Original Article

# Combined Effect of Blood Pressure and Total Cholesterol Levels on Long-Term Risks of Subtypes of Cardiovascular Death

## Evidence for Cardiovascular Prevention From Observational Cohorts in Japan

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***Abstract***—No large-scale, longitudinal studies have examined the combined effects of blood pressure (BP) and total cholesterol levels on long-term risks for subtypes of cardiovascular death in an Asian population. To investigate these relationships, a meta-analysis of individual participant data, which included 73 916 Japanese subjects (age, 57.7 years; men, 41.1%) from 11 cohorts, was conducted. During a mean follow-up of 15.0 years, deaths from coronary heart disease, ischemic stroke, and intraparenchymal hemorrhage occurred in 770, 724, and 345 cases, respectively. Cohort-stratified Cox proportional hazard models were used. After stratifying the participants by 4 systolic BP ×4 total cholesterol categories, the group with systolic BP ≥160 mm Hg with total cholesterol ≥5.7 mmol/L had the greatest risk for coronary heart disease death (adjusted hazard ratio, 4.39; $P<0.0001$ versus group with systolic BP <120 mm Hg and total cholesterol <4.7 mmol/L). The adjusted hazard ratios of systolic BP (per 20 mm Hg) increased with increases in total cholesterol categories (hazard ratio, 1.52; $P<0.0001$ in group with total cholesterol ≥5.7 mmol/L). Similarly, the adjusted hazard ratios of total cholesterol increased with increases in systolic BP categories ($P$ for interaction ≤0.04). Systolic BP was positively associated with ischemic stroke and intraparenchymal hemorrhage death, and total cholesterol was inversely associated with intraparenchymal hemorrhage, but no significant interactions between BP and total cholesterol were observed for stroke. High BP and high total cholesterol can synergistically increase the risk for coronary heart disease death but not for stroke in the Asian population. **(*Hypertension*. 2015;65:00-00. DOI: 10.1161/HYPERTENSIONAHA.114.04639.)**
● **Online Data Supplement**

**Key Words:** Asia ■ coronary disease ■ epidemiology ■ hypercholesterolemia ■ hypertension ■ meta-analysis ■ stroke

Previous cohort studies in Western countries demonstrated that high total cholesterol levels strengthened the association between high blood pressure (BP) and the risk for death from coronary heart disease (CHD).[1–3] However, the research group of the Asia Pacific Cohort Studies Collaboration (APCSC) reported that the positive associations of BP with the risk for CHD was weaker in the group with higher cholesterol levels than in those with lower cholesterol levels.[4] Because the APCSC study was based on a population including not only whites from Australia and New Zealand but also

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**The online-only Data Supplement is available with this article at http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYPERTENSIONAHA.114.04639/-/DC1.**

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**Table 1. Baseline Characteristics in Each Systolic BP-Total Cholesterol Group**

| Characteristic | Systolic BP, mm Hg | | | | All |
|---|---|---|---|---|---|
| | <120 | 120–139 | 140–159 | ≥160 | |
| Total cholesterol, mmol/L | | | | | |
| <4.7 | | | | | |
| n | 6022 | 8839 | 4493 | 2056 | 21410 |
| Men, % | 41.4 | 54.4 | 59.9 | 62.3 | 52.7 |
| Age, y | 52.6±10.2 | 56.3±10.8 | 60.5±10.5 | 63.6±10.5 | 56.9±11.1 |
| Body mass index, kg/m$^2$ | 21.8±2.7 | 22.6±2.9 | 22.9±3.1 | 22.9±3.2 | 22.5±3.0 |
| Current smoker, % | 29.6 | 33.8 | 35.8 | 38.7 | 33.5 |
| Current drinker, % | 28.9 | 30.6 | 32.7 | 34.6 | 31.0 |
| Systolic BP, mm Hg | 108.8±7.1 | 128.5±5.9 | 147.1±5.7 | 171.5±12.5 | 131.0±20.1 |
| Diastolic BP, mm Hg | 68.3±8.0 | 77.6±8.4 | 85.2±9.3 | 92.9±11.6 | 78.1±11.7 |
| Total cholesterol, mmol/L | 4.1±0.4 | 4.1±0.4 | 4.1±0.4 | 4.1±0.4 | 4.1±0.4 |
| 4.7–5.1 | | | | | |
| n | 4241 | 6651 | 3510 | 1530 | 15932 |
| Men, % | 36.9 | 44.9 | 47.8 | 49.7 | 43.9 |
| Age, y | 53.3±9.8 | 56.5±10.3 | 60.5±10.1 | 63.3±10.0 | 57.2±10.6 |
| Body mass index, kg/m$^2$ | 22.2±2.8 | 23.0±2.9 | 23.5±3.2 | 23.7±3.5 | 23.0±3.1 |
| Current smoker, % | 24.9 | 26.2 | 25.5 | 28.6 | 25.9 |
| Current drinker, % | 28.2 | 29.1 | 28.0 | 30.8 | 28.8 |
| Systolic BP, mm Hg | 109.0±6.9 | 128.8±5.9 | 147.0±5.6 | 171.9±12.9 | 131.7±19.9 |
| Diastolic BP, mm Hg | 68.8±8.0 | 78.2±8.3 | 85.9±9.1 | 93.3±11.6 | 78.8±11.6 |
| Total cholesterol, mmol/L | 4.9±0.1 | 4.9±0.1 | 4.9±0.1 | 4.9±0.1 | 4.9±0.1 |
| 5.2–5.6 | | | | | |
| n | 3682 | 6360 | 3469 | 1497 | 15008 |
| Men, % | 33.7 | 39.2 | 39.8 | 40.0 | 38.1 |
| Age, y | 54.3±9.7 | 57.2±9.9 | 60.9±9.7 | 63.0±9.8 | 57.9±10.2 |
| Body mass index, kg/m$^2$ | 22.4±2.8 | 23.4±3.0 | 24.0±3.2 | 24.0±3.4 | 23.4±3.1 |
| Current smoker, % | 21.5 | 22.7 | 20.8 | 22.8 | 21.9 |
| Current drinker, % | 28.3 | 28.8 | 26.0 | 29.1 | 28.1 |
| Systolic BP, mm Hg | 109.1±6.9 | 128.8±5.8 | 147.2±5.6 | 171.5±12.8 | 132.5±19.8 |
| Diastolic BP, mm Hg | 69.4±8.0 | 78.5±8.3 | 85.7±9.3 | 93.5±11.9 | 79.4±11.5 |
| Total cholesterol, mmol/L | 5.4±0.1 | 5.4±0.1 | 5.4±0.1 | 5.4±0.2 | 5.4±0.1 |
| ≥5.7 | | | | | |
| n | 4735 | 8950 | 5399 | 2482 | 21566 |
| Men, % | 27.3 | 31.5 | 29.3 | 28.2 | 29.6 |
| Age, y | 55.6±9.1 | 58.2±9.4 | 61.0±9.3 | 63.3±9.4 | 58.9±9.6 |
| Body mass index, kg/m$^2$ | 22.8±2.9 | 23.7±3.1 | 24.2±3.2 | 24.7±3.5 | 23.8±3.2 |
| Current smoker, % | 19.8 | 18.7 | 17.1 | 16.0 | 18.2 |
| Current drinker, % | 24.8 | 25.3 | 22.4 | 22.2 | 24.1 |
| Systolic BP, mm Hg | 109.6±6.8 | 129.2±5.9 | 147.3±5.7 | 171.3±12.2 | 134.3±19.9 |
| Diastolic BP, mm Hg | 69.9±8.0 | 78.9±8.4 | 85.9±9.3 | 93.7±11.8 | 80.4±11.6 |
| Total cholesterol, mmol/L | 6.3±0.6 | 6.3±0.6 | 6.4±0.6 | 6.4±0.7 | 6.3±0.6 |
| All | | | | | |
| n | 18680 | 30800 | 16871 | 7565 | 73916 |
| Men, % | 35.3 | 42.5 | 43.4 | 44.2 | 41.1 |
| Age, y | 53.9±9.8 | 57.1±10.1 | 60.7±9.9 | 63.3±9.9 | 57.7±10.4 |
| Body mass index, kg/m$^2$ | 22.3±2.8 | 23.2±3.0 | 23.7±3.2 | 23.9±3.5 | 23.1±3.1 |
| Current smoker, % | 24.5 | 25.5 | 24.6 | 26.1 | 25.1 |

(*Continued*)

**Table 1. Continued**

| Characteristic | Systolic BP, mm Hg | | | | All |
|---|---|---|---|---|---|
| | <120 | 120–139 | 140–159 | ≥160 | |
| Current drinker, % | 27.6 | 28.3 | 27.1 | 28.7 | 27.9 |
| Systolic BP, mm Hg | 109.1±7.0 | 128.8±5.9 | 147.2±5.7 | 171.5±12.5 | 132.4±20.0 |
| Diastolic BP, mm Hg | 69.1±8.0 | 78.3±8.4 | 85.7±9.3 | 93.4±11.7 | 79.2±11.7 |
| Total cholesterol, mmol/L | 5.1±0.9 | 5.2±0.9 | 5.3±1.0 | 5.3±1.0 | 5.2±1.0 |

The analyses included 73 916 Japanese from 11 cohorts. Data are shown as mean±SD for continuous variables. BP indicates blood pressure.

Asians,[4] ethnic heterogeneity could have contributed to the inconsistent results of the combined effects of BP and total cholesterol. Although the Suita study reported the combined effect of total cholesterol and BP levels on the risk for CHD in a Japanese population, the relatively small sample size and the small number of events limit the interpretation of the results.[5]

Asian populations have a higher incidence of stroke and a lower incidence of CHD than Western populations.[6] Although it is well reported that high BP is a strong risk factor for ischemic stroke or intraparenchymal hemorrhage,[4,5,7] there remains debate about the inverse association between total cholesterol and an increased risk for intraparenchymal hemorrhage, which was mainly reported by Japanese cohorts.[8–14] Furthermore, there is limited information on the combined effect of BP and total cholesterol levels on the risk for subtypes of stroke, especially for intraparenchymal hemorrhage.[4,5]

Although these issues remain unsolved, there has been no large-scale, longitudinal study examining the combined effects of BP and total cholesterol levels on the risk for subtypes of cardiovascular disease (CVD) in an exclusively Asian population. The objective of the present study was to examine these points by conducting a meta-analysis of the individual participant data (meta-analysis), which included Japanese cohorts enrolled in the Evidence for Cardiovascular Prevention from Observational Cohorts in Japan (EPOCH–JAPAN).

## Methods

### Study Populations

The construction of the EPOCH–JAPAN database has been described previously.[15] Figure S1 in the online-only Data Supplement shows cohort and participant selection. Finally, 73 916 participants from 11 cohorts (Ohsaki, Ohasama, Oyabe, YKK workers, Suita, RERF cohort, Hisayama, JACC, NIPPON DATA 80, NIPPON DATA 90, and Osaka; Table S1) were included the present analyses. The details are provided in the online-only Data Supplement.

### Data Collection and Outcomes

BP was measured using a mercury sphygmomanometer when each participant was in a seated position, except for the Ohasama study[16] in which an automated device was used. Serum total cholesterol levels were measured enzymatically in all cohorts, with the exception of the NIPPON DATA80 cohort.[17]

The underlying causes of death were coded according to the Ninth *International Classification of Disease* (*ICD-9*) to the end of 1994 and the 10th *International Classification of Disease* (*ICD-10*) from the beginning of 1995.

The details are provided in the online-only Data Supplement.

### Statistical Analysis

The participants were classified into 4 categories according to their systolic BP levels (120, 120–139, 140–159, and ≥160 mm Hg) and further classified into 4 groups according to their total cholesterol levels (<4.7, 4.7–5.1, 5.2–5.6, and ≥5.7 mmol/L). Multivariable adjusted hazard ratios for death from CHD, ischemic stroke, intraparenchymal hemorrhage, or total CVD in each systolic BP-total cholesterol category were estimated. Then, cohort-stratified Cox proportional hazard models, which accounted for the variability of baseline hazards among cohorts, with reference to the group with systolic BP <120 mm Hg with total cholesterol <4.7 mmol/L, were used. Covariates included in the model were sex, age, body mass index, former smoking, current smoking, former drinking, and current drinking. The adjusted hazard ratios per 1 SD increase in systolic BP or total cholesterol after stratifying the participants according to the total cholesterol categories and the systolic BP categories, respectively, were also calculated. The details are provided in the online-only Data Supplement.

