Although the methodology (e.g. the type of endpoint and the definition of nonsmokers, hypertension and high serum cholesterol) was not exactly the same between studies, our results are consistent with the results of the first cohort of the Hisayama study [32], which only investigated the effects of these risk factors on coronary heart disease and cerebral infarction. The coexistence of smoking and hypertension increased the risk of incident coronary heart disease by approximately 5-fold and the risk of incident nonembolic cerebral infarction by approximately 4-fold, compared with the absence of these two risk factors in a Japanese population [32]. In addition, the coexistence of smoking and high serum cholesterol increased coronary risk by approximately 4-fold [32]. Our large-scale study provided reliable information on this topic, emphasizing the need to consider concomitant hypertension or high serum cholesterol on the cardiovascular risks of smoking. Smokers with high serum cholesterol were broadly comparable to hypertensive smokers only for coronary mortality risk, as there is evidence that high serum cholesterol has little effect on cerebral infarction in the Japanese [18, 39]. However, unlike our study and the first cohort of the Hisayama study [32], the third cohort of the Hisayama study [33] recently reported that the risk of incident ischemic stroke was higher in smokers with than without hypercholesterolemia. Despite the absence of interaction between smoking habit and blood pressure or serum total cholesterol for coronary heart disease and cerebral infarction, there was some evidence of an interaction between smoking habit and blood pressure for intracerebral hemorrhage. However, it is difficult to explain the observed interaction (i.e. synergistic or otherwise) and the pathophysiological mechanisms responsible for the interaction. Furthermore, the power of this analysis could have been limited by an insufficient number of intracerebral hemorrhage deaths in hypertensive smokers and in hypercholesterolemic smokers. As a consequence, these results regarding intracerebral hemorrhage may have been due to chance.

Our PAF estimates suggest that male hypertensive smokers are special targets for reducing the global burden of premature death and disability due to cardiovascular disease in the Japanese population because of the large contribution of these smokers to the burden of cardiovascular disease deaths among men. NIPPON DATA80 [20] estimated that the PAF of cardiovascular disease due to the coexistence of current smoking and hypertension in Japanese men was 42.4% for those less than 60 years and 18.6% for those 60 years or older, but did not estimate the PAF for coronary heart disease and stroke separately. Our study indicates that male hypertensive smokers contribute significantly to the burden of deaths from both coronary heart disease and stroke. However, hypercholesterolemic smokers contribute less than hypertensive smokers to the total burden of cardiovascular disease deaths because of the lower prevalence of hypercholesterolemic smokers among Japanese men and their lower risk of cardiovascular mortality.

Several limitations should be acknowledged in the present study. First, to maximize the availability of data on smoking habits from potentially participating cohorts, we defined the three categories of smoking habits without considering the number of cigarettes smoked. Second, we assumed that the smoking habit at baseline remained unchanged throughout the follow-up period although it is likely that some current smokers quit smoking during the follow-up period. Moreover, extensive passive exposure to environmental tobacco smoke either at home or in the workplace may have been common, due to the high prevalence of smoking among Japanese men [20] and insufficient restriction of smoking in public places at that time. These limitations may have led to an underestimation of the true harm of active smoking [40]. Third, both hypertension and high serum cholesterol were defined without considering the use of medications that lower blood pressure or serum cholesterol. Furthermore, the levels of blood pressure and serum total cholesterol could have changed due to lifestyle modification and/or prescribed medications over the follow-up period although this was also present in other prospective studies in which the baseline levels of these factors were assumed to remain unchanged throughout the follow-up period. As a whole, these limitations may also have led to misclassification of the blood pressure and serum cholesterol categories, which may have resulted in an underestimation of the cardiovascular mortality risk due to the coexistence of smoking and hypertension or high serum cholesterol. Fourth, we could not calculate hazard ratios for subarachnoid hemorrhage mortality because there were only 75 documented deaths due to this subtype (20 in men and 55 in women). Fifth, we could not determine the cardiovascular mortality risk in smokers who had both hypertension and high serum cholesterol, because of the small number of cardiovascular deaths in this group. Finally, due to limited baseline information, no adjustment was made for diabetes in our analyses. However, this may not have had a large effect on our results because of the low prevalence of diabetes at that time in Japan [41].

