Relation of Blood Pressure and All-Cause Mortality in 180 000 Japanese Participants
Pooled Analysis of 13 Cohort Studies

Yoshitaka Murakami, Atsushi Hozawa, Tomonori Okamura, Hirotsugu Ueshima; and the Evidence for Cardiovascular Prevention From Observational Cohorts in Japan Research Group (EPOCH-JAPAN)

Abstract—Hypertension is a leading cause of death because of cardiovascular disease and predominantly affects total mortality. To reduce avoidable deaths from hypertension, we need to collect blood pressure data and assess their impact on total mortality. To examine this issue, a meta-analysis of 13 cohort studies was conducted in Japan. Poisson regression was used for estimating all-cause mortality rates and ratios. In the model, blood pressure data were treated as continuous (10-mm Hg increase) and categorical (every 10 mm Hg) according to recommendations of the Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of Hypertension. Potential confounders included body mass index, smoking, drinking, and cohort. The impact of hypertension was measured by the population-attributable fraction. After excluding participants with cardiovascular disease history, 176 389 participants were examined in the analysis. Adjusted mortality rates became larger as the blood pressure increased, and these were more distinct in younger men and women. Hazard ratios also showed the same trends, and these trends were more apparent in younger men (hazard ratio [unit: 10-mm Hg increase] aged 40 to 49 years: systolic blood pressure 1.37 [range: 1.15 to 1.62]; diastolic blood pressure 1.46 [range: 1.05 to 2.03]) than older ones (hazard ratio: aged 80 to 89 years: systolic blood pressure 1.09 [range: 1.05 to 1.13] and diastolic blood pressure 1.12 [range: 1.03 to 1.22]). Population-attributable fraction of hypertension was $\approx$20% when the normal category was used as a reference level and was 10% when we included the prehypertension group in the reference level. In conclusion, high blood pressure raised the risk of total mortality, and this trend was higher in the younger Japanese population. (Hypertension. 2008;51:1483-1491.)

Key Words: pooled analysis • total mortality • cohort study • blood pressure • population attributable fraction

High blood pressure is a well-established leading cause of cardiovascular disease mortality. The contribution of hypertension to total mortality is also large, and the importance of management of hypertension is widely accepted not only in clinical practice but also in public health practice. Before measures for reducing hypertension are implemented, more information about the relationship between hypertension and total mortality is needed. For example, one study found that the hazard ratio of cardiovascular disease in those with high blood pressure was larger in younger than in older participants, suggesting that the contribution of high blood pressure to mortality differed at different ages. The examination of this important issue requires a large number of participants, and a single cohort study estimating this contribution is limited by small sample size. The Joint National Committee of Hypertension 7 (JNC-7) also mentioned the importance of the risk of mortality and the contribution of prehypertension to total mortality. The relation between blood pressure and total mortality is, therefore, of great interest. It is difficult to address this issue in a single cohort study, because few events can be observed in cohorts sub-grouped, eg, by age or prehypertension status. A large-scale cohort study could answer these questions, but the huge amount of cost and effort involved represent serious obstacles. Meta-analysis using data on individual participants is an efficient way to deal with this issue, and the approach has been used in studies of cardiovascular disease epidemiology.

In Japan, meta-analysis of individual participants’ data for cardiovascular disease was conducted in the Japanese population. The study, called Evidence for Cardiovascular Prevention From Observational Cohorts in Japan (EPOCH-JAPAN), included 13 cohort studies of existing Japanese cohorts. The total number of EPOCH-JAPAN participants was 188 321, with 10 years of follow-up. The purpose of this study was to examine sex- and age-specific hazard ratios and the effect of blood pressure on total mortality and to estimate the contribution of high blood pressure to all-cause death by...
performing a meta-analysis of the data from 13 population-based cohort studies conducted in Japan.

### Study Participants and Methods

#### Study Cohorts

The EPOCH-JAPAN Study is the pooled analysis of 13 cohort studies examining the relation between health measures (laboratory measures and lifestyle and behavioral factors) and disease (mortality and incidence) in the Japanese population. The criteria for inclusion of meta-analysis were as follows: collection of health examination measures, follow-up of ≥10 years, and a number of participants ≥1000 persons. Both nationwide and single-site cohort studies were included. The name of each cohort study¹⁻²² is listed in Table 1.