## Results

Table 1 shows the baseline characteristics according to the combination of 4 systolic BP categories and 4 total cholesterol categories. Significant differences among the groups were observed in all characteristics ($P<0.0001$).

During a mean follow-up of 15.0 years (median [25th–75th percentiles], 15.0 [12.7–19.3]; maximum: 24.0 years), deaths from total CVD occurred in 3696 participants. Total CVD deaths were because of CHD in 770 and total stroke in 1587 (ischemic stroke in 724 and intraparenchymal hemorrhage in 345). Table 2 shows the numbers of deaths and the sex- and age-adjusted death rates per 1000 person-year in each group. Figure (A) indicates the adjusted hazard ratios for deaths from CHD in each group (the corresponding 95% confidence intervals are shown in Table S2). Among the 16 groups, the group with systolic BP ≥160 mm Hg with total cholesterol ≥5.7 mmol/L had the greatest risk for CHD death (adjusted hazard ratio [95% confidence interval], 4.39 [2.68–7.18]; $P<0.0001$ versus group with systolic BP <120 mm Hg and total cholesterol <4.7 mmol/L; Figure [A]). In relation to the risk for stroke death, stepwise relationships were observed between systolic BP and the risk for ischemic stroke death and intraparenchymal hemorrhage death, whereas total cholesterol was inversely associated with the risk for intraparenchymal hemorrhage death (Figure [B] and [C]). The greatest risk for total CVD death was observed in the group with systolic BP ≥160 mm Hg with total cholesterol ≥5.7 mmol/L (Figure [D]). When all of the analyses were repeated using diastolic BP instead of systolic BP, similar results were obtained (Table S3).

Each 1 SD increase in systolic BP (20.0 mm Hg) was significantly associated with an increased risk for CHD death

**Table 2. Numbers of Deaths (Sex- and Age-Standardized Death Rates, per 1000 Person-Years*) in Each Group According to Systolic BP-Total Cholesterol Levels**

| | | Systolic BP, mm Hg | | | |
|---|---|---|---|---|---|
| Category | End Point | <120 | 120–139 | 140–159 | ≥160 |
| Total cholesterol, mmol/L | | | | | |
| <4.7 | CHD | 21 (0.4) | 72 (0.6) | 64 (0.9) | 41 (1.1) |
| 4.7–5.1 | | 17 (0.5) | 52 (0.6) | 54 (0.9) | 36 (1.2) |
| 5.2–5.6 | | 14 (0.4) | 50 (0.6) | 56 (1.0) | 38 (1.5) |
| ≥5.7 | | 13 (0.3) | 75 (0.7) | 87 (1.1) | 80 (2.0) |
| <4.7 | Ischemic stroke | 28 (0.6) | 68 (0.7) | 77 (1.0) | 74 (1.9) |
| 4.7–5.1 | | 15 (0.5) | 46 (0.6) | 48 (0.8) | 45 (1.5) |
| 5.2–5.6 | | 10 (0.3) | 37 (0.4) | 47 (0.8) | 46 (1.6) |
| ≥5.7 | | 18 (0.5) | 55 (0.5) | 63 (0.7) | 47 (1.2) |
| <4.7 | Intraparenchymal hemorrhage | 18 (0.3) | 51 (0.4) | 45 (0.7) | 32 (1.0) |
| 4.7–5.1 | | 8 (0.2) | 20 (0.3) | 29 (0.5) | 20 (0.7) |
| 5.2–5.6 | | 5 (0.1) | 16 (0.2) | 20 (0.3) | 19 (0.7) |
| ≥5.7 | | 5 (0.1) | 14 (0.1) | 22 (0.3) | 21 (0.5) |
| <4.7 | CVD | 147 (2.8) | 402 (3.6) | 352 (4.9) | 289 (8.0) |
| 4.7–5.1 | | 81 (2.3) | 246 (3.0) | 252 (4.3) | 184 (6.3) |
| 5.2–5.6 | | 69 (2.0) | 222 (2.7) | 238 (4.2) | 184 (6.8) |
| ≥5.7 | | 76 (1.6) | 296 (2.6) | 357 (4.1) | 301 (7.4) |

The analyses included 73 916 Japanese from 11 cohorts. BP indicates blood pressure; CHD, coronary heart disease; and CVD, cardiovascular disease.
*Death rates were standardized by the direct method for sex and age (<50, 50–64, and ≥65 y).

($P$<0.0001; Table 3). The adjusted hazard ratio of systolic BP for CHD death increased gradually with increases in total cholesterol categories ($P$ for interaction=0.04; Table 3). Similarly, each 1 SD increase in total cholesterol levels (=1.0 mmol/L) was significantly associated with CHD death, and the adjusted hazard ratio increased with increases in systolic BP categories ($P$ for interaction=0.0006; Table 4). A higher systolic BP was significantly associated with an increased risk for ischemic stroke death or intraparenchymal hemorrhage death, whereas total cholesterol was inversely associated with intraparenchymal hemorrhage death. There were no significant interactions between systolic BP and total cholesterol levels on the risk for ischemic stroke death or intraparenchymal hemorrhage death ($P$ for interaction ≥0.09; Tables 3 and 4). Total cholesterol levels were inversely associated with total CVD in the group with systolic BP <120 mm Hg, but they were positively associated with total CVD in the group with systolic BP ≥160 mm Hg ($P$ for interaction=0.0006; Table 4).

Similar results were obtained after excluding the first 3 years (Table S4). There were no significant interactions between sex (men/women), as well as age (<65/≥65 years), and the 16 categories on the risk for CHD death (Table S5), ischemic stroke death (Table S6), and intraparenchymal hemorrhage death (Table S7; $P$ for interaction ≥0.06). The association between higher systolic BP and higher total cholesterol and the risk for total CVD death was marked in participants aged <65 years and men ($P$ for interaction ≤0.03; Table S8), but it was weak in participants aged ≥65 or ≥75 years and in women (Tables S8 and S9). There were no significant interactions when stratified analyses according to the use of antihypertensive agents were done among participants with information on antihypertensive treatments (n=37 326; $P$ for interaction ≥0.09). After including 5407 individuals without history of CVD and without data on body mass index or smoking or drinking status, similar results were observed (Table S10). Table S11 shows the results when including systolic BP and total cholesterol in the same model.

In the analyses of Tables 3 and 4, the highest heterogeneity was observed in the analysis of the association between total cholesterol and the risk for total CVD death ($I^2$=61.6; $P$=0.007), whereas heterogeneity across cohorts was low or modest for most analyses ($0 \le I^2 \le 58.5\%$; $P \ge 0.01$).

## Discussion

This is one of the largest epidemiological studies with long follow-up demonstrating the risks for subtypes of cardiovascular death according to BP and total cholesterol levels in an Asian population.

The positive association between BP and the risk for CHD death was greater in individuals with higher total cholesterol levels than in those with lower levels in the present study. The association between total cholesterol and the risk for CHD death was clearer in the group with higher systolic BP. The previous studies in 19 189 Americans aged 40 to 64 years[1] or in 193 810 French people aged 18 to 55 years[2] reported a greater risk for CHD mortality in people with higher BP combined with higher total cholesterol levels. The Multiple Risk Factor Intervention Trial (MRFIT) also demonstrated the graded association between total cholesterol (from 4.65 mmol/L [180 mg/dL]) or systolic BP (from 110 mm Hg) and the risk for CHD death.[3] Although similar tendencies were observed in the APCSC study, they reported that the association of systolic

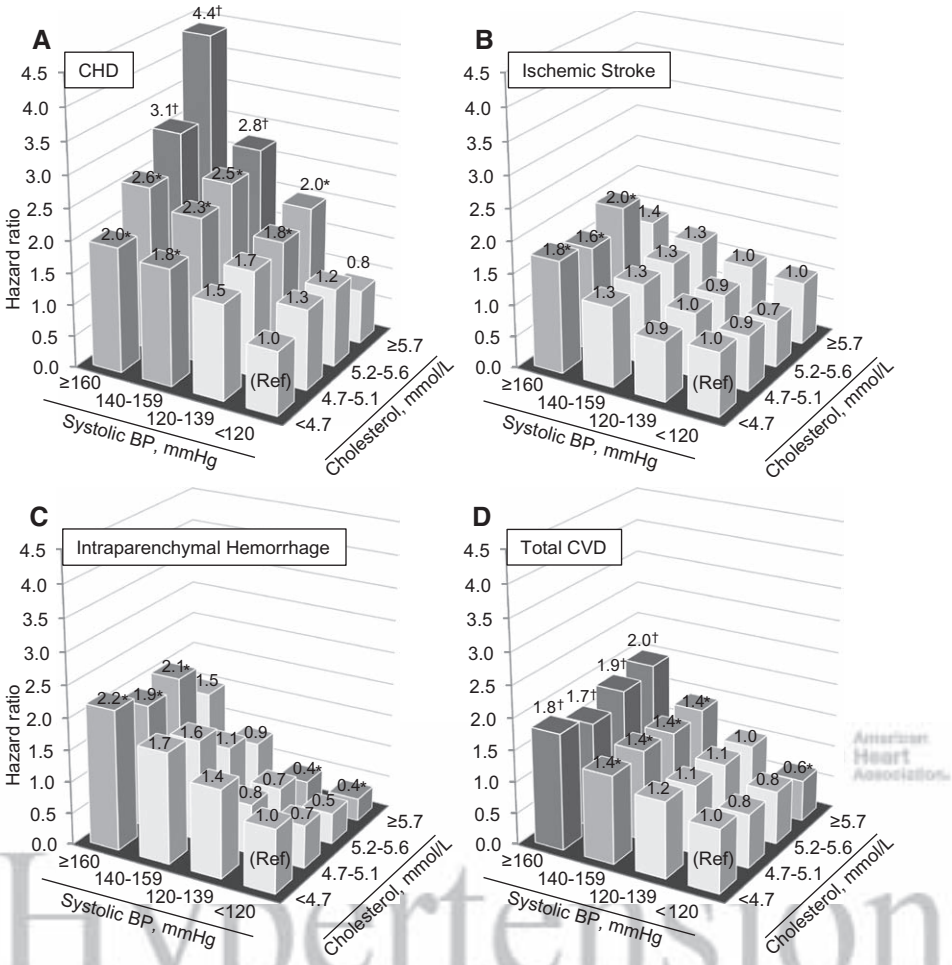


**Figure.** Adjusted hazard ratios for death from (**A**) coronary heart disease (CHD), (**B**) ischemic stroke, (**C**) intraparenchymal hemorrhage, and (**D**) total cardiovascular disease (CVD) in each group according to the levels of systolic blood pressure (BP) and total cholesterol were calculated using cohort-stratified Cox proportional hazards models. All analyses were stratified by cohort. The analyses included 73 916 Japanese people from 11 cohorts. Covariates were sex, age, body mass index, former smoking, current smoking, former drinking, and current drinking. **P*<0.05, †*P*<0.0001 vs group with systolic BP <120 mm Hg with total cholesterol <4.7 mmol/L.

BP with the risk for CHD death was steeper in individuals with lower cholesterol levels than in those with higher levels, in contrast to the present findings.[4] The variation in results between the APCSC study and the present study might be partly caused by the differences in mean follow-up duration (6.7 versus 15.0 years) or ethnic heterogeneity (population from Asian and Australasian regions versus only a Japanese population).[4] The impact of metabolic syndrome factors on the

**Table 3. Adjusted Hazard Ratios per 1 SD Increase in Systolic BP for Subtypes of CVD Death**

| | Adjusted Hazard Ratios (95% Confidence Intervals) per 1 SD Increase in Systolic BP | | | |
|---|---|---|---|---|
| Category | CHD | Ischemic Stroke | Intraparenchymal Hemorrhage | Total CVD |
| All participants | 1.36 (1.27–1.45)* | 1.20 (1.12–1.28)* | 1.43 (1.30–1.58)* | 1.27 (1.23–1.31)* |
| Subgroups | | | | |
| Total cholesterol, mmol/L | | | | |
| <4.7 | 1.24 (1.09–1.42)† | 1.26 (1.12–1.41)† | 1.35 (1.16–1.57)† | 1.24 (1.18–1.31) * |
| 4.7–5.1 | 1.26 (1.09–1.46)† | 1.18 (1.01–1.37)† | 1.29 (1.05–1.59)† | 1.21 (1.13–1.29)* |
| 5.2–5.6 | 1.36 (1.17–1.58)* | 1.26 (1.08–1.48)† | 1.53 (1.22–1.91)† | 1.29 (1.20–1.38)* |
| ≥5.7 | 1.52 (1.36–1.71)* | 1.11 (0.96–1.28) | 1.72 (1.38–2.14)* | 1.36 (1.28–1.44)* |
| *P* for interaction | 0.04 | 0.3 | 0.09 | 0.008 |

Hazard ratios were adjusted for sex, age, body mass index, former smoking, current smoking, former drinking, and current drinking. All analyses were stratified by cohort. The analyses included 73 916 Japanese from 11 cohorts. One SD of systolic BP is 20.0 mm Hg. BP indicates blood pressure; CHD, coronary heart disease; CVD, cardiovascular disease.