In conclusion, smoking is definitely an undesirable habit that can lead to an increased risk of mortality from

both coronary heart disease and cerebral infarction. Furthermore, smoking increases the burden of cardiovascular disease in Japan due to its high popularity. Particular attention should be given to smokers who have another cardiovascular risk factor, such as hypertension or high serum cholesterol, because the combination of these risk factors substantially increases the mortality risk from coronary heart disease and cerebral infarction. Therefore, smokers with a concomitant risk factor should have rigorous counseling for smoking cessation and other lifestyle modifications. From a public health perspective in Japan, priority should be given to hypertensive smokers since this group makes a large contribution to the burden of both coronary deaths and cerebral infarction deaths.

Acknowledgments

This study was supported by a Grant-in-Aid from the Ministry of Health, Labor and Welfare, Health and Labor Sciences Research Grants, Japan (Research on Health Services: H17-Kenkou-007; Comprehensive Research on Cardiovascular and Life-Style Related Diseases: H18-Junkankitou [Seishuu]-Ippan-012; Comprehensive Research on Cardiovascular and Life-Style Related Diseases: H20-Junkankitou [Seishuu]-Ippan-013; and Comprehensive Research on Cardiovascular and Life-Style Related Diseases: H23-Junkankitou [Seishuu]-Ippan-005).

Disclosure Statement

None declared.

Appendix

The EPOCH-JAPAN Research Group

Chairperson: Hirotsugu Ueshima (Shiga University of Medical Science);

Executive committee: Hirotsugu Ueshima (Shiga University of Medical Science), Yutaka Imai (Tohoku University Graduate School of Medicine), Fujiko Irie (Ibaraki Prefecture), Hiroyasu Iso (Osaka University Graduate School of Medicine), Yutaka Kiyohara (Kyushu University Graduate School of Medicine), Katsuyuki Miura, Yoshitaka Murakami (Shiga University of Medical Science), Hideaki Nakagawa (Kanazawa Medical University), Takeo Nakayama (Kyoto University School of Public Health), Tomonori Okamura (Keio University), Akira Okayama (Japan Anti-Tuberculosis Association), Toshimi Sairenchi (Dokkyo Medical University), Shigeyuki Saitoh (Sapporo Medical University), Kiyomi Sakata (Iwate Medical University), Akiko Tamakoshi (Aichi Medical University), Ichiro Tsuji (Tohoku University Graduate School of Medicine), Michiko Yamada (Radiation Effects Research Foundation).

References

1 Mathers CD, Boerma T, Ma Fat D: Global and regional causes of death. Br Med Bull 2009;92:7–32.

2 Health and Welfare Statistics Association: 2010/2011 Kokumin Eisei No Doko (Trend for National Health and Hygiene, Japan) (in Japanese). Tokyo, Health and Welfare Statistics Association, 2010.

3 Asia Pacific Cohort Studies Collaboration: Smoking, quitting, and the risk of cardiovascular disease among women and men in the Asia-Pacific region. Int J Epidemiol 2005;34:1036–1045.

4 Katanoda K, Marugame T, Saika K, Satoh H, Tajima K, Suzuki T, Tamakoshi A, Tsugane S, Sobue T: Population attributable fraction of mortality associated with tobacco smoking in Japan: a pooled analysis of three large-scale cohort studies. J Epidemiol 2008;18:251–264.

5 Honjo K, Iso H, Tsugane S, Tamakoshi A, Satoh H, Tajima K, Suzuki T, Sobue T: The effects of smoking and smoking cessation on mortality from cardiovascular disease among Japanese: pooled analysis of three large-scale cohort studies in Japan. Tob Control 2010;19:50–57.

6 Gu D, Kelly TN, Wu X, Chen J, Samet JM, Huang JF, Zhu M, Chen JC, Chen CS, Duan X, Klag MJ, He J: Mortality attributable to smoking in China. N Engl J Med 2009;360:150–159.