#### Statistical Methods

Hazard ratios for total mortality were estimated in men and women separately. Participants were stratified into 10-year age groups from 40 to 80 years, and a statistical model was made to analyze the data of each age group separately. They were also divided on the basis of systolic blood pressure (SBP) into 10-mm Hg groups from <120 mm Hg to ≥160 mm Hg and on the basis of diastolic blood pressure (DBP) into 10-mm Hg groups from <70 mm Hg to ≥100 mm Hg. The lowest blood pressure group (<120 mm Hg for SBP and <70 mm Hg for DBP) served as the reference group.

### Table 1. Baseline Characteristics of Study Participants in Each Cohort: EPOCH-JAPAN

<table>
<thead>
<tr>
<th>Cohort Name</th>
<th>Geographic Location (Prefecture)</th>
<th>Source of Baseline Survey, Year, Reference(s)</th>
<th>Follow-Up Periods</th>
<th>No. of Participants</th>
<th>Age at Study Entry</th>
<th>Blood Pressure</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Average SD</td>
<td>Average SD</td>
<td>Average SD</td>
<td>Systolic</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>Average SD</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>Tanno-Sobetsu</td>
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<td>1977²⁻⁸</td>
<td>18 5</td>
<td>840</td>
<td>51 7</td>
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<tr>
<td></td>
<td>Osaki</td>
<td>Miyagi</td>
<td>1994</td>
<td>6 1</td>
<td>6918</td>
<td>63 10</td>
</tr>
<tr>
<td></td>
<td>Ohasama</td>
<td>Iwate</td>
<td>1987¹⁰</td>
<td>10 3</td>
<td>1122</td>
<td>61 11</td>
</tr>
<tr>
<td></td>
<td>Oyabe</td>
<td>Ishikawa</td>
<td>1988¹¹</td>
<td>10 2</td>
<td>1509</td>
<td>61 10</td>
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<tr>
<td></td>
<td>YKK workers</td>
<td>Toyama</td>
<td>1990¹²</td>
<td>11 2</td>
<td>3177</td>
<td>51 6</td>
</tr>
<tr>
<td></td>
<td>SPMI cohort</td>
<td>Shiga</td>
<td>1989⁻¹⁹¹³</td>
<td>9 3</td>
<td>1939</td>
<td>54 8</td>
</tr>
<tr>
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<td>Suita</td>
<td>Osaka</td>
<td>1987¹⁵⁻¹⁶</td>
<td>6 2</td>
<td>2339</td>
<td>60 11</td>
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<tr>
<td></td>
<td>RERF cohort</td>
<td>Hiroshima</td>
<td>1986¹⁶</td>
<td>14 5</td>
<td>1506</td>
<td>60 13</td>
</tr>
<tr>
<td></td>
<td>Hisayama</td>
<td>Fukuoka</td>
<td>1988¹⁷</td>
<td>10 3</td>
<td>1113</td>
<td>58 12</td>
</tr>
<tr>
<td></td>
<td>JACC study</td>
<td>Nationwide‡</td>
<td>1988⁻¹⁹¹⁰</td>
<td>9 2</td>
<td>11 041</td>
<td>58 10</td>
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<tr>
<td></td>
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<td>Nationwide‡</td>
<td>1980</td>
<td>16 5</td>
<td>3161</td>
<td>56 11</td>
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<tr>
<td></td>
<td>NIPPON DATA90</td>
<td>Nationwide‡</td>
<td>1990¹⁰⁻¹¹</td>
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<td>2759</td>
<td>57 11</td>
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<tr>
<td></td>
<td>Ibaraki</td>
<td>Ibaraki</td>
<td>1993¹¹²⁻²²</td>
<td>10 2</td>
<td>33 134</td>
<td>61 10</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td></td>
<td></td>
<td>10 3</td>
<td>70 558</td>
<td>60 10</td>
</tr>
</tbody>
</table>