**P*<0.0001 and †*P*<0.05.

**Table 4. Adjusted Hazard Ratios per 1 SD Increase in Total Cholesterol for Subtypes of CVD Death**

| | Adjusted Hazard Ratios (95% Confidence Intervals) per 1 SD Increase in Total Cholesterol | | | |
|---|---|---|---|---|
| Category | CHD | Ischemic Stroke | Intraparenchymal Hemorrhage | Total CVD |
| All participants | 1.25 (1.16–1.34)* | 1.00 (0.92–1.09) | 0.75 (0.67–0.85)* | 1.00 (0.96–1.03) |
| Subgroups | | | | |
| Systolic BP, mm Hg | | | | |
| <120 | 0.94 (0.71–1.23) | 0.97 (0.75–1.26) | 0.60 (0.41–0.89)† | 0.84 (0.75–0.94)† |
| 120–139 | 1.19 (1.05–1.35)† | 0.97 (0.83–1.12) | 0.70 (0.56–0.88)† | 0.94 (0.88–1.00)† |
| 140–159 | 1.13 (1.00–1.29) | 1.03 (0.90–1.18) | 0.73 (0.59–0.90)† | 1.01 (0.95–1.08) |
| ≥160 | 1.50 (1.33–1.69)* | 0.99 (0.86–1.16) | 0.86 (0.68–1.07) | 1.08 (1.01–1.16)† |
| *P* for interaction | 0.0006 | 0.9 | 0.3 | 0.0006 |

Hazard ratios were adjusted for sex, age, body mass index, former smoking, current smoking, former drinking, and current drinking. All analyses were stratified by cohort. The analyses included 73 916 Japanese from 11 cohorts. One SD of total cholesterol is 1.0 mmol/L. BP indicates blood pressure; CHD, coronary heart disease; and CVD, cardiovascular disease.

*$P<0.0001$ and †$P<0.05$.

risk of CVD has been reported to differ between the population in the United States and that in Japan.[18] The present findings suggest that, in the Asian population, high BP and high total cholesterol levels may synergistically interact to increase the risk of CHD death. This may partly support the response-to-injury hypothesis[19] or the inflammation hypothesis,[20] that is, both vascular injury by hypertension and lipid deposition may be necessary for CHD.

There was no significant synergistic effect of systolic BP and total cholesterol levels on the risk for ischemic stroke death. Similar to the results of the previous study,[21] no significant association between total cholesterol and the risk of ischemic stroke death was observed. However, the mechanisms related to the risk for cardioembolic infarction are thought to differ from those for atherothrombotic infarction,[12,22] and cardioembolic infarctions are more common in Japanese than Western populations.[12] Therefore, the same conclusion may not apply to the risk of atherothrombotic infarction death.

Similar to the present finding, the inverse association between total cholesterol and intraparenchymal hemorrhage death was also reported by previous studies in Japanese populations[8–12] or non-Japanese[13,14] or and by a recent meta-analysis based on 19 European or Asian cohorts.[23] The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial, which had stroke as the primary end point, demonstrated that hemorrhage was more frequent in patients treated with statins, especially in those with a history of hemorrhage or hypertension.[24] There are several hypotheses for this issue,[25] which has been raised in a National Heart, Lung, and Blood Institute Conference.[26] First, low total cholesterol levels may reflect malnutrition or poor general condition, which relates to death after onset, not to onset per se, because a clear association between low cholesterol and hemorrhage tends to be observed in epidemiological studies having mortality as an end point.[9,13,14,27,28] Second, some remaining confounding factors such as socioeconomic status, nutrient balance, or excess alcohol intake might exist. These hypotheses suggest that low total cholesterol itself may not cause hemorrhage. Further studies taking into account nonfatal events and residual confounding factors are needed to examine these possibilities. The third hypothesis is that low total cholesterol may induce angionecrosis, especially with the coexistence of hypertension. However, this was not proven by the present study because there was no significant interaction between BP and total cholesterol on the risk for intraparenchymal hemorrhage stoke death (Tables 3 and 4). This result is similar to previous findings of the Ibaraki Prefectural Health Study.[9]

In relation to the risk for total CVD, the combined effect of systolic BP and total cholesterol level was remarkable among men or participants aged <65 years in the present study (Tables S8 and S9). Similar tendencies have been reported by the APCSC and the French study.[2,4] Therefore, the present findings suggest that, also in Asian populations, the impact of the joint effect of BP and total cholesterol on the risk for total CVD would be greater in men or in a younger population.

The present findings must be interpreted within the context of their potential limitations. First, the use of cholesterol-lowering therapy, including statins, was not taken into account because the information on cholesterol-lowering therapy was available in only 10 153 participants (13.7%). However, baseline surveys in 11 cohorts of EPOCH–JAPAN were mostly performed before 1989, which is when statin use started in Japan. Therefore, it is less likely that the use of statins at baseline affected the present findings. Second, BP and total cholesterol levels were measured at the beginning of the follow-up period, and regression dilution bias was not taken into account.[29] Participants might have been reclassified if they had been examined during the follow-up period. Third, we excluded several cohorts without data on CVD outcomes or on history of CVD. Furthermore, the methods of BP measurement and ascertainment of events were not identical among cohorts. This was taken into account by considering the cohort as strata in the Cox proportional hazard models.[30] However, the interactions between BP and total cholesterol on the risk for death from CVD or its subtypes might partly be affected by the heterogeneity in the cohorts' characteristics. Fourth, the present study predominantly included a middle-aged and older Asian population. This limits the generalizability of our findings. Fifth, we did not consider the low- or high-density lipoprotein and triglyceride levels. These lipids have different effects on the prothrombotic tendency, atherosclerosis, or CVD. Further studies considering the detailed lipid status are

needed. Finally, the EPOCH–JAPAN database did not have data on any nonfatal CVD events at the time of writing this report.

### Perspective

People with higher BP and higher total cholesterol levels had the greatest risk for CHD death. Furthermore, there was a synergistic interaction between higher BP and higher total cholesterol levels for the risk for CHD death but not for stroke. These results suggest that poor lipid management may increase the adverse effect of high BP on CHD risk and vice versa in the Asian population.

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## Disclosures

None.

## References

1. Lowe LP, Greenland P, Ruth KJ, Dyer AR, Stamler R, Stamler J. Impact of major cardiovascular disease risk factors, particularly in combination, on 22-year mortality in women and men. *Arch Intern Med*. 1998;158:2007–2014.
2. Thomas F, Bean K, Guize L, Quentzel S, Argyriadis P, Benetos A. Combined effects of systolic blood pressure and serum cholesterol on cardiovascular mortality in young (<55 years) men and women. *Eur Heart J*. 2002;23:528–535. doi:10.1053/euhj.2001.2888.
3. Neaton JD, Wentworth D. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease. Overall findings and differences by age for 316,099 white men. Multiple Risk Factor Intervention Trial Research Group. *Arch Intern Med*. 1992;152:56–64.
4. Asia Pacific Cohort Studies Collaboration. Joint effects of systolic blood pressure and serum cholesterol on cardiovascular disease in the Asia Pacific region. *Circulation*. 2005;112:3384–3390.
5. Tsukinoki R, Okamura T, Watanabe M, Kokubo Y, Higashiyama A, Nishimura K, Takegami M, Murakami Y, Okayama A, Miyamoto Y. Blood pressure, low-density lipoprotein cholesterol, and incidences of coronary artery disease and ischemic stroke in Japanese: the Suita study. *Am J Hypertens*. 2014;27:1362–1369. doi:10.1093/ajh/hpu059.
6. Ueshima H, Sekikawa A, Miura K, Turin TC, Takashima N, Kita Y, Watanabe M, Kadota A, Okuda N, Kadowaki T, Nakamura Y, Okamura T. Cardiovascular disease and risk factors in Asia: a selected review. *Circulation*. 2008;118:2702–2709. doi:10.1161/CIRCULATIONAHA.108.790048.
7. Asayama K, Satoh M, Murakami Y, Ohkubo T, Nagasawa SY, Tsuji I, Nakayama T, Okayama A, Miura K, Imai Y, Ueshima H, Okamura T; Evidence for Cardiovascular Prevention From Observational Cohorts in Japan (EPOCH-JAPAN) Research Group. Cardiovascular risk with and without antihypertensive drug treatment in the Japanese general population: participant-level meta-analysis. *Hypertension*. 2014;63:1189–1197. doi:10.1161/HYPERTENSIONAHA.113.03206.
8. Ueshima H, Iida M, Shimamoto T, Konishi M, Tsujioka K, Tanigaki M, Nakanishi N, Ozawa H, Kojima S, Komachi Y. Multivariate analysis of risk factors for stroke. Eight-year follow-up study of farming villages in Akita, Japan. *Prev Med*. 1980;9:722–740.
9. Noda H, Iso H, Irie F, Sairenchi T, Ohtaka E, Doi M, Izumi Y, Ohta H. Low-density lipoprotein cholesterol concentrations and death due to intraparenchymal hemorrhage: the Ibaraki Prefectural Health Study. *Circulation*. 2009;119:2136–2145. doi:10.1161/CIRCULATIONAHA.108.795666.
10. Yano K, Reed DM, MacLean CJ. Serum cholesterol and hemorrhagic stroke in the Honolulu Heart Program. *Stroke*. 1989;20:1460–1465.
11. Tanaka H, Ueda Y, Hayashi M, Date C, Baba T, Yamashita H, Shoji H, Tanaka Y, Owada K, Detels R. Risk factors for cerebral hemorrhage and cerebral infarction in a Japanese rural community. *Stroke*. 1982;13:62–73.
12. Nagasawa SY, Okamura T, Iso H, Tamakoshi A, Yamada M, Watanabe M, Murakami Y, Miura K, Ueshima H; Evidence for Cardiovascular Prevention from Observational Cohorts in Japan (EPOCH-JAPAN) Research Group. Relation between serum total cholesterol level and cardiovascular disease stratified by sex and age group: a pooled analysis of 65 594 individuals from 10 cohort studies in Japan. *J Am Heart Assoc*. 2012;1:e001974. doi:10.1161/JAHA.112.001974.
13. Iso H, Jacobs DR Jr, Wentworth D, Neaton JD, Cohen JD. Serum cholesterol levels and six-year mortality from stroke in 350,977 men screened for the multiple risk factor intervention trial. *N Engl J Med*. 1989;320:904–910. doi:10.1056/NEJM198904063201405.
14. Neaton JD, Blackburn H, Jacobs D, Kuller L, Lee DJ, Sherwin R, Shih J, Stamler J, Wentworth D. Serum cholesterol level and mortality findings for men screened in the Multiple Risk Factor Intervention Trial. Multiple Risk Factor Intervention Trial Research Group. *Arch Intern Med*. 1992;152:1490–1500.
15. Murakami Y, Hozawa A, Okamura T, Ueshima H; Evidence for Cardiovascular Prevention From Observational Cohorts in Japan Research Group (EPOCH-JAPAN). Relation of blood pressure and all-cause mortality in 180,000 Japanese participants: pooled analysis of 13 cohort studies. *Hypertension*. 2008;51:1483–1491. doi:10.1161/HYPERTENSIONAHA.107.102459.
16. Ohkubo T, Kikuya M, Metoki H, Asayama K, Obara T, Hashimoto J, Totsune K, Hoshi H, Satoh H, Imai Y. Prognosis of "masked" hypertension and "white-coat" hypertension detected by 24-h ambulatory blood pressure monitoring 10-year follow-up from the Ohasama study. *J Am Coll Cardiol*. 2005;46:508–515. doi:10.1016/j.jacc.2005.03.070.
17. Ueshima H, Choudhury SR, Okayama A, Hayakawa T, Kita Y, Kadowaki T, Okamura T, Minowa M, Iimura O. Cigarette smoking as a risk factor for stroke death in Japan: NIPPON DATA80. *Stroke*. 2004;35:1836–1841. doi:10.1161/01.STR.0000131747.84423.74.
18. Liu L, Miura K, Fujiyoshi A, Kadota A, Miyagawa N, Nakamura Y, Ohkubo T, Okayama A, Okamura T, Ueshima H. Impact of metabolic syndrome on the risk of cardiovascular disease mortality in the United States and in Japan. *Am J Cardiol*. 2014;113:84–89. doi:10.1016/j.amjcard.2013.08.042.
19. Ross R. Atherosclerosis–an inflammatory disease. *N Engl J Med*. 1999;340:115–126. doi:10.1056/NEJM199901143400207.
20. Libby P. Inflammation in atherosclerosis. *Nature*. 2002;420:868–874. doi:10.1038/nature01323.
21. Prospective Studies Collaboration, Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, Halsey J, Qizilbash N, Peto R, Collins R. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. *Lancet*. 2007;370:1829–1839.
22. Imamura T, Doi Y, Arima H, Yonemoto K, Hata J, Kubo M, Tanizaki Y, Ibayashi S, Iida M, Kiyohara Y. LDL cholesterol and the development of stroke subtypes and coronary heart disease in a general Japanese