7 Kelly TN, Gu D, Chen J, Huang JF, Chen JC, Duan X, Wu X, Chen CS, He J: Cigarette smoking and risk of stroke in the Chinese adult population. Stroke 2008;39:1688–1693.

8 Jee SH, Suh I, Kim IS, Appel LJ: Smoking and atherosclerotic cardiovascular disease in men with low levels of serum cholesterol: the Korea Medical Insurance Corporation Study. JAMA 1999;282:2149–2155.

9 Jee SH, Park J, Jo I, Lee J, Yun S, Yun JE, Jang Y: Smoking and atherosclerotic cardiovascular disease in women with lower levels of serum cholesterol. Atherosclerosis 2007;190:306–312.

10 Lawlor DA, Song YM, Sung J, Ebrahim S, Smith GD: The association of smoking and cardiovascular disease in a population with low cholesterol levels: a study of 648,346 men from the Korean national health system prospective cohort study. Stroke 2008;39:760–767.

11 Nakamura K, Huxley R, Ansary-Moghaddam A, Woodward M: The hazards and benefits associated with smoking and smoking cessation in Asia: a meta-analysis of prospective studies. Tob Control 2009;18:345–353.

12 Martiniuk AL, Lee CM, Lam TH, Huxley R, Suh I, Jamrozik K, Gu DF, Woodward M; Asia Pacific Cohort Studies Collaboration: The fraction of ischaemic heart disease and stroke attributable to smoking in the WHO Western Pacific and South-East Asian regions. Tob Control 2006;15:181–188.

13 Asia Pacific Cohort Studies Collaboration: Blood pressure and cardiovascular disease in the Asia Pacific region. J Hypertens 2003;21:707–716.

14 Nippon Data 80 Research Group: Impact of elevated blood pressure on mortality from all causes, cardiovascular diseases, heart disease and stroke among Japanese: 14 year follow-up of randomly selected population from Japanese-Nippon data 80. J Hum Hypertens 2003;17:851–857.