| Women             | Tanno-Sobetsu                    | Hokkaido                                     | 1977²⁻⁸           | 18 4                | 971               | 51 7            | 134 20         | 82 10          |
|                   | Osaki                            | Miyagi                                       | 1994             | 6 1                 | 9312              | 62 9            | 130 18         | 78 11          |
|                   | Ohasama                          | Iwate                                        | 1987¹⁰           | 10 2                | 1678              | 60 10           | 130 17         | 73 11          |
|                   | Oyabe                            | Ishikawa                                     | 1988¹¹           | 10 1                | 3208              | 58 10           | 126 20         | 75 11          |
|                   | YKK workers                      | Toyama                                       | 1990¹²           | 11 2                | 1724              | 50 6            | 115 15         | 70 11          |
|                   | SPMI cohort                      | Shiga                                        | 1989⁻¹⁹¹³         | 9 3                 | 2596              | 55 8            | 132 17         | 79 10          |
|                   | Suita                            | Osaka                                        | 1987¹⁵⁻¹⁶         | 6 2                 | 2619              | 58 11           | 129 22         | 77 12          |
|                   | RERF cohort                      | Hiroshima                                    | 1986¹⁶           | 15 5                | 3121              | 63 12           | 135 23         | 81 12          |
|                   | Hisayama                         | Fukuoka                                      | 1988¹⁷           | 11 3                | 1518              | 59 12           | 133 22         | 76 11          |
|                   | JACC study                       | Nationwide‡                                   | 1988⁻¹⁹¹⁰         | 10 2                | 19 210            | 57 9            | 132 19         | 78 11          |
|                   | NIPPON DATA80                    | Nationwide‡                                   | 1980¹⁰⁻¹¹         | 17 4                | 4020              | 56 11           | 139 22         | 81 12          |
|                   | NIPPON DATA90                    | Nationwide‡                                   | 1990¹⁰⁻¹¹         | 10 2                | 3697              | 58 12           | 138 20         | 81 12          |
|                   | Ibaraki                          | Ibaraki                                      | 1993¹¹²⁻²²        | 10 2                | 63 909            | 59 10           | 132 18         | 78 11          |
|                   | Total                            |                                              |                   | 10 3                | 117 583           | 58 10           | 132 19         | 78 11          |

*In the studies of Tanno-Sobetsu, Ohasama, and Oyabe, ex-smokers were classified as never-smokers.
†In the studies of Tanno-Sobetsu, Ohasama, and Oyabe, ex-drinkers were classified as never-drinkers.
‡In this nationwide cohort study, study participants were from all areas of Japan.

(Continued)
blood pressure data to estimate the hazard ratio. Body mass index, smoking status (smokers, ex-smokers, or never-smokers), drinking status (drinkers, ex-drinkers or never-drinkers), and cohort were included in the model as confounders. Person-years of observation was separated into 5 categories (1 for every 10 years from age 40 to age 80 years) and used as an offset variable in Poisson regression. Multivariate adjusted mortality rates were estimated from the Poisson regression. Mortality rates among groups were calculated after adjusting for the population-averaged effects of confounders (eg, smoking, drinking, and mean body mass index).

The MacMahon and Peto method was used to correct for regression dilution bias of blood pressure.4,23 The dilution factors of blood pressure were derived from longitudinal blood pressure measurements made by the Ohasama Study that followed 1900 participants from 1999 to 2002. From the data, the calculated regression dilution ratio was 0.59 for SBP and 0.48 for DBP. Hazard ratio for total mortality according to the JNC-7 definition was also estimated in the analysis. The prehypertension (120≤SBP<140 mm Hg or 80≤DBP<90 mm Hg), hypertension stage 1 (140≤SBP<160 mm Hg or 90≤DBP<100 mm Hg), and hypertension stage 2 (160 mm Hg≤SBP or 100 mm Hg≤DBP) groups were compared with the normal reference groups (<120 mm Hg for SBP and <80 mm Hg for DBP).

The population-attributable fraction of high blood pressure according to the JNC 7 classification was calculated from the hazard ratio. Two reference levels (the normal and below prehypertension [normal plus prehypertension]) and the excess hazard ratio were used to calculate the population-attributable fraction. The prevalence of hypertension was set as the total number of participants in this study.24 All of the statistical analysis was performed using SAS release 9.13 (SAS Institute Inc).