population: the Hisayama study. *Stroke*. 2009;40:382–388. doi:10.1161/STROKEAHA.108.529537.
23. Wang X, Dong Y, Qi X, Huang C, Hou L. Cholesterol levels and risk of hemorrhagic stroke: a systematic review and meta-analysis. *Stroke*. 2013;44:1833–1839. doi:10.1161/STROKEAHA.113.001326.
24. Amarenco P, Bogousslavsky J, Callahan A 3rd, Goldstein LB, Hennerici M, Rudolph AE, Sillesen H, Simunovic L, Szarek M, Welch KM, Zivin JA; Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med*. 2006;355:549–559. doi:10.1056/NEJMoa061894.
25. Okamura T. Low blood cholesterol and intraparenchymal hemorrhage in cohort studies. *J Atheroscler Thromb*. 2010;17:312–314.
26. Jacobs D, Blackburn H, Higgins M, Reed D, Iso H, McMillan G, Neaton J, Nelson J, Potter J, Rifkind B. Report of the Conference on Low Blood Cholesterol: Mortality Associations. *Circulation*. 1992;86:1046–1060.
27. Cui R, Iso H, Toyoshima H, Date C, Yamamoto A, Kikuchi S, Kondo T, Watanabe Y, Koizumi A, Inaba Y, Tamakoshi A; JACC Study Group. Serum total cholesterol levels and risk of mortality from stroke and coronary heart disease in Japanese: the JACC study. *Atherosclerosis*. 2007;194:415–420. doi:10.1016/j.atherosclerosis.2006.08.022.
28. Okamura T, Kadowaki T, Hayakawa T, Kita Y, Okayama A, Ueshima H; Nippon Data80 Research Group. What cause of mortality can we predict by cholesterol screening in the Japanese general population? *J Intern Med*. 2003;253:169–180.
29. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, Abbott R, Godwin J, Dyer A, Stamler J. Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet*. 1990;335:765–774.
30. Woodward M. *Epidemiology: Study Design and Data Analysis (Texts in Statistical Science)*. 2nd ed. London: Chapman and Hall/CRC; 2005.

## Novelty and Significance

### What Is New?

- We have conducted the participant-level meta-analysis including 73 916 Japanese from 11 cohorts with a mean of 15.0 years follow-up. Individuals with systolic blood pressure ≥160 mm Hg with total cholesterol ≥5.7 mmol/L had the greatest risk for coronary heart disease death (hazard ratio, 4.39; 95% confidence intervals, 2.68–7.18) compared with those with systolic blood pressure <120 mm Hg with total cholesterol <4.7 mmol/L.

### What Is Relevant?

- There was a significant interaction between higher blood pressure and higher total cholesterol levels for the risk of coronary heart disease death (interaction $P \leq 0.04$).
- The interaction between blood pressure and total cholesterol level was not significant for ischemic stroke death or intraparenchymal hemorrhage death (interaction $P \geq 0.09$).
- Total cholesterol levels were inversely associated with total cardiovascular death in the group with systolic blood pressure <120 mm Hg, but positively associated in the group with systolic blood pressure ≥160 mm Hg (interaction $P=0.0006$).

### Summary

We demonstrated that the positive association between blood pressure and the risk of coronary heart disease death was remarkably observed in participants with higher total cholesterol levels. High blood pressure and high total cholesterol can synergistically increase the risk for coronary heart disease death. These findings suggest that poor lipid management may enhance the adverse effect of high blood pressure on coronary heart disease risk and vice versa in the Asian population.

*Hypertension*

# SUPPLEMENTAL MATERIAL

This Online Data Supplement has been provided by the authors to give readers additional information about the work.

Supplement to:

Combined Effect of Blood Pressure and Total Cholesterol Levels on Long-Term

Risks of Subtypes of Cardiovascular Death

Evidence for Cardiovascular Prevention From Observational Cohorts in Japan

*Hypertension* 2015; published online.

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# Methods

## Study Populations

The construction of the EPOCH-JAPAN database has been described previously.[1] The inclusion criteria for the EPOCH-JAPAN project were as follows: collection of BP, anthropometric indices, and health examination measures; follow-up period >5 years and >1000 participants in principle; and nationwide, as well as regional, Japanese cohort study. All studies contributing to the EPOCH-JAPAN project received ethical approval and have been described in detail in peer-reviewed publications.

Figure S1 shows the selection of cohorts and participants. At the time of writing this report, the EPOCH–JAPAN database included 12 eligible cohorts with data on CVD outcomes.[1-13] Of the total 101250 participants, 90438, aged 40 to 90 years with data on the cause of death, were included. Finally, 73916 participants from 11 cohorts were analyzed.[2-12] All participants gave their informed consent. The characteristics of each cohort are shown in Table S1.

## Data Collection

Blood pressure was measured using a mercury sphygmomanometer when each participant was in a seated position, except for the Ohasama study [3] in which an automated device was used. Participants rested before measurement except in

the Ohsaki study.[2] Two (Ohasama[3] and Suita[6] studies) or three (Hisayama study[8]) consecutive values, or otherwise one reading at the examination center was obtained and used in the analysis. In one study (JACC[9]), the BP values were based on self-recorded values after BP had been measured at a health check-up.

Serum total cholesterol levels were measured enzymatically in all cohorts, with the exception of the NIPPON DATA80 cohort[10], in which total cholesterol was measured by the Lieberman-Burchard direct method. In all cohorts, a questionnaire was used to obtain detailed information on each participant's medical history, intake of medications, and drinking and smoking habits.

**Outcomes**

In accordance with the Family Registration Law in Japan, all death certificates are forwarded to the Ministry of Health, Labour and Welfare via the public health center in the area of residence.[14] Registration of death is required by law and believed to be complete. Other sources used in some studies included autopsy reports[6, 8], medical records[3, 6, 8], health examinations[2, 3], and questionnaires. The underlying causes of death were coded according to the 9th International Classification of Disease (ICD-9) to the end of 1994 and the 10th International Classification of Disease (ICD-10) from the beginning of 1995. The cause of death used in the current study was defined as follows: total CVD (390 to 459; I00 to I99), CHD (410 to 414; I20 to I25), total stroke (430 to 438; I60 to I69),

ischemic stroke (433 or 434 or 437.8; I63 or I69.3), and intraparenchymal hemorrhage (431 to 432; I61 or I69.1).

**Statistical Analysis**

In accordance with the current hypertension guidelines[15, 16], the participants were classified into 4 categories according to their systolic (diastolic) BP levels: <120 (<80) mmHg, 120-139 (80-89) mmHg, 140-159 (90-99) mmHg, and ≥160 (100) mmHg. Participants were further classified into 4 groups according to their total cholesterol levels [<4.7 mmol/L (180 mg/dL), 4.7-5.1 mmol/L (180-199 mg/dL), 5.2-5.6 mmol/L (200-219 mg/dL), and ≥ 5.7 mmol/L (220 mg/dL)], which were chosen on the basis of cut-off values used in a previous study[17], and of approximate quartiles [25$^{th}$, 50$^{th}$, and 75$^{th}$ percentiles of total cholesterol: 4.5 mmol/L (176 mg/dL), 5.1 mmol/L (199 mg/dL), and 5.8 mmol/L (224 mg/dL)]. Therefore, all participants were assigned to one of 16 categories.

To analyze the relationship between the 16 groups and participants' characteristics, means and proportions were compared using analysis of variance (ANOVA) and the $\chi^2$ test for univariate analysis. Death rates were calculated stratified by the 16 groups according to systolic BP and total cholesterol levels while standardizing rates for sex and age (<50, 50-64, and ≥65 years) by the direct method. Multivariable adjusted hazard ratios for death from CHD, ischemic stroke, intraparenchymal hemorrhage, or total CVD in each systolic BP-total cholesterol category were also estimated. Then, cohort-stratified Cox proportional hazard

models, which accounted for the variability of baseline hazards among cohorts, with reference to the group with systolic BP <120 mmHg with total cholesterol <4.7 mmol/L, were used. Covariates included in the model were sex, age, body mass index, former smoking, current smoking, former drinking, and current drinking. The adjusted hazard ratios per 1 standard deviation (SD) increase in systolic BP or total cholesterol after stratifying the participants according to the total cholesterol categories and the systolic BP categories, respectively, were also calculated. Interactions were assessed by adding an interaction term to the Cox model. Heterogeneity in the hazard ratios among the 11 cohorts was assessed by the $I^2$ statistic. Statistical significance was an α-level of less than 0.05 on two-sided tests. SAS software, version 9.3 (SAS Institute, Cary, NC) was used in the present study.

## Appendix

The Evidence for Cardiovascular Prevention from Observational Cohorts in Japan (EPOCH-JAPAN) Research Group is composed of the following investigators. Chairperson: Hirotsugu Ueshima (Shiga University of Medical Science); Co-Chairperson: Tomonori Okamura (Keio University); Executive committee: Hirotsugu Ueshima (Shiga University of Medical Science), Yutaka Imai (Tohoku University Graduate School of Pharmaceutical Sciences), Takayoshi Ohkubo (Teikyo University School of Medicine), Fujiko Irie (Ibaraki Prefecture), Hiroyasu Iso, Akihiko Kitamura (Osaka University Graduate School of Medicine), Yutaka Kiyohara (Kyushu University Graduate School of Medicine), Katsuyuki Miura (Shiga University of Medical Science), Yoshitaka Murakami (Toho University), Hideaki Nakagawa (Kanazawa Medical University), Takeo Nakayama (Kyoto University School of Public Health), Tomonori Okamura (Keio University), Akira Okayama (Research Institute of Strategy for Prevention), Toshimi Sairenchi (Dokkyo Medical University), Shigeyuki Saitoh (Sapporo Medical University), Kiyomi Sakata (Iwate Medical University), Akiko Tamakoshi (Hokkaido University Graduate School of Medicine), Ichiro Tsuji (Tohoku University Graduate School of Medicine), Michiko Yamada (Radiation Effects Research Foundation), Masahiko Kiyama (Osaka Center for Cancer and Cardiovascular Disease Prevention), Yoshihiro Miyamoto (National Cerebral and Cardiovascular Center), Shizukiyo Ishikawa (Jichi Medical University) and Hiroshi Yatsuya (Fujita Health University).

## References for Online Supplement

**1.** Murakami Y, Hozawa A, Okamura T, Ueshima H, Evidence for Cardiovascular Prevention From Observational Cohorts in Japan Research Group. Relation of blood pressure and all-cause mortality in 180,000 Japanese participants: pooled analysis of 13 cohort studies. *Hypertension.* 2008;51:1483-1491.

**2.** Kuriyama S, Shimazu T, Ohmori K, Kikuchi N, Nakaya N, Nishino Y, Tsubono Y, Tsuji I. Green tea consumption and mortality due to cardiovascular disease, cancer, and all causes in Japan: the Ohsaki study. *JAMA.* 2006;296:1255-1265.

**3.** Ohkubo T, Kikuya M, Metoki H, Asayama K, Obara T, Hashimoto J, Totsune K, Hoshi H, Satoh H, Imai Y. Prognosis of "masked" hypertension and "white-coat" hypertension detected by 24-h ambulatory blood pressure monitoring 10-year follow-up from the Ohasama study. *J Am Coll Cardiol.* 2005;46:508-515.

**4.** Soyama Y, Miura K, Morikawa Y, Nishijo M, Nakanishi Y, Naruse Y, Kagamimori S, Nakagawa H, Oyabe S. High-density lipoprotein cholesterol and risk of stroke in Japanese men and women: the Oyabe Study. *Stroke.*

2003;34:863-868.

**5.** Yoshita K, Miura K, Morikawa Y, Ishizaki M, Kido T, Naruse Y, Soyama Y, Suwazono Y, Nogawa K, Nakagawa H. Relationship of alcohol consumption to 7-year blood pressure change in Japanese men. *J Hypertens.* 2005;23:1485-1490.

**6.** Mannami T, Konishi M, Baba S, Nishi N, Terao A. Prevalence of asymptomatic carotid atherosclerotic lesions detected by high-resolution ultrasonography and its relation to cardiovascular risk factors in the general population of a Japanese city: the Suita study. *Stroke.* 1997;28:518-525.

**7.** Nakanishi S, Yamada M, Hattori N, Suzuki G. Relationship between HbA(1)c and mortality in a Japanese population. *Diabetologia.* 2005;48:230-234.

**8.** Arima H, Tanizaki Y, Kiyohara Y, Tsuchihashi T, Kato I, Kubo M, Tanaka K, Ohkubo K, Nakamura H, Abe I, Fujishima M, Iida M. Validity of the JNC VI recommendations for the management of hypertension in a general population of Japanese elderly: the Hisayama study. *Arch Intern Med.* 2003;163:361-366.

**9.** Iso H, Date C, Yamamoto A*, et al.* Perceived mental stress and mortality from cardiovascular disease among Japanese men and women: the Japan

Collaborative Cohort Study for Evaluation of Cancer Risk Sponsored by Monbusho (JACC Study). *Circulation.* 2002;106:1229-1236.

**10.** Ueshima H, Choudhury SR, Okayama A, Hayakawa T, Kita Y, Kadowaki T, Okamura T, Minowa M, Iimura O. Cigarette smoking as a risk factor for stroke death in Japan: NIPPON DATA80. *Stroke.* 2004;35:1836-1841.

**11.** Okamura T, Hayakawa T, Kadowaki T, Kita Y, Okayama A, Ueshima H, Nippon Data Research Group. The inverse relationship between serum high-density lipoprotein cholesterol level and all-cause mortality in a 9.6-year follow-up study in the Japanese general population. *Atherosclerosis.* 2006;184:143-150.

**12.** Imano H, Kitamura A, Sato S, Kiyama M, Ohira T, Yamagishi K, Noda H, Tanigawa T, Iso H, Shimamoto T. Trends for blood pressure and its contribution to stroke incidence in the middle-aged Japanese population: the Circulatory Risk in Communities Study (CIRCS). *Stroke.* 2009;40:1571-1577.

**13.** Ohnishi H, Saitoh S, Takagi S, Katoh N, Chiba Y, Akasaka H, Nakamura Y, Shimamoto K. Incidence of type 2 diabetes in individuals with central obesity in a rural Japanese population: The Tanno and Sobetsu study. *Diabetes Care.* 2006;29:1128-1129.

**14.** The Ministry of Health Labour and Welfare. Mannual to fill in a death certificate (in Japanese). In The Ministry of Health, Labour, and Welfare, ed. 2014. Available at: http://www.mhlw.go.jp/toukei/manual/. Accessed September 24, 2014. . 2014.

**15.** Shimamoto K, Ando K, Fujita T*, et al.* The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2014). *Hypertens Res.* 2014;37:253-387.

**16.** Mancia G, Fagard R, Narkiewicz K*, et al.* 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens.* 2013;31:1281-1357.

**17.** Nippon Data Research Group. Risk assessment chart for death from cardiovascular disease based on a 19-year follow-up study of a Japanese representative population. *Circ J.* 2006;70:1249-1255.

**Table S1–1. Baseline Characteristics of Study Participants in Each Cohort: EPOCH–JAPAN**

| Cohort Name | N | Men, N (%) | Age, Years | BMI, kg/m$^2$ | BP, mmHg | | Total Cholesterol, mmol/L |
|---|---|---|---|---|---|---|---|
| | | | | | Systolic | Diastolic | |
| Ohsaki[2] | 12734 | 6131 (48.1) | 61.6±9.6 | 23.8±3.1 | 130.9±17.5 | 78.7±11.0 | 5.3±0.9 |
| Ohasama[3] | 2240 | 877 (39.2) | 58.8±9.9 | 23.6±3.1 | 130.9±16.7 | 74.1±10.9 | 5.1±0.9 |
| Oyabe[4] | 4627 | 1461 (31.6) | 58.8±9.8 | 23.0±3.0 | 127.7±20.0 | 76.0±11.1 | 5.1±0.9 |
| YKK workers[5] | 2789 | 1872 (67.1) | 47.1±5.3 | 22.5±2.6 | 119.4±16.0 | 74.2±12.2 | 5.2±0.9 |
| Suita[6] | 5099 | 2442 (47.9) | 58.9±10.8 | 22.6±3.1 | 130.1±22.2 | 78.5±12.1 | 5.4±1.0 |
| RERF cohort[7] | 3549 | 1132 (31.9) | 59.8±11.0 | 22.7±3.4 | 132.8±21.8 | 82.4±11.8 | 5.5±1.0 |
| Hisayama[8] | 2619 | 1106 (42.2) | 58.9±11.7 | 22.8±3.2 | 133.6±21.3 | 77.8±11.3 | 5.3±1.1 |
| JACC[9] | 24932 | 8987 (36.0) | 57.0±9.7 | 23.1±3.1 | 133.0±19.3 | 79.1±11.3 | 5.1±0.9 |
| NIPPON DATA 80[10] | 6807 | 2974 (43.7) | 56.0±10.8 | 22.8±3.2 | 140.1±21.7 | 82.9±12.2 | 5.0±0.9 |
| NIPPON DATA 90[11] | 5609 | 2384 (42.5) | 56.9±11.4 | 23.1±3.2 | 138.7±20.5 | 82.7±11.8 | 5.3±1.0 |
| Osaka[12] | 2911 | 1001 (34.4) | 55.2±9.6 | 22.9±3.0 | 127.6±16.6 | 79.1±10.0 | 5.5±0.9 |

The analyses included 73916 Japanese from 11 cohorts. Data were shown as mean±standard deviation for continuous variables. BMI, body mass index. BP, blood pressure. JACC, Japan Collaborative Cohort. NIPPON DATA, National Integrated Project for Prospective Observation of Non–communicable Disease And its Trends in the Aged. RERF, Radiation Effects Research Foundation. YKK, Yoshida Kogyo Kabushikigaisya.

**Table S1–2. Baseline Characteristics of Study Participants in Each Cohort: EPOCH–JAPAN**

| Cohort Name | Baseline Year | Follow–up, Years | Death, N (Sex– and Age– Standardized Death Rates*) | | | |
|---|---|---|---|---|---|---|
| | | | CHD | Ischemic Stroke | Intraparenchymal Hemorrhage Stroke | CVD |
| Ohsaki[2] | 1994 | 11.1±3.5 | 88 (0.5) | 72 (0.4) | 32 (0.2) | 358 (1.8) |
| Ohasama[3] | 1987 | 12.9±3.2 | 21 (0.8) | 19 (0.7) | 13 (0.5) | 95 (3.5) |
| Oyabe[4] | 1988 | 10.0±1.7 | 27 (0.7) | 30 (0.8) | 14 (0.3) | 118 (2.9) |
| YKK workers[5] | 1990 | 18.3±5.3 | 1 (0.0) | 2 (0.0) | 2 (0.0) | 23 (0.3) |
| Suita[6] | 1989 | 13.7±3.5 | 78 (1.0) | 39 (0.5) | 15 (0.2) | 236 (3.2) |
| RERF cohort[7] | 1986 | 17.8±4.8 | 47 (0.8) | 26 (0.5) | 19 (0.3) | 294 (4.6) |
| Hisayama[8] | 1988 | 12.6±3.2 | 21 (0.6) | 30 (0.9) | 17 (0.5) | 167 (5.1) |
| JACC study[9] | 1988 | 17.1±4.5 | 243 (0.7) | 181 (0.6) | 119 (0.3) | 1187 (3.4) |
| NIPPON DATA 80[10] | 1980 | 20.2±6.3 | 174 (1.8) | 246 (2.8) | 84 (0.9) | 883 (9.4) |
| NIPPON DATA 90[11] | 1990 | 13.8±3.1 | 61 (0.9) | 77 (1.2) | 23 (0.3) | 296 (4.4) |
| Osaka[12] | 1985 | 12.3±2.3 | 9 (0.3) | 2 (0.1) | 7 (0.3) | 39 (1.5) |

The analyses included 73916 Japanese from 11 cohorts. Data were shown as mean±standard deviation for continuous variables. BP, blood pressure. CHD, coronary heart disease. CVD, cardiovascular disease. JACC, Japan Collaborative Cohort. NIPPON DATA, National Integrated Project for Prospective Observation of Non–communicable Disease And its Trends in the Aged. RERF, Radiation Effects Research Foundation. YKK, Yoshida Kogyo Kabushikigaisya. *Death rates were standardized by the direct method for sex and age (<50, 50–64, and ≥65 years).

**Table S2. Adjusted Hazard Ratios (95% Confidence Intervals) According to Systolic BP–Total Cholesterol Levels.**

| Endpoint | Category | Systolic BP, mmHg <120 | 120–139 | 140–159 | ≥160 |
|---|---|---|---|---|---|
| | Total Cholesterol, mmol/L | | | | |
| CHD | | | | | |
| | <4.7 | 1.00 (ref) | 1.50 (0.92–2.45) | 1.84 (1.12–3.02)* | 1.97 (1.16–3.35)* |
| | 4.7–5.1 | 1.27 (0.67–2.40) | 1.66 (1.00–2.76) | 2.29 (1.38–3.80)* | 2.58 (1.50–4.45)* |
| | 5.2–5.6 | 1.23 (0.62–2.42) | 1.78 (1.06–2.96)* | 2.51 (1.51–4.17)* | 3.13 (1.82–5.38)† |
| | ≥5.7 | 0.85 (0.42–1.70) | 1.99 (1.22–3.24)* | 2.75 (1.69–4.46)† | 4.39 (2.68–7.18)† |
| Ischemic stroke | | | | | |
| | <4.7 | 1.00 (ref) | 0.94 (0.61–1.46) | 1.26 (0.82–1.96) | 1.77 (1.14–2.76)* |
| | 4.7–5.1 | 0.87 (0.46–1.63) | 1.01 (0.63–1.62) | 1.26 (0.79–2.02) | 1.64 (1.01–2.65)* |
| | 5.2–5.6 | 0.74 (0.36–1.54) | 0.94 (0.57–1.54) | 1.26 (0.78–2.02) | 1.96 (1.21–3.17)* |
| | ≥5.7 | 0.99 (0.54–1.79) | 1.05 (0.66–1.66) | 1.25 (0.80–1.98) | 1.40 (0.87–2.27) |
| Intraparenchymal hemorrhage | | | | | |
| | <4.7 | 1.00 (ref) | 1.39 (0.81–2.38) | 1.74 (1.00–3.04) | 2.20 (1.21–3.98)* |
| | 4.7–5.1 | 0.67 (0.29–1.54) | 0.78 (0.41–1.48) | 1.59 (0.87–2.88) | 1.94 (1.01–3.73)* |
| | 5.2–5.6 | 0.48 (0.18–1.30) | 0.67 (0.34–1.32) | 1.13 (0.59–2.16) | 2.06 (1.06–3.99)* |
| | ≥5.7 | 0.35 (0.13–0.95)* | 0.43 (0.21–0.87)* | 0.86 (0.45–1.62) | 1.50 (0.78–2.87) |
| CVD | | | | | |
| | <4.7 | 1.00 (ref) | 1.20 (0.99–1.45) | 1.39 (1.14–1.69)* | 1.83 (1.50–2.25)† |
| | 4.7–5.1 | 0.84 (0.64–1.11) | 1.08 (0.88–1.33) | 1.42 (1.16–1.75)* | 1.66 (1.33–2.07)† |
| | 5.2–5.6 | 0.83 (0.62–1.11) | 1.06 (0.86–1.31) | 1.37 (1.11–1.68)* | 1.86 (1.49–2.32)† |
| | ≥5.7 | 0.65 (0.49–0.86)* | 1.01 (0.83–1.24) | 1.41 (1.16–1.72)* | 1.97 (1.61–2.41)† |

Hazard ratios were adjusted for sex, age, body mass index, former smoking, current smoking, former drinking, and current drinking. All analyses were stratified by cohort. The analyses included 73916 Japanese from 11 cohorts. The numbers of death were 770 for CHD, 724 for ischemic stroke, 345 for intraparenchymal hemorrhage, and CVD for 3696. BP, blood pressure. CHD, coronary heart disease. CVD, cardiovascular disease. *$P$<0.05, †$P$<.0001.

**Table S3. Adjusted Hazard Ratios (95% Confidence Intervals) in Each Group According to Diastolic BP–Total Cholesterol Levels**

| | | Diastolic BP, mmHg | | | |
|---|---|---|---|---|---|
| Endpoint | Category | <80 | 80–89 | 90–99 | ≥100 |
| | Total Cholesterol, mmol/L | | | | |
| CHD | | | | | |
| | <4.7 | 1.00 (ref) | 1.39 (1.00–1.94) | 1.79 (1.22–2.61)* | 1.81 (1.02–3.21)* |
| | 4.7–5.1 | 1.34 (0.96–1.89) | 1.58 (1.10–2.25)* | 1.97 (1.31–2.97)* | 2.14 (1.13–4.06)* |
| | 5.2–5.6 | 1.58 (1.13–2.23)* | 1.79 (1.26–2.55)* | 1.55 (0.96–2.48) | 2.83 (1.66–4.83)* |
| | ≥5.7 | 1.50 (1.09–2.07)* | 1.98 (1.43–2.74)† | 2.62 (1.83–3.75)† | 3.80 (2.49–5.81)† |
| Ischemic stroke | | | | | |
| | <4.7 | 1.00 (ref) | 0.96 (0.71–1.31) | 1.39 (0.99–1.96) | 2.42 (1.55–3.76)* |
| | 4.7–5.1 | 0.97 (0.71–1.34) | 1.04 (0.74–1.47) | 1.23 (0.81–1.85) | 2.32 (1.36–3.95)* |
| | 5.2–5.6 | 1.11 (0.80–1.55) | 0.98 (0.68–1.41) | 1.46 (0.97–2.20) | 1.18 (0.63–2.21) |
| | ≥5.7 | 1.03 (0.76–1.40) | 1.06 (0.76–1.48) | 1.38 (0.95–2.01) | 0.91 (0.50–1.67) |
| Intraparenchymal hemorrhage | | | | | |
| | <4.7 | 1.00 (ref) | 0.93 (0.62–1.40) | 1.63 (1.06–2.53)* | 2.31 (1.28–4.15)* |
| | 4.7–5.1 | 0.53 (0.32–0.86)* | 0.92 (0.58–1.45) | 1.32 (0.79–2.23) | 2.17 (1.07–4.41)* |
| | 5.2–5.6 | 0.32 (0.17–0.59)* | 0.83 (0.51–1.35) | 1.19 (0.67–2.11) | 2.07 (1.05–4.07)* |
| | ≥5.7 | 0.24 (0.13–0.44)† | 0.55 (0.33–0.91)* | 0.84 (0.48–1.47) | 1.65 (0.88–3.11) |
| CVD | | | | | |
| | <4.7 | 1.00 (ref) | 1.11 (0.96–1.27) | 1.60 (1.37–1.87)† | 2.26 (1.83–2.79)† |
| | 4.7–5.1 | 0.92 (0.79–1.06) | 1.14 (0.98–1.33) | 1.36 (1.13–1.63)* | 1.85 (1.42–2.42)† |
| | 5.2–5.6 | 0.92 (0.79–1.08) | 1.09 (0.93–1.28) | 1.43 (1.18–1.72)* | 1.89 (1.48–2.41)† |
| | ≥5.7 | 0.81 (0.70–0.93)* | 1.17 (1.02–1.35)* | 1.60 (1.36–1.87)† | 1.78 (1.44–2.20)† |

Hazard ratios were adjusted for sex, age, body mass index, former smoking, current smoking, former drinking, and current drinking. All analyses were stratified by cohort. The analyses included 73916 Japanese from 11 cohorts. The numbers of death were 770 for CHD, 724 for ischemic stroke, 345 for intraparenchymal hemorrhage, and CVD for 3696. BP, blood pressure. CHD, coronary heart disease. CVD, cardiovascular disease. *$P$<0.05, †$P$<.0001.

**Table S4. Adjusted Hazard Ratios (95% Confidence Intervals) in Each Group According to Systolic BP–Total Cholesterol Levels after Censoring of the First 3 Years**

| | | Systolic BP, mmHg | | | |
|---|---|---|---|---|---|
| Endpoint | Category | <120 | 120–139 | 140–159 | ≥160 |
| | Total Cholesterol, mmol/L | | | | |
| CHD | | | | | |
| | <4.7 | 1.00 (ref) | 1.42 (0.86–2.35) | 1.70 (1.02–2.84)* | 1.69 (0.96–2.95) |
| | 4.7–5.1 | 1.33 (0.70–2.54) | 1.63 (0.97–2.74) | 2.19 (1.30–3.69)* | 2.21 (1.25–3.92)* |
| | 5.2–5.6 | 1.29 (0.65–2.56) | 1.74 (1.03–2.94)* | 2.31 (1.37–3.90)* | 3.03 (1.74–5.28)† |
| | ≥5.7 | 0.81 (0.40–1.67) | 2.01 (1.22–3.31)* | 2.53 (1.54–4.17)* | 4.08 (2.46–6.78)† |
| Ischemic stroke | | | | | |
| | <4.7 | 1.00 (ref) | 0.86 (0.54–1.38) | 1.23 (0.78–1.94) | 1.83 (1.15–2.89)* |
| | 4.7–5.1 | 0.81 (0.42–1.58) | 0.99 (0.61–1.62) | 1.25 (0.77–2.04) | 1.76 (1.07–2.88)* |
| | 5.2–5.6 | 0.80 (0.38–1.66) | 0.97 (0.59–1.62) | 1.35 (0.83–2.20) | 2.08 (1.27–3.40)* |
| | ≥5.7 | 0.94 (0.50–1.75) | 1.06 (0.66–1.70) | 1.30 (0.81–2.07) | 1.36 (0.82–2.25) |
| Intraparenchymal hemorrhage | | | | | |
| | <4.7 | 1.00 (ref) | 1.55 (0.87–2.79) | 1.90 (1.04–3.47)* | 2.22 (1.16–4.26)* |
| | 4.7–5.1 | 0.71 (0.29–1.73) | 0.80 (0.40–1.61) | 1.73 (0.91–3.30) | 2.03 (1.00–4.14) |
| | 5.2–5.6 | 0.58 (0.21–1.60) | 0.81 (0.40–1.64) | 1.30 (0.66–2.60) | 1.99 (0.96–4.14) |
| | ≥5.7 | 0.25 (0.07–0.88)* | 0.44 (0.21–0.96)* | 0.90 (0.45–1.79) | 1.48 (0.72–3.03) |
| CVD | | | | | |
| | <4.7 | 1.00 (ref) | 1.20 (0.98–1.46) | 1.35 (1.10–1.66)* | 1.77 (1.43–2.19)† |
| | 4.7–5.1 | 0.84 (0.63–1.12) | 1.12 (0.91–1.39) | 1.46 (1.18–1.81)* | 1.68 (1.33–2.11)† |
| | 5.2–5.6 | 0.85 (0.63–1.15) | 1.10 (0.89–1.37) | 1.37 (1.10–1.70)* | 1.86 (1.47–2.35)† |
| | ≥5.7 | 0.64 (0.47–0.85)* | 1.02 (0.82–1.25) | 1.41 (1.15–1.73)* | 1.92 (1.55–2.38)† |

Hazard ratios were adjusted for sex, age, body mass index, former smoking, current smoking, former drinking, and current drinking. All analyses were stratified by cohort. The analyses included 73916 Japanese from 11 cohorts. After censoring of the first 3 Years, the numbers of death were 705 for CHD, 674 for ischemic stroke, 301 for intraparenchymal hemorrhage, and 3372 for CVD. BP, blood pressure. CHD, coronary heart disease. CVD, cardiovascular disease. *$P$<0.05, †$P$<.0001.

**Table S5. Adjusted Hazard Ratios (95% Confidence Intervals) for CHD Death in Each Group According to Systolic BP–Total Cholesterol Levels after Stratifying Participants by Age or Sex**

| Stratum | Category | Systolic BP, mmHg | | | | *P* for Interaction |
|---|---|---|---|---|---|---|
| | | <120 | 120–139 | 140–159 | ≥160 | |
| | Total Cholesterol, mmol/L | | | | | |
| Age<65 years | | | | | | |
| | <4.7 | 1.00 (ref) | 1.65 (0.78–3.49) | 1.72 (0.77–3.86) | 3.17 (1.37–7.33)* | |
| | 4.7–5.1 | 0.90 (0.30–2.69) | 1.29 (0.56–2.96) | 2.20 (0.96–5.01) | 4.14 (1.77–9.69)* | |
| | 5.2–5.6 | 1.53 (0.57–4.12) | 1.92 (0.86–4.26) | 2.83 (1.25–6.41)* | 4.13 (1.72–9.94)* | |
| | ≥5.7 | 1.18 (0.44–3.19) | 2.26 (1.06–4.82)* | 3.35 (1.57–7.15)* | 8.13 (3.78–17.48)† | |
| Age≥65 years | | | | | | 0.2 |
| | <4.7 | 1.00 (ref) | 1.36 (0.72–2.59) | 1.80 (0.95–3.41) | 1.53 (0.77–3.05) | |
| | 4.7–5.1 | 1.53 (0.69–3.41) | 1.82 (0.95–3.49) | 2.16 (1.13–4.16)* | 1.92 (0.95–3.91) | |
| | 5.2–5.6 | 1.04 (0.41–2.65) | 1.63 (0.83–3.18) | 2.22 (1.15–4.26)* | 2.53 (1.26–5.06)* | |
| | ≥5.7 | 0.64 (0.24–1.71) | 1.76 (0.93–3.35) | 2.29 (1.22–4.31)* | 3.04 (1.59–5.78)* | |
| Men | | | | | | |
| | <4.7 | 1.00 (ref) | 1.29 (0.75–2.20) | 1.50 (0.86–2.61) | 1.72 (0.95–3.14) | |
| | 4.7–5.1 | 1.22 (0.59–2.54) | 1.30 (0.72–2.33) | 1.43 (0.77–2.64) | 2.72 (1.47–5.04)* | |
| | 5.2–5.6 | 0.67 (0.25–1.80) | 1.69 (0.94–3.03) | 2.34 (1.30–4.22)* | 2.64 (1.35–5.17)* | |
| | ≥5.7 | 0.99 (0.43–2.28) | 1.53 (0.85–2.78) | 2.73 (1.55–4.80)* | 3.71 (2.02–6.81)† | |
| Women | | | | | | 0.1 |
| | <4.7 | 1.00 (ref) | 2.82 (0.83–9.64) | 4.23 (1.25–14.3)* | 4.16 (1.17–14.85)* | |
| | 4.7–5.1 | 1.84 (0.44–7.68) | 3.56 (1.06–11.96)* | 6.29 (1.91–20.71)* | 3.46 (0.96–12.51) | |
| | 5.2–5.6 | 3.51 (0.95–12.95) | 2.92 (0.86–9.87) | 4.31 (1.30–14.36)* | 5.63 (1.66–19.07)* | |
| | ≥5.7 | 1.17 (0.28–4.88) | 4.08 (1.27–13.16)* | 4.62 (1.43–14.92)* | 8.11 (2.51–26.20)* | |

Hazard ratios were adjusted for sex, age, body mass index, former smoking, current smoking, former drinking, and current drinking. All analyses were stratified by cohort. Total number of participants was 73916 from 11 cohorts in Japan. The numbers of CHD death were 273 in 53979 aged <65 years, 497 in 19937 aged ≥65 years, 427 in 30367 men, and 343 in 43549 women. BP, blood pressure. CHD, coronary heart disease. *$P$<0.05, †$P$<.0001.

**Table S6. Adjusted Hazard Ratios (95% Confidence Intervals) for Ischemic Stroke Death in Each Group According to Systolic BP–Total Cholesterol Levels after Stratifying Participants by Age or Sex**

| Stratum | Category | Systolic BP, mmHg | | | | *P* for Interaction |
|---|---|---|---|---|---|---|
| | | <120 | 120–139 | 140-159 | ≥160 | |
| | Total Cholesterol, mmol/L | | | | | |
| Age<65 years | | | | | | |
| | <4.7 | 1.00 (ref) | 0.92 (0.41–2.07) | 1.35 (0.60–3.06) | 3.67 (1.67–8.07)* | |
| | 4.7–5.1 | 0.53 (0.14–1.97) | 0.97 (0.41–2.31) | 1.17 (0.47–2.92) | 2.63 (1.08–6.36)* | |
| | 5.2–5.6 | 0.83 (0.26–2.72) | 0.93 (0.38–2.31) | 1.67 (0.69–4.04) | 2.85 (1.16–7.01)* | |
| | ≥5.7 | 0.66 (0.20–2.15) | 0.98 (0.41–2.32) | 1.41 (0.60–3.28) | 2.06 (0.81–5.22) | |
| Age≥65 years | | | | | | 0.3 |
| | <4.7 | 1.00 (ref) | 0.93 (0.55–1.59) | 1.22 (0.72–2.05) | 1.38 (0.81–2.36) | |
| | 4.7–5.1 | 1.05 (0.51–2.16) | 1.02 (0.58–1.79) | 1.26 (0.72–2.20) | 1.40 (0.79–2.48) | |
| | 5.2–5.6 | 0.71 (0.28–1.77) | 0.93 (0.51–1.67) | 1.13 (0.64–1.99) | 1.69 (0.96–3.00) | |
| | ≥5.7 | 1.14 (0.57–2.29) | 1.07 (0.61–1.85) | 1.19 (0.69–2.04) | 1.23 (0.70–2.16) | |
| Men | | | | | | |
| | <4.7 | 1.00 (ref) | 0.94 (0.53–1.65) | 1.58 (0.91–2.72) | 2.24 (1.28–3.90)* | |
| | 4.7–5.1 | 1.18 (0.54–2.58) | 1.00 (0.53–1.87) | 1.35 (0.73–2.52) | 2.36 (1.28–4.35)* | |
| | 5.2–5.6 | 1.29 (0.53–3.11) | 0.65 (0.30–1.38) | 1.84 (1.00–3.40) | 3.08 (1.63–5.83)* | |
| | ≥5.7 | 1.20 (0.50–2.92) | 1.24 (0.65–2.36) | 1.43 (0.75–2.72) | 2.32 (1.21–4.47)* | |
| Women | | | | | | 0.06 |
| | <4.7 | 1.00 (ref) | 0.97 (0.48–1.99) | 0.78 (0.37–1.66) | 1.21 (0.57–2.56) | |
| | 4.7–5.1 | 0.52 (0.18–1.50) | 0.95 (0.46–1.95) | 1.08 (0.52–2.22) | 0.92 (0.42–2.00) | |
| | 5.2–5.6 | 0.35 (0.10–1.24) | 1.02 (0.50–2.07) | 0.72 (0.34–1.52) | 1.11 (0.53–2.32) | |
| | ≥5.7 | 0.73 (0.32–1.70) | 0.80 (0.40–1.58) | 0.95 (0.48–1.86) | 0.80 (0.39–1.63) | |

Hazard ratios were adjusted for sex, age, body mass index, former smoking, current smoking, former drinking, and current drinking. All analyses were stratified by cohort. Total number of participants was 73916 from 11 cohorts in Japan. The numbers of ischemic stroke death were 183 in 53979 aged <65 years, 541 in 19937 aged ≥65 years, 401 in 30367 men, and 323 in 43549 women. BP, blood pressure. *$P$<0.05, †$P$<.0001.

**Table S7. Adjusted Hazard Ratios (95% Confidence Intervals) for Intraparenchymal Hemorrhage Death in Each Group According to Systolic BP–Total Cholesterol Levels after Stratifying Participants by Age or Sex**

| Stratum | Category | Systolic BP, mmHg | | | | *P* for Interaction |
|---|---|---|---|---|---|---|
| | | <120 | 120–139 | 140-159 | ≥160 | |
| | Total Cholesterol, mmol/L | | | | | |
| Age<65 years | | | | | | |
| | <4.7 | 1.00 (ref) | 1.68 (0.78–3.61) | 1.84 (0.80–4.23) | 3.62 (1.53–8.56)* | |
| | 4.7–5.1 | 0.82 (0.28–2.45) | 0.55 (0.19–1.55) | 1.27 (0.48–3.33) | 4.32 (1.77–10.52)* | |
| | 5.2–5.6 | 0.55 (0.15–2.05) | 0.69 (0.26–1.87) | 1.38 (0.52–3.65) | 2.63 (0.96–7.23) | |
| | ≥5.7 | 0.70 (0.23–2.10) | 0.51 (0.19–1.38) | 1.24 (0.50–3.07) | 2.11 (0.79–5.66) | |
| Age≥65 years | | | | | | 0.1 |
| | <4.7 | 1.00 (ref) | 1.08 (0.50–2.32) | 1.46 (0.69–3.11) | 1.38 (0.61–3.12) | |
| | 4.7–5.1 | 0.50 (0.14–1.86) | 0.87 (0.38–2.02) | 1.51 (0.68–3.32) | 0.90 (0.34–2.36) | |
| | 5.2–5.6 | 0.40 (0.09–1.87) | 0.60 (0.24–1.51) | 0.86 (0.36–2.08) | 1.51 (0.63–3.67) | |
| | ≥5.7 | NA | 0.34 (0.12–0.91)* | 0.57 (0.23–1.39) | 1.05 (0.44–2.51) | |
| Men | | | | | | |
| | <4.7 | 1.00 (ref) | 1.62 (0.80–3.28) | 1.66 (0.79–3.46) | 2.04 (0.93–4.48) | |
| | 4.7–5.1 | 0.75 (0.24–2.40) | 0.72 (0.29–1.78) | 1.10 (0.45–2.67) | 2.60 (1.12–6.06)* | |
| | 5.2–5.6 | 0.77 (0.21–2.80) | 0.92 (0.37–2.27) | 1.14 (0.44–2.92) | 1.49 (0.50–4.42) | |
| | ≥5.7 | 0.24 (0.03–1.90) | 0.51 (0.17–1.50) | 1.77 (0.76–4.11) | 1.36 (0.46–4.07) | |
| Women | | | | | | 0.1 |
| | <4.7 | 1.00 (ref) | 1.01 (0.42–2.41) | 1.92 (0.82–4.49) | 2.50 (1.01–6.18)* | |
| | 4.7–5.1 | 0.59 (0.18–1.95) | 0.82 (0.33–2.05) | 1.96 (0.84–4.55) | 1.29 (0.45–3.64) | |
| | 5.2–5.6 | 0.30 (0.06–1.42) | 0.48 (0.17–1.33) | 1.06 (0.43–2.64) | 2.19 (0.89–5.40) | |
| | ≥5.7 | 0.38 (0.11–1.26) | 0.37 (0.14–0.98)* | 0.46 (0.17–1.21) | 1.43 (0.59–3.45) | |

Hazard ratios were adjusted for sex, age, body mass index, former smoking, current smoking, former drinking, and current drinking. All analyses were stratified by cohort. Total number of participants was 73916 from 11 cohorts in Japan. The numbers of intraparenchymal hemorrhage death were 152 in 53979 aged <65 years, 193 in 19937 aged ≥65 years, 178 in 30367 men, and 167 in 43549 women. BP, blood pressure. NA, not applicable. *$P$<0.05, †$P$<.0001.

**Table S8. Adjusted Hazard Ratios (95% Confidence Intervals) for Total CVD Death in Each Group According to Systolic BP–Total Cholesterol Levels after Stratifying Participants by Age or Sex**

| Stratum | Category | Systolic BP, mmHg | | | | *P* for interaction |
|---|---|---|---|---|---|---|
| | | <120 | 120–139 | 140-159 | ≥160 | |
| | Total Cholesterol, mmol/L | | | | | |
| Age<65 years | | | | | | |
| | <4.7 | 1.00 (ref) | 1.34 (1.00–1.79) | 1.52 (1.11–2.08)* | 2.86 (2.06–3.96)† | |
| | 4.7–5.1 | 0.71 (0.46–1.10) | 1.06 (0.77–1.47) | 1.48 (1.05–2.08)* | 2.30 (1.59–3.33)† | |
| | 5.2–5.6 | 0.75 (0.48–1.18) | 1.04 (0.74–1.45) | 1.71 (1.22–2.40)* | 2.95 (2.07–4.22)† | |
| | ≥5.7 | 0.60 (0.38–0.92)* | 1.00 (0.72–1.37) | 1.78 (1.30–2.43)* | 3.09 (2.22–4.30)† | |
| Age≥65 years | | | | | | <.0001 |
| | <4.7 | 1.00 (ref) | 1.10 (0.86–1.41) | 1.30 (1.01–1.67)* | 1.49 (1.15–1.93)* | |
| | 4.7–5.1 | 0.96 (0.68–1.36) | 1.08 (0.83–1.41) | 1.36 (1.04–1.76)* | 1.40 (1.06–1.86)* | |
| | 5.2–5.6 | 0.92 (0.63–1.34) | 1.05 (0.80–1.38) | 1.20 (0.92–1.57) | 1.45 (1.09–1.92)* | |
| | ≥5.7 | 0.70 (0.49–1.00) | 1.00 (0.77–1.30) | 1.24 (0.96–1.60) | 1.57 (1.21–2.04)* | |
| Men | | | | | | |
| | <4.7 | 1.00 (ref) | 1.21 (0.95–1.54) | 1.46 (1.14–1.87)* | 2.01 (1.56–2.60)† | |
| | 4.7–5.1 | 0.93 (0.65–1.33) | 1.04 (0.79–1.37) | 1.30 (0.99–1.72) | 2.07 (1.55–2.76)† | |
| | 5.2–5.6 | 0.82 (0.54–1.25) | 1.17 (0.88–1.55) | 1.69 (1.28–2.23)* | 2.24 (1.64–3.05)† | |
| | ≥5.7 | 0.68 (0.44–1.05) | 1.20 (0.90–1.59) | 1.66 (1.26–2.19)* | 2.68 (2.01–3.58)† | |
| Women | | | | | | 0.03 |
| | <4.7 | 1.00 (ref) | 1.22 (0.89–1.66) | 1.33 (0.96–1.83) | 1.73 (1.24–2.42)* | |
| | 4.7–5.1 | 0.74 (0.49–1.13) | 1.11 (0.80–1.52) | 1.50 (1.09–2.05)* | 1.27 (0.89–1.79) | |
| | 5.2–5.6 | 0.82 (0.55–1.24) | 0.94 (0.68–1.29) | 1.09 (0.79–1.50) | 1.49 (1.07–2.08)* | |
| | ≥5.7 | 0.61 (0.41–0.89)* | 0.87 (0.64–1.17) | 1.20 (0.90–1.62) | 1.54 (1.14–2.09)* | |

Hazard ratios were adjusted for sex, age, body mass index, former smoking, current smoking, former drinking, and current drinking. All analyses were stratified by cohort. Total number of participants was 73916 from 11 cohorts in Japan. The numbers of total CVD death were 1245 in 53979 aged <65 years, 2451 in 19937 aged ≥65 years, 1856 in 30367 men, and 1840 in 43549 women. BP, blood pressure. CVD, cardiovascular disease. *$P$<0.05, †$P$<.0001.

**Table S9. Adjusted Hazard Ratios (95% Confidence Intervals) in Each Group According to Systolic BP–Total Cholesterol Levels in 4435 Participants Aged ≥75 Years**

| | | Systolic BP, mmHg | | | |
|---|---|---|---|---|---|
| Endpoint | Category | <120 | 120–139 | 140–159 | ≥160 |
| | Total Cholesterol, mmol/L | | | | |
| CHD | | | | | |
| | <4.7 | 1.00 (ref) | 1.24 (0.41–3.79) | 2.09 (0.71–6.13) | 1.55 (0.51–4.76) |
| | 4.7–5.1 | 2.76 (0.80–9.45) | 1.27 (0.40–4.05) | 1.71 (0.55–5.26) | 2.00 (0.62–6.45) |
| | 5.2–5.6 | 0.45 (0.05–4.01) | 1.77 (0.57–5.46) | 1.52 (0.47–4.90) | 2.45 (0.78–7.65) |
| | ≥5.7 | 0.62 (0.11–3.39) | 1.22 (0.39–3.89) | 1.80 (0.60–5.40) | 2.66 (0.90–7.89) |
| Ischemic stroke | | | | | |
| | <4.7 | 1.00 (ref) | 1.72 (0.66–4.53) | 1.80 (0.69–4.73) | 1.59 (0.60–4.25) |
| | 4.7–5.1 | 1.53 (0.41–5.72) | 1.47 (0.53–4.10) | 1.99 (0.73–5.43) | 2.01 (0.72–5.60) |
| | 5.2–5.6 | 1.04 (0.20–5.38) | 1.74 (0.61–4.91) | 0.98 (0.32–3.01) | 2.80 (1.03–7.59)* |
| | ≥5.7 | 1.34 (0.36–5.06) | 1.74 (0.63–4.80) | 1.94 (0.72–5.21) | 1.82 (0.66–4.99) |
| Intraparenchymal hemorrhage | | | | | |
| | <4.7 | 1.00 (ref) | 0.77 (0.24–2.51) | 0.66 (0.19–2.27) | 0.97 (0.29–3.24) |
| | 4.7–5.1 | 0.47 (0.05–4.24) | 0.78 (0.22–2.80) | 0.56 (0.14–2.25) | 0.18 (0.02–1.63) |
| | 5.2–5.6 | 0.54 (0.06–4.93) | 0.45 (0.10–2.02) | 0.84 (0.23–3.00) | 1.69 (0.49–5.85) |
| | ≥5.7 | NA | 0.13 (0.02–1.21) | 0.33 (0.07–1.49) | 0.53 (0.13–2.21) |
| CVD | | | | | |
| | <4.7 | 1.00 (ref) | 0.89 (0.60–1.33) | 1.15 (0.78–1.70) | 1.09 (0.73–1.62) |
| | 4.7–5.1 | 1.17 (0.69–1.99) | 0.78 (0.51–1.20) | 1.08 (0.71–1.64) | 1.10 (0.71–1.70) |
| | 5.2–5.6 | 0.95 (0.52–1.72) | 0.99 (0.64–1.51) | 0.87 (0.56–1.35) | 1.34 (0.88–2.05) |
| | ≥5.7 | 0.74 (0.42–1.30) | 0.94 (0.62–1.43) | 1.00 (0.67–1.50) | 1.27 (0.85–1.90) |

Hazard ratios were adjusted for sex, age, body mass index, former smoking, current smoking, former drinking, and current drinking. All analyses were stratified by cohort. The analyses included 4435 Japanese aged ≥75 years from 11 cohorts. The numbers of deaths were 182 for CHD, 229 for ischemic stroke, 67 for intraparenchymal hemorrhage, and 967 for CVD. BP, blood pressure. CHD, coronary heart disease. CVD, cardiovascular disease. NA, not applicable.

*$P$<0.05.

**Table S10. Adjusted Hazard Ratios (95% Confidence Intervals) in Each Group According to Systolic BP–Total Cholesterol Levels in 79323 participants, including 5407 Participants without Data on Covariates**

| | | Systolic BP, mmHg | | | |
|---|---|---|---|---|---|
| Endpoint | Category | <120 | 120–139 | 140–159 | ≥160 |
| | Total Cholesterol, mmol/L | | | | |
| CHD | | | | | |
| | <4.7 | 1.00 (ref) | 1.35 (0.86–2.12) | 1.61 (1.01–2.55)* | 1.65 (1.00–2.73)* |
| | 4.7–5.1 | 1.12 (0.61–2.05) | 1.51 (0.94–2.42) | 2.07 (1.29–3.32)* | 2.39 (1.44–3.97)* |
| | 5.2–5.6 | 1.02 (0.53–1.96) | 1.61 (1.00–2.58) | 2.19 (1.36–3.51)* | 2.77 (1.67–4.59)† |
| | ≥5.7 | 0.75 (0.39–1.45) | 1.74 (1.11–2.75)* | 2.53 (1.62–3.96)† | 3.87 (2.45–6.11)† |
| Ischemic stroke | | | | | |
| | <4.7 | 1.00 (ref) | 0.99 (0.64–1.53) | 1.36 (0.88–2.10) | 1.81 (1.16–2.81)* |
| | 4.7–5.1 | 0.97 (0.53–1.77) | 1.13 (0.71–1.80) | 1.33 (0.84–2.12) | 1.75 (1.08–2.81)* |
| | 5.2–5.6 | 0.73 (0.35–1.50) | 0.98 (0.60–1.60) | 1.25 (0.78–2.01) | 2.06 (1.28–3.31)* |
| | ≥5.7 | 1.06 (0.60–1.89) | 1.09 (0.69–1.72) | 1.29 (0.82–2.02) | 1.63 (1.02–2.61)* |
| Intraparenchymal hemorrhage | | | | | |
| | <4.7 | 1.00 (ref) | 1.46 (0.85–2.50) | 1.77 (1.02–3.09)* | 2.28 (1.27–4.10)* |
| | 4.7–5.1 | 0.90 (0.43–1.91) | 0.77 (0.41–1.46) | 1.56 (0.86–2.84) | 2.06 (1.08–3.92)* |
| | 5.2–5.6 | 0.47 (0.18–1.27) | 0.74 (0.38–1.42) | 1.23 (0.65–2.32) | 2.15 (1.12–4.13)* |
| | ≥5.7 | 0.42 (0.16–1.05) | 0.57 (0.30–1.09) | 0.97 (0.52–1.80) | 1.65 (0.87–3.11) |
| CVD | | | | | |
| | <4.7 | 1.00 (ref) | 1.20 (1.00–1.44) | 1.40 (1.16–1.69)* | 1.77 (1.46–2.16)† |
| | 4.7–5.1 | 0.86 (0.66–1.11) | 1.11 (0.92–1.36) | 1.43 (1.17–1.75)* | 1.67 (1.35–2.07)† |
| | 5.2–5.6 | 0.79 (0.59–1.04) | 1.07 (0.88–1.31) | 1.37 (1.12–1.68)* | 1.86 (1.50–2.31)† |
| | ≥5.7 | 0.68 (0.53–0.89)* | 1.04 (0.86–1.26) | 1.43 (1.18–1.72)* | 1.98 (1.63–2.42)† |

The 79323 Japanese include 5407 without a history of CVD and without data on covariates and were from 11 cohorts. Hazard ratios were adjusted for sex, age, body mass index, former smoking, current smoking, former drinking, current drinking, and each missing value (missing = 1, present = 0) for smoking/drinking status. Missing body mass index values were interpolated from the regression slope on age by sex. All analyses were stratified by cohort. The numbers of deaths were 830 for CHD, 767 for ischemic stroke, 371 for intraparenchymal hemorrhage, and 3996 for CVD. BP, blood pressure. CHD, coronary heart disease. CVD, cardiovascular disease. *$P$<0.05.

**Table S11. Adjusted Hazard Ratios (95% Confidence Intervals) per 1 SD increase in Systolic BP and Total Cholesterol after Including These Variables in the Same Model**

| | Adjusted Hazard Ratios (95% Confidence Intervals) per 1 SD Increase in Independent Variable | | | |
|---|---|---|---|---|
| Independent Variable | CHD | Ischemic Stroke | Intraparenchymal Hemorrhage | Total CVD |
| Systolic BP (1 SD = 20 mmHg) | 1.35 (1.26–1.44) *P*<.0001 | 1.20 (1.12–1.28) *P*<.0001 | 1.44 (1.31–1.59) *P*<.0001 | 1.27 (1.23–1.31) *P*<.0001 |
| Total Cholesterol (1 SD = 1 mmol/L) | 1.23 (1.15–1.33) *P*<.0001 | 0.99 (0.92–1.08) *P*=0.9 | 0.74 (0.66–0.84) *P*<.0001 | 0.99 (0.96–1.24) *P*=0.5 |

Systolic BP and total cholesterol were included in the same model. Hazard ratios were adjusted for sex, age, body mass index, former smoking, current smoking, former drinking, and current drinking. The analyses included 73916 Japanese from 11 cohorts. The numbers of deaths were 770 for CHD, 724 for ischemic stroke, 345 for intraparenchymal hemorrhage, and 3696 for CVD. BP, blood pressure. CHD, coronary heart disease. CVD, cardiovascular disease.

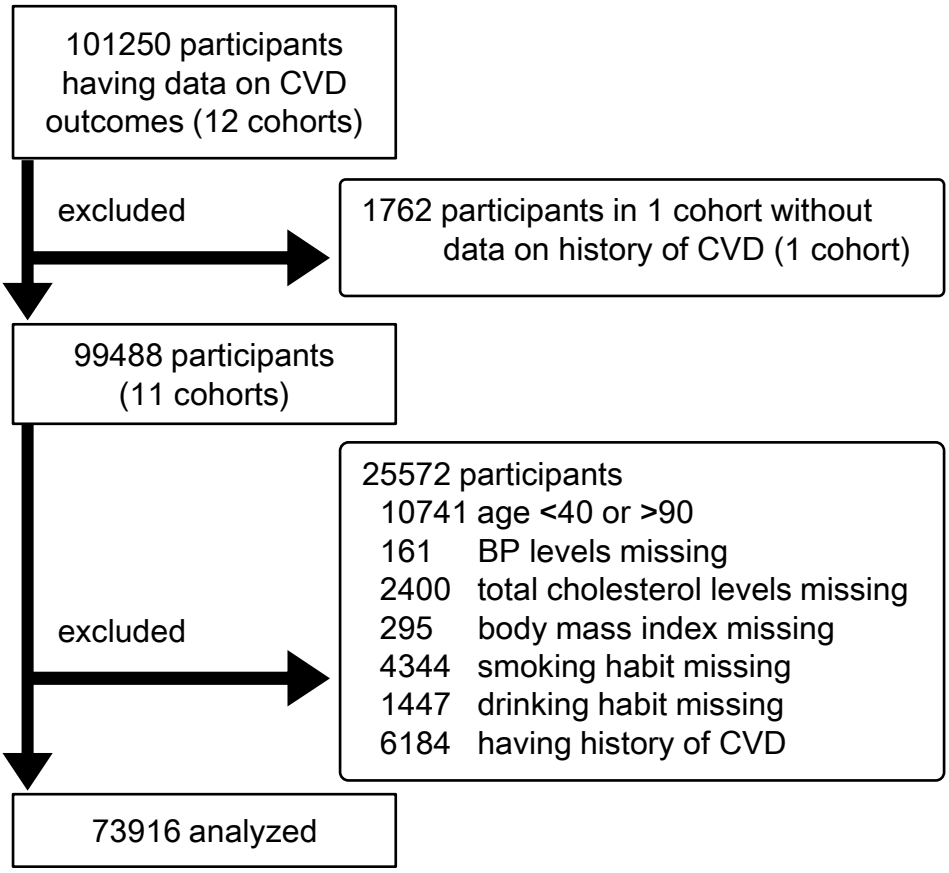


**Figure S1.**

Flow diagram of study population. BP, blood pressure. CVD, cardiovascular disease. EPOCH-JAPAN, Evidence for Cardiovascular Prevention from Observational Cohorts in Japan.

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# Combined Effect of Blood Pressure and Total Cholesterol Levels on Long-Term Risks of Subtypes of Cardiovascular Death: Evidence for Cardiovascular Prevention From Observational Cohorts in Japan

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