15 Suzuki K, Izumi M, Sakamoto T, Hayashi M: Blood pressure and total cholesterol level are critical risks especially for hemorrhagic stroke in Akita, Japan. Cerebrovasc Dis 2011; 31:100–106.
16 Asia Pacific Cohort Studies Collaboration: Cholesterol, coronary heart disease, and stroke in the Asia Pacific region. Int J Epidemiol 2003;32:563–572.
17 Okamura T, Tanaka H, Miyamatsu N, Hayakawa T, Kadowaki T, Kita Y, Nakamura Y, Okayama A, Ueshima H; NIPPON DATA80 Research Group: The relationship between serum total cholesterol and all-cause or cause-specific mortality in a 17.3-year study of a Japanese cohort. Atherosclerosis 2007; 190:216–223.
18 Tanabe N, Iso H, Okada K, Nakamura Y, Harada A, Ohashi Y, Ando T, Ueshima H; Japan Arteriosclerosis Longitudinal Study Group: Serum total and non-high-density lipoprotein cholesterol and the risk prediction of cardiovascular events – the JALS-ECC. Circ J 2010;74:1346–1356.
19 Martiniuk AL, Lee CM, Lawes CM, Ueshima H, Suh I, Lam TH, Gu D, Feigin V, Jamrozik K, Ohkubo T, Woodward M; Asia-Pacific Cohort Studies Collaboration: Hypertension: its prevalence and population-attributable fraction for mortality from cardiovascular disease in the Asia-Pacific region. J Hypertens 2007;25:73–79.
20 Hozawa A, Okamura T, Murakami Y, Kadowaki T, Nakamura K, Hayakawa T, Kita Y, Nakamura Y, Abbott RD, Okayama A, Ueshima H; NIPPON DATA80 Research Group: Joint impact of smoking and hypertension on cardiovascular disease and all-cause mortality in Japan: NIPPON DATA80, a 19-year follow-up. Hypertens Res 2007;30: 1169–1175.
21 Japan Heart Foundation: The Fifth National Survey on Circulatory Disorders (in Japanese). Tokyo, Chuohoki Publishers, 2003.
22 Woodward M, Martiniuk A, Ying Lee CM, Lam TH, Vanderhoorn S, Ueshima H, Fang X, Kim HC, Rodgers A, Patel A, Jamrozik K, Huxley R; Asia Pacific Cohort Studies Collaboration: Elevated total cholesterol: its prevalence and population attributable fraction for mortality from coronary heart disease and ischaemic stroke in the Asia-Pacific region. Eur J Cardiovasc Prev Rehabil 2008; 15:397–401.
23 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.
24 Ueshima H: Explanation for the Japanese paradox: prevention of increase in coronary heart disease and reduction in stroke. J Atheroscler Thromb 2007;14:278–286.
25 Khalili P, Nilsson PM, Nilsson JA, Berglund G: Smoking as a modifier of the systolic blood pressure-induced risk of cardiovascular events and mortality: a population-based prospective study of middle-aged men. J Hypertens 2002;20:1759–1764.
26 Shaten BJ, Kuller LH, Neaton JD: Association between baseline risk factors, cigarette smoking, and CHD mortality after 10.5 years. MRFIT Research Group. Prev Med 1991;20:655–659.
27 Cullen P, Schulte H, Assmann G: Smoking, lipoproteins and coronary heart disease risk. Data from the Münster Heart Study (PROCAM). Eur Heart J 1998;19:1632–1641.
28 Janzon E, Hedblad B, Berglund G, Engström G: Tobacco and myocardial infarction in middle-aged women: a study of factors modifying the risk. J Intern Med 2004;256:111–118.
29 Hozawa A, Folsom AR, Sharrett AR, Payne TJ, Chambless LE: Does the impact of smoking on coronary heart disease differ by low-density lipoprotein cholesterol level?: the Atherosclerosis Risk in Communities (ARIC) Study. Circ J 2006;70:1105–1110.
30 Wolf PA, D'Agostino RB, Kannel WB, Bonita R, Belanger AJ: Cigarette smoking as a risk factor for stroke. The Framingham Study. JAMA 1988;259:1025–1029.
31 Shaper AG, Phillips AN, Pocock SJ, Walker M, Macfarlane PW: Risk factors for stroke in middle aged British men. BMJ 1991;302: 1111–1115.
32 Kiyohara Y, Ueda K, Fujishima M: Smoking and cardiovascular disease in the general population in Japan. J Hypertens 1990; 8(suppl 5):S9–S15.
33 Hata J, Doi Y, Ninomiya T, Fukuhara M, Ikeda F, Mukai N, Hirakawa Y, Kitazono T, Kiyohara Y: Combined effects of smoking and hypercholesterolemia on the risk of stroke and coronary heart disease in Japanese: the Hisayama study. Cerebrovasc Dis 2011;31: 477–484.
34 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.
35 Murakami Y, Miura K, Okamura T, Ueshima H; for the EPOCH-JAPAN Research Group: Population attributable numbers and fractions of deaths due to smoking: a pooled analysis of 180,000 Japanese. Prev Med 2011; 52:60–65.
36 Woodward M: Epidemiology: Study Design and Data Analysis, ed 2. Boca Raton, Chapman & Hall/CRC, 2005.
37 Rockhill B, Newman B, Weinberg C: Use and misuse of population attributable fractions. Am J Public Health 1998;88:15–19. erratum in: Am J Public Health 2008;98:2119.
38 Mannami T, Iso H, Baba S, Sasaki S, Okada K, Konishi M, Tsugane S; Japan Public Health Center-Based Prospective Study on Cancer and Cardiovascular Disease Group: Cigarette smoking and risk of stroke and its subtypes among middle-aged Japanese men and women: the JPHC Study Cohort I. Stroke 2004;35:1248–1253.
39 Okamura T, Kokubo Y, Watanabe M, Higashiyama A, Miyamoto Y, Yoshimasa Y, Okayama A: Low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol and the incidence of cardiovascular disease in an urban Japanese cohort study: The Suita study. Atherosclerosis 2009; 203:587–592.
40 McGhee SM, Ho SY, Schooling M, Ho LM, Thomas GN, Hedley AJ, Mak KH, Peto R, Lam TH: Mortality associated with passive smoking in Hong Kong. BMJ 2005;330:287–288.
41 Tamaki J, Ueshima H, Hayakawa T, Choudhury SR, Kodama K, Kita Y, Okayama A; NIPPON DATA80 Research Group: Effect of conventional risk factors for excess cardiovascular death in men: NIPPON DATA80. Circ J 2006;70:370–375.