### Results

Table 1 shows baseline characteristics of participants in each cohort. There were 188 141 participants (men: 70 558; women: 117 583). Average age at study entry was 59.6 years in men and 58.4 years in women, and the average follow-up...
The period was 9.6 years in men and 9.9 years in women. The total number of deaths (all-cause) was 17,757 (men: 9,880; women: 7,877). The characteristics of the cohorts were similar, and no apparent differences in hazard ratio were found at each blood pressure level. In our study, we analyzed participants without cardiovascular disease history. Because there was no information of cardiovascular disease history in the Tanno-Sobetsu cohort, we excluded these participants, and, therefore, 176,389 (male: 65,463; female: 110,926) participants were investigated in our study.

Table 2 shows the multivariate-adjusted mortality ratio for all-cause mortality for each 10-mm Hg blood pressure increase. In all of the age groups and categories, the hazard ratios were statistically significant. The hazard ratio was larger in the younger group than in the older group. The effect of modifying age was apparent when we included the interaction terms of age and blood pressure into the model (men: $P<0.01$ in both SBP and DBP; women: $P=0.02$ in SBP and $P=0.05$ in DBP). Although we excluded body mass index or alcohol drinking from confounding factors, our result did not change largely.

Table 3 shows the multivariate-adjusted hazard ratio for all-cause mortality according to JNC-7 criteria. Although they fluctuated in some categories to some extent, hazard ratio gradually increased in all of the sex and age categories. With some exceptions, the hazard ratio in groups with hypertension was consistently higher for almost every age range in both men and women.
The population-attributable fraction for each age range was similar in men and women. In men, except for age 80 to 89 years, 10.5%, the population-attributable fraction was approximately 20% to 30%. Except for the lowest population-attributable fraction in women aged 40 to 49 and aged 80 to 89 years, the population-attributable fraction was approximately 10% to 20%. For the overall population, the population-attributable fraction of nonnormal blood pressure was 22.7% in men and 17.9% in women. The population-attributable fraction became smaller when the reference was the combination of normal and nonnormal blood pressure as compared with the normal group alone.

### Discussion

On the basis of a meta-analysis of individual data from 176,389 Japanese participants, we confirmed that high blood pressure affects total mortality in all age categories. We found that there was an apparent effect modification by age and blood pressure and that hazard ratio was higher in younger than in older groups. We also examined the impact of primary prevention of high blood pressure on total mortality by calculating the population-attributable fraction and found that it was considerable in both men and women.

Blood pressure values are known to be relatively higher in Japan than other developed countries. Thus, the contribution of high blood pressure to all-cause mortality should be higher in Japan than other countries. Thus, it should be important to know how many all-cause deaths are attributable to high blood pressure in different age groups. Our huge data set from 180,000 participants can be used to show the health consequence of high blood pressure in Japan. Each of our cohort studies was well administered and provided reliable data sets. The cohort studies were conducted all over Japan, confirming that our results are applicable to the general population in Japan.

Prospective studies collaboration showed that the relation of blood pressure to cardiovascular disease mortality was stronger in younger than in older subjects. Recent studies in Japan showed that risk (all causes and cardiovascular disease) of high blood pressure in the Japanese population has increased. The increasing trends in age-specific and age-adjusted hazard ratios were observed in nationwide cohort studies, and sex- and age- (aged 40 to 59 years and aged 60 to 79 years) specific hazard ratios showed increasing trends in the large-scale cohort study of the Ibaraki prefecture. These studies raised the possibility that the association of blood pressure with all-cause mortality was stronger in the younger than in the older Japanese population. A data set from a huge population after fine age stratification could be used to prove findings that were never shown in Asian (Japanese) populations. We found significant interaction between age and blood pressure for all-cause mortality. This

<table>
<thead>
<tr>
<th>Age Category, y</th>
<th>No. of Deaths</th>
<th>SBP Hazard Ratio (95% CI)</th>
<th>DBP Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 to 49</td>
<td>137</td>
<td>1.37 (1.15 to 1.62)</td>
<td>1.46 (1.05 to 2.03)</td>
</tr>
<tr>
<td>50 to 59</td>
<td>566</td>
<td>1.23 (1.14 to 1.33)</td>
<td>1.42 (1.21 to 1.65)</td>
</tr>
<tr>
<td>60 to 69</td>
<td>1900</td>
<td>1.16 (1.11 to 1.21)</td>
<td>1.28 (1.17 to 1.40)</td>
</tr>
<tr>
<td>70 to 79</td>
<td>3782</td>
<td>1.14 (1.11 to 1.17)</td>
<td>1.21 (1.13 to 1.29)</td>
</tr>
<tr>
<td>80 to 89</td>
<td>2183</td>
<td>1.09 (1.05 to 1.13)</td>
<td>1.12 (1.03 to 1.22)</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 to 49</td>
<td>128</td>
<td>1.19 (1.00 to 1.41)</td>
<td>1.40 (1.00 to 1.95)</td>
</tr>
<tr>
<td>50 to 59</td>
<td>518</td>
<td>1.16 (1.07 to 1.26)</td>
<td>1.38 (1.17 to 1.64)</td>
</tr>
<tr>
<td>60 to 69</td>
<td>1392</td>
<td>1.21 (1.15 to 1.27)</td>
<td>1.29 (1.16 to 1.44)</td>
</tr>
<tr>
<td>70 to 79</td>
<td>2708</td>
<td>1.12 (1.08 to 1.16)</td>
<td>1.25 (1.15 to 1.35)</td>
</tr>
<tr>
<td>80 to 89</td>
<td>2258</td>
<td>1.07 (1.03 to 1.11)</td>
<td>1.12 (1.03 to 1.22)</td>
</tr>
<tr>
<td>Men and women combined</td>
<td>40 to 49</td>
<td>265</td>
<td>1.27 (1.13 to 1.44)</td>
</tr>
<tr>
<td>50 to 59</td>
<td>1084</td>
<td>1.20 (1.14 to 1.27)</td>
<td>1.40 (1.25 to 1.58)</td>
</tr>
<tr>
<td>60 to 69</td>
<td>3292</td>
<td>1.18 (1.15 to 1.22)</td>
<td>1.29 (1.20 to 1.38)</td>
</tr>
<tr>
<td>70 to 79</td>
<td>6490</td>
<td>1.13 (1.11 to 1.16)</td>
<td>1.22 (1.16 to 1.29)</td>
</tr>
<tr>
<td>80 to 89</td>
<td>4441</td>
<td>1.08 (1.05 to 1.11)</td>
<td>1.12 (1.05 to 1.19)</td>
</tr>
</tbody>
</table>

Poisson regression models were used for estimating hazard ratio after adjusting for smoking, drinking and body mass index. To correct regression dilution bias, parameter estimates were multiplied by regression dilution factors (SBP: 0.59; DBP: 0.48).

The population-attributable fraction for each age range was similar in men and women. In men, except for age 80 to 89 years, 10.5%, the population-attributable fraction was approximately 20% to 30%. Except for the lowest population-attributable fraction in women aged 40 to 49 and aged 80 to 89 years, the population-attributable fraction was approximately 10% to 20%. For the overall population, the population-attributable fraction of nonnormal blood pressure was 22.7% in men and 17.9% in women. The population-attributable fraction became smaller when the reference was the combination of normal and prehypertension groups as compared with the normal group alone.

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Table 3. Multivariate Adjusted Hazard Ratio of All-Cause Mortality According to JNC-7 Classification, During Average 9.8 Years of Follow-Up

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age Category</th>
<th>Total deaths</th>
<th>Person-years</th>
<th>Hazard ratio</th>
<th>95% CI (Reference: Normal)</th>
<th>PAF (%) (Reference: Normal)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Normal</td>
<td>Prehypertension</td>
<td>Hypertension (Stage 1)</td>
<td>Hypertension (Stage 2)</td>
<td>Normal Prehypertension</td>
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<tr>
<td>Men</td>
<td>40 to 49</td>
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<td>67</td>
<td>26</td>
<td>21</td>
<td>30.2</td>
</tr>
<tr>
<td></td>
<td>Person-years</td>
<td>18 883</td>
<td>36 082</td>
<td>15 004</td>
<td>4899</td>
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<tr>
<td></td>
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<td>1</td>
<td>1.45</td>
<td>1.28</td>
<td>3.38</td>
<td>(0.89 to 2.38)</td>
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<tr>
<td></td>
<td>50 to 59</td>
<td>101</td>
<td>222</td>
<td>144</td>
<td>99</td>
<td>18.9</td>
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<td></td>
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<td>66 316</td>
<td>38 648</td>
<td>15 206</td>
<td>1.11</td>
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<td></td>
<td></td>
<td>1</td>
<td>1.11</td>
<td>1.27</td>
<td>2.24</td>
<td>(0.87 to 1.41)</td>
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<td>691</td>
<td>644</td>
<td>367</td>
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<td></td>
<td>Person-years</td>
<td>28 313</td>
<td>79 508</td>
<td>69 671</td>
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<td>55 249</td>
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<td>25 027</td>
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<td>1.12</td>
<td>1.36</td>
<td>1.60</td>
<td>(0.99 to 1.27)</td>
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<td></td>
<td>80 to 89</td>
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<td>844</td>
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<td>Person-years</td>
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<td>10 787</td>
<td>13 091</td>
<td>60 82</td>
<td>1.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>1.05</td>
<td>1.11</td>
<td>1.31</td>
<td>(0.88 to 1.25)</td>
</tr>
<tr>
<td>Women</td>
<td>40 to 49</td>
<td>48</td>
<td>53</td>
<td>21</td>
<td>6</td>
<td>9.6</td>
</tr>
<tr>
<td></td>
<td>Person-years</td>
<td>56 053</td>
<td>59 600</td>
<td>17 701</td>
<td>4 817</td>
<td>1.09</td>
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<td>Person-years</td>
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<tr>
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<td>91 441</td>
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<td>Person-years</td>
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<td>120</td>
<td>47</td>
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<td>Person-years</td>
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<td>1</td>
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<td>1.28</td>
<td>2.48</td>
<td>(0.90 to 1.65)</td>
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(Continued)
Table 3. Continued

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<th>Sex</th>
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<td>Normal</td>
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<td>(1.72 to 2.69)</td>
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<td>1.39</td>
<td>1.95</td>
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<tr>
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<td>95% CI</td>
<td>(1.09 to 1.37)</td>
<td>(1.23 to 1.57)</td>
<td>(1.70 to 2.23)</td>
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<tr>
<td>70 to 79</td>
<td>Total deaths</td>
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<td>2070</td>
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<td>1.54</td>
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<tr>
<td></td>
<td>95% CI</td>
<td>(0.96 to 1.16)</td>
<td>(1.18 to 1.41)</td>
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<td>80 to 89</td>
<td>Total deaths</td>
<td>377</td>
<td>1349</td>
<td>1685</td>
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<tr>
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<td>95% CI</td>
<td>(0.90 to 1.15)</td>
<td>(0.96 to 1.22)</td>
<td>(1.08 to 1.39)</td>
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</table>

Poisson regression models were used for estimating hazard ratio after adjusting for smoking, drinking, and body mass index. Classification of blood pressure status is according to JNC 7 guidelines (unit: mm Hg). Normal: SBP<120 and DBP<80; prehypertension: 120≤SBP<140 and 80≤DBP<90; hypertension (stage 1): 140≤SBP<160 and 90≤DBP<100; hypertension (stage 2): 160≤SBP and 100≤DBP, participants with hypertensive medication. Normal blood pressure level was set as the reference level. Population attributable fraction (PAF) was calculated in 2 ways. The reference level was set at (1) the normal blood pressure level and (2) below prehypertension (normal and prehypertension) level. Weighted averages of age-specific PAF, of which weights were person-years in each age category, were calculated as common PAFs. Common PAF was 22.7% in men, 17.9% in women, and 20.6% in men and women combined (reference: normal) and 11.9% in men, 10.9% in women, and 11.9% in men and women combined (reference: normal + prehypertension).

suggests that aggressive primary prevention of high blood pressure by all-cause mortality reduction benefits younger more than older people, although the absolute level of all-cause mortality was lower in younger than in older participants. As a consequence, absolute risk reduction should be lower in younger than in older people. Conversely, although the hazard ratio of high blood pressure was relatively lower in the elderly, absolute risk reduction should be higher in older than in younger people. Thus, the risk of hypertension should be age dependent. Because risk reduction is smaller in younger people, the high-risk approach might not be cost-effective. Therefore, the population approach is more suitable in younger than in older individuals. Conversely, for older individuals, the high-risk approach might be more beneficial.

The impact of lower blood pressure on the total mortality was determined by the population-attributable fraction. The study by Sairenchi et al21 showed that the population-attributable fraction is ≈10% in men and 3% in women. In our study, the EPOCH-JAPAN estimated an age-specific population-attributable fraction for the contribution of blood pressure. In younger age ranges, a large number of deaths can be avoided by lowering blood pressure. This impact of blood pressure decreased with increasing age. When the prehypertension group was used for reference, the population-attributable fraction was ≈10% in each group. This proportion showed that lowering blood pressure is still effective even when all of the participants have prehypertension, which is a level of blood pressure that is achievable in practice.

We confirmed that all-cause mortality is consistently higher in individuals with prehypertension than in individuals with normal blood pressure. Thus, recommending lifestyle modification for them might reduce their all-cause mortality. However, because the absolute risk difference between normal blood pressure and prehypertension was not large, and population-attributable fraction was small, antihypertensive medication for them might not be recommended. Thus, we considered that the JNC-7 recommendation to modify lifestyle is the appropriate measure for prehypertension participants.

Hypertension is a leading cause of cardiovascular disease mortality and, thus, is a main contributor to total mortality. One of the advantages of selecting total mortality as an end point is that there is no misclassification issue in all-cause deaths compared with disease-specific ones. Although the interpretation of hypertension effect on total mortality was not intuitive, our examination of total mortality provided substantial information for public health purposes.

There were limitations in this study. First, the pooled data of most of the cohort studies were from baseline surveys performed during community health examinations. Participants in the cohort study volunteered to receive their health examinations, and for that reason their characteristics might be somewhat different from those of nonparticipants. This would influence the absolute measure of effect (mortality rate) and might underestimate the risk. However, these differences have little effect on relative measures of effect (such as hazard ratio). Thus, we considered that comparing
hazard ratios between age groups or population-attributable fractions might be largely unaffected. Second, we did not adjust for diabetes in this study. Because diabetes is an obesity-related risk factor for hypertension, we might have overestimated the risk posed by hypertension, per se. However, because prevalence of diabetes was very low during the baseline period in Japan, we believe that not adjusting for diabetes should have no substantial effect on our result.

In conclusion, high blood pressure raised the risk of total mortality, and this increase was higher relatively, but not absolutely, in younger than in older individuals. A relatively large amount of the population-attributable fraction was observed in the younger age group. Blood pressure management is an important preventive measure for the Japanese population regardless of age.

**Perspectives**

The present study showed the relation between blood pressure and total mortality in the Japanese population in detail. The results showed that apparent relation between blood pressure and total mortality was present not only in the elderly but also in a younger age group for both men and women. The result encourages us that blood pressure management was an important preventive measure for Japanese participants regardless of age. Furthermore, the people with prehypertension showed high hazard ratios in most age groups. This detailed information would provide effective public health policy and clinical practice not only in the Japanese but also in the Asian population.

**Appendix**

Evidence for Cardiovascular Prevention From Observational Cohorts in Japan Research Group is composed of the following individuals: chairperson: Hirotsugu Ueshima (Shiga University of Medical Science); writing committee: Yoshitaka Murakami, Atsushi Hozawa, Tomonori Okamura, and Hirotsugu Ueshima; statistical analysis: Yoshitaka Murakami; and the executive committee: Hirotsugu Ueshima (Shiga University of Medical Science), Yutaka Tsubono (Tohoku University Graduate School of Medicine), Yutaka Kiyohara (Kyushu University Graduate School of Medicine), Kazunori Kodama (Radiation Effects Research Foundation), Hideaki Nakagawa (Kanazawa Medical University), Takeo Nakayama (Kyoto University School of Public Health), Tomomori Okamura (National Cardiovascular Center), Akira Okayama (Japan Anti-Tuberculosis Association), Shigeyuki Saitho (Sapporo Medical University), Akiko Tamakoshi (National Center for Geriatrics and Gerontology), Ichiro Tsuji (Tohoku University Graduate School of Medicine), and Yoko Izumi (Ibaraki Prefecture).

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**Disclosures**

None.

**References**


Relation of Blood Pressure and All-Cause Mortality in 180 000 Japanese Participants: Pooled Analysis of 13 Cohort Studies

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