively. In other studies, the rates of progression to hypertension during 2- to 4-year follow-up were 5% to 7%, 15% to 21%, and 31% to 43% for optimal, normal, and high-normal BP, respectively.[13–15] Here, we derived 8-year rates of hypertension assuming a constant risk (data not shown), and our results (6%, 32%, and 63% for optimal, normal, and high-normal BP, respectively) are consistent with the previous studies.[12–15]

4.4 | Age-related risk of a new-onset hypertension by BP category

In the present study, the risk of developing hypertension increased with the BP category at baseline (*P* for trend <.001). In the age-stratified analysis, the risk of developing hypertension in accord with the BP category at baseline compared with optimal BP was higher in the subjects younger than 50 years than in those 50 years and older (BP category by age interaction *P*<.01). This is because the incidence of hypertension with optimal BP in our older group was increased via the aging effect. Thus, the relative risk was higher in the younger subjects than in the older subjects, although the absolute risk was higher in the older subjects compared with the younger subjects.

Several studies investigated the relationship between BP category at baseline and the risk of developing hypertension by age in a multivariate analysis.[13,16,17] In the Framingham Heart Study, Vasan and colleagues[13] showed that among 9845 participants aged 35 to 94 years, the odds ratios for developing hypertension among

normal and high-normal BP subjects compared with optimum BP subjects over the 4-year interval were higher in the subjects aged 35 to 64 years (normal BP: odds ratio, 4.1; high-normal BP: odds ratio, 11.6) than those aged 65 to 94 years (normal BP: odds ratio, 2.0; high-normal BP: odds ratio, 5.5). Zhang and colleagues[16] replicated the Framingham Heart Study and showed that the Framingham results can be extrapolated to a Western European population. Winegarden and colleagues[17] showed that among 2048 subjects aged 35 to 74 years (divided into four 10-year age brackets), the tendency of the relative risk of developing hypertension at a 7-year follow-up declined with the increase in age at baseline.

4.5 | Effect of DBP vs SBP on the risk of developing hypertension

To our knowledge, the present study is the first to show that the effect of DBP was greater than that of SBP on the risk of developing hypertension associated with normal and high-normal BP in subjects younger than 50 years (HR=17.5 for IDHN vs HR=10.5 for ISHN, $P<.001$; HR=8.0 for IDN vs HR=4.1 for ISN, $P<.001$). Our results are compatible with previous reports on the associations between BP components and CVD. Parikh and colleagues[26] showed that among 1717 nonhypertensive white individuals aged 20 to 69 years, the multivariable-adjusted HRs for hypertension during the median 3.8-year follow-up were greater for DBP compared with SBP (HR=1.16 and 1.07 for DBP and SBP in increments of 5 mm Hg, respectively), and they suggested that the effect of DBP was more pronounced at younger ages. Franklin and colleagues[27] reported that among 3060 men and 3479 women aged 20 to 79 years, DBP was predictive of coronary heart disease (CHD) risk and SBP was not in subjects younger than 50 years (HRs=1.42 and 0.95, respectively). In the subjects aged 50 to 59 years, neither SBP nor DBP predicted the risk of coronary heart disease. In the subjects 60 years and older, SBP and DBP were predictive of CHD risk (HR=1.24 and 0.83, respectively).

4.6 | Hemodynamic mechanisms

We observed that increased DBP constituted a risk for developing hypertension in subjects younger than 50 years, whereas in the subjects 50 years and older, increased SBP was the risk factor. Although our study could not address the mechanism explaining why the factors of BP elevation differ between younger and older subjects, a plausible explanation might be found in the previous reports. The elevation of DBP is closely related to increased vascular resistance caused by sympathetic nervous activation, which decreases with age.[28] Regarding younger subjects, the population-based Coronary Artery Risk Development in Young Adults (CARDIA) study of subjects aged 18 to 30 years showed that increased heart rate was an independent predictor for increased DBP.[29] Conversely, mainly increased vascular stiffness contributes to elevated BP in elderly subjects. This is because an increase in stiffness of the large arteries is accompanied by early wave reflection, which results in a significant augmentation of central SBP in late systole and further adds to the increased cardiac afterload.[30] The result of this phenomenon could explain the increase in SBP and decrease in DBP in the elderly population. Moreover, recent studies showed that increased SBP variability, which is more closely associated with vascular stiffness,[31,32] was related to age, whereas DBP variability showed no relation to age.[33,34]

4.7 | Study strengths and limitations

The strengths of this study are its very large sample size, the longitudinal follow-up period, and the uniform manner of data collection at a single medical center. However, there were several limitations due to the characteristics of the population and the measurement of the study indices. First, the subjects were not a population sample, and they were generally healthy individuals undergoing a health checkup. Second, the subjects were comprised of members of organizations and employees of companies in Tokyo who might be categorized as middle-class, who might be healthier than the general population in Japan. In addition, there were few subjects older than 70 years. Therefore, the study could have underestimated the incidence of hypertension. Third, a single measure of BP and biochemical measurements by standard methods in each period might not be accurate, which might lead to a misclassification of BP and risk factors. Fourth, because we did not have information about some known and important CVD risk factors such as smoking, alcohol consumption, and physical activity, we could not adjust the analysis for those potential confounding effects. Finally, since the health checkup was conducted only once every year, it is possible that during this interval some subjects had severe disease without the detection of hypertension.

5 | CONCLUSIONS

The novelty of our study is that it clarified the differential age-related impacts of BP components on new-onset hypertension in a large prospective design. In the subjects younger than 50 years, the effect of DBP was much more powerful (by approximately twofold) than that of SBP on the risk of developing hypertension associated with normal and high-normal BP compared with optimal BP, and thus reducing DBP is important to prevent hypertension, whereas in our subjects 50 years and older with normal or high-normal BP, the effects of DBP and SBP were similar. Clinicians should pay much more attention to slight increases in DBP and begin early nonpharmacological intervention in younger adults with DBP >80 mm Hg.

ACKNOWLEDGMENTS

None.

DISCLOSURES

The authors report no specific funding in relation to this research and have no conflicts of interest to disclose.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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