Hypertension Research (2012) 35, 947–953

www.nature.com/hr

ORIGINAL ARTICLE

Blood pressure categories and long-term risk of cardiovascular disease according to age group in Japanese men and women

Akira Fujiyoshi[1], Takayoshi Ohkubo[1], Katsuyuki Miura[1], Yoshitaka Murakami[2], Shin-ya Nagasawa[3], Tomonori Okamura[4] and Hirotsugu Ueshima[1,5], for the Evidence for Cardiovascular Prevention From Observational Cohorts in Japan (EPOCH-JAPAN) Research Group[6]

Blood pressure (BP) categories defined by systolic BP (SBP) and diastolic BP (DBP) are commonly used. However, the BP category-specific risk of cardiovascular disease (CVD) has not been thoroughly investigated in different age groups. The aim of this study was to assess long-term CVD risk and its impact according to BP categories and age group. Pooling individual data from 10 cohorts, we studied 67 309 Japanese individuals (40–89 years old) who were free of CVD at baseline: we categorized them as belonging to three age groups: 'middle-aged' (40–64 years), 'elderly' (65–74 years) and 'very elderly' (75–89 years). BP was classified according to the 2009 Japanese Society of Hypertension Guidelines. Cox models were used to estimate adjusted hazard ratios for CVD deaths. We observed 1944 CVD deaths over a mean follow-up of 10.2 years. In all age groups, the overall relationship between BP category and CVD risk was positive, with a greater strength observed for younger age groups. We observed a trend of increased risk from SBP/DBP ⩾ 130/85 mm Hg in the very elderly, and a significant increase from SBP/DBP ⩾ 120/80 mm Hg in the other age groups. The population attributable fractions (PAFs) of CVD death in reference to the SBP/DBP < 120/80 mm Hg category ranged from 23.4% in the very elderly to 60.3% in the middle-aged. We found an overall graded increase in CVD risk with higher BP category in the very elderly. The PAFs suggest that keeping BP levels low is an important strategy for primary CVD prevention, even in an elderly population.
Hypertension Research (2012) **35**, 947–953; doi:10.1038/hr.2012.87; published online 28 June 2012

Keywords: blood pressure category; cardiovascular death; cohort; elderly; population attributable fraction

INTRODUCTION

Epidemiological studies have shown that the effect of both systolic blood pressure (SBP) and diastolic blood pressure (DBP) on the risk of cardiovascular disease (CVD) is continuous and consistent.[1,2] Because both SBP and DBP are independent predictors of CVD risk,[3–7] most guidelines for adult blood pressure (BP) management have proposed similar BP categorization systems with regard to the following: (1) BP categories are defined by taking both SBP and DBP into account, and (2) the most favorable BP category is SBP < 120 mm Hg and DBP < 80 mm Hg, irrespective of age.[8–11]

Although such BP categorization is widely used, there is only limited evidence assessing long-term CVD risk according to BP category, particularly for elderly populations. Given the worldwide trend of aging,[12] assessing the long-term risk of elevated BP and its impact on the aged population is increasingly important from both clinical and public health standpoints. The Framingham Heart Study (FHS) reported graded increases in major CVD risk across higher BP categories among 1932 participants aged ⩾80 years.[13] However, the follow-up period was relatively short (mean, 2.7 years).[13] Therefore, long-term CVD risk was not fully assessed in that study. Other Western studies seeking to assess the BP category-specific risk of CVD events were based on subjects aged ⩽75 years.[5,14–16] Epidemiological studies on long-term CVD risk among an elderly population have also been limited,[17,18] and hence needed,[19] in Asia.

The objectives of this study were (1) to estimate long-term CVD mortality risk according to BP categories defined by both SBP and DBP, (2) to examine whether the relationship between BP categories and CVD risk differs according to age group and (3) to compare the impact of increased BP on long-term CVD risk for different age groups by estimating population attributable fractions (PAFs). We focused particularly on an elderly population.

[1]Department of Health Science, Shiga University of Medical Science, Otsu, Japan; [2]Medical Statistics, Shiga University of Medical Science, Otsu, Japan; [3]Department of Epidemiology and Public Health, Kanazawa Medical University, Uchinada, Japan; [4]Department of Preventive Medicine and Public Health, School of Medicine, Keio University, Tokyo, Japan and [5]Lifestyle-Related Disease Prevention Center, Shiga University of Medical Science, Otsu, Japan
[6]For the member list of the EPOCH-JAPAN Research Group, please see the Appendix
Correspondence: Dr A Fujiyoshi, Department of Health Science, Shiga University of Medical Science, Setatsukinowa-cho, Otsu, Shiga 520-2192, Japan.
E-mail: afujiy@belle.shiga-med.ac.jp
Received 5 December 2011; revised 3 March 2012; accepted 19 March 2012; published online 28 June 2012

METHODS

Design

This study is part of a pooling project in which individual participants' data from 13 observational cohorts across Japan were combined. The project was designed to examine the relationship between disease mortality and various exposure factors, including laboratory and lifestyle/behavioral factors. The project is called Evidence for Cardiovascular Prevention from Observational Cohorts in Japan. The inclusion criteria for the cohorts were as follows: collection of health examination measures, follow-up of almost 10 years and more than 1000 participants. Both nationwide and regional cohort studies were included. Other details are reported elsewhere.[20]

Study population

In all, 10 of 13 cohorts provided data on cause of death ($n=90\,528$). Of those, we used the following exclusion criteria for the present study: age <40 years or >89 years at baseline ($n=10\,528$); history of CVD at baseline ($n=5031$); missing values for SBP, DBP or both ($n=147$); and missing adjusting covariates ($n=7513$). Thus, 67 309 individuals from 10 cohort studies were pooled (Tanno-Sobetsu, Ohsaki, Ohasama, Oyabe, YKK workers, the Radiation Effects Research Foundation cohort, Hsayama, JACC study, NIPPON DATA80 and NIPPON DATA90; see Supplementary Table S1 for the demographics of each cohort).

Death ascertainment

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. Registration of death is required by law and believed to be complete. The underlying cause of death is coded according to the International Classification of Disease (ICD) for National Vital Statistics, based on the criteria proposed by the World Health Organization.[21]

Cause of death was sought in great detail using the available sources in each cohort study. In most studies, death certificates were reviewed and/or National Vital Statistics were used after obtaining permission. Other sources used in some studies included autopsy, medical records, health examination and questionnaires. The cause of death was coded based on either ICD-9 or ICD-10. The classification codes used in the study were as follows: death from CVD (390–459 by ICD-9; I00–I99 by ICD-10), total stroke (410–414 or 430–438; I20–I25 or I60–I69), ischemic stroke (433 or 434 or 437.8; I63 or I69.3), intracerebral hemorrhage (431–432; I61 or I69.1), coronary heart disease (410–414; I20–I25) and heart failure (428; I50).

BP measurement

Detailed information on the BP measurement method for each cohort is provided in Supplementary Table S2. BP measurements were obtained using a mercury sphygmomanometer when each participant was in a seated position in all but two cohort studies. In one cohort (Ohasama), an automated device was used.[22] In the other study (JACC), the BP values were based on self-recorded values after BP had been measured at a health check-up.[23] In most cohorts, BP was measured once with a participant in a seated position after rest.

BP categories

Participants were categorized according to the modified classification of the 2009 Japanese Society of Hypertension Guidelines (JSH2009).[10] The cutoff values for the BP classification were the same as those in the 2007 Guidelines from the European Society of Hypertension and the European Society of Cardiology (ESH-ESC 2007).[8] Optimal BP was defined as SBP <120 mm Hg and DBP <80 mm Hg; the corresponding SBP and DBP values were 120–129 and 80–84 mm Hg for normal/non-optimal BP, 130–139 or 85–89 mm Hg (whichever was greater) for high-normal BP, 140–159 or 90–99 mm Hg for grade I hypertension, 160–179 or 100–109 mm Hg for grade II hypertension, and $\geqslant 180$ or $\geqslant 110$ mm Hg for grade III hypertension, respectively.

Statistical analysis

We estimated multivariable adjusted hazard ratios (HRs) of death from total CVD and its subtypes for each BP category by Cox proportional hazard models, in reference to the optimal BP category. We constructed two models to adjust for potential confounders. First, we adjusted for age (years), sex and cohort (model 1). Second, we further adjusted for serum total cholesterol ($mmol\,l^{-1}$), body mass index ($kg\,m^{-2}$), smoking status (current, past, never)[24] and alcohol intake (current, past, never) (model 2).

To examine whether the relationship between BP category and risk of CVD death differed according to age, we divided participants into three groups based on their age at baseline: 'middle-aged' represented those 40–64 years old, 'elderly' represented those 65–74 years old and 'very elderly' represented those 75–89 years old. The HR and the corresponding PAF for CVD deaths were estimated for each BP category in each age group. To assess heterogeneity, we assumed a monotonic association between CVD risk and BP category and created pertinent variables. In assessing heterogeneity among cohorts, we created a Forest plot.

PAF was calculated as $pd \times (RR-1)/RR$, where pd represents the proportion of exposed deaths in a specific BP category and RR is the corresponding multivariable-adjusted HR in reference to the optimal BP category.[25] Additionally, we calculated gender-specific mortality risks and PAFs for CVD, total stroke, ischemic stroke, intracerebral hemorrhage, coronary heart disease and heart failure according to the BP category. In testing statistical evidence of interaction between sex and BP category on the effect of CVD risk, we first visually confirmed the overall positive relationship between BP category and CVD risk in both sexes. Then, we created an ordinal variable for BP category and its interaction term with sex, and inserted them in the models.

We performed the following sensitivity analyses: (1) excluding those who died from any cause within the first 3 years as an attempt to eliminate potential reverse causality from low BP;[26,27] (2) restricting the subjects to non-users of antihypertensive medication at baseline; and (3) adding diabetes mellitus (DM) status (yes or no) to the models for those participants for whom diabetes-defining variables were available ($n=36\,393$). We defined DM as either a fasting glucose level of $\geqslant 126\,mg\,dl^{-1}$ ($7.0\,mmol\,l^{-1}$), a casual glucose level of $\geqslant 200\,mg\,dl^{-1}$ ($11.1\,mmol\,l^{-1}$), a Hb A1c level of $\geqslant 6.5\%$, a history of DM, or taking medication for DM.

All statistical analyses were performed using SAS version 9.13 (SAS Institute, Cary, NC, USA). All of the P values for statistical tests were two-tailed, and $P<0.05$ were regarded as statistically significant. The study protocol was approved by the internal review board at each study center.

RESULTS

The participants' characteristics at baseline according to BP category are shown in Table 1. The proportion of the participants ($n=67\,309$) in each BP category was 21.9 (optimal BP), 20.2 (normal/non-optimal BP), 21.3 (high-normal BP), 24.9 (grade I hypertension), 9.0 (Grade II hypertension) and 2.7% (grade III hypertension) at baseline. Compared with participants in higher BP categories, those in the optimal BP category tended to be younger and to have a lower body mass index and lower total cholesterol level at baseline. The number of participants categorized as middle-aged, elderly and very elderly was 49 935 (74.2%), 13 707 (20.4%) and 3667 (5.4%), respectively.

During a mean follow-up of 10.2 years, we observed 1944 CVD deaths: 917 from total stroke, 479 from ischemic stroke, 220 from intracerebral hemorrhage, 388 from coronary heart disease and 343 from heart failure in all age groups combined. In the Cox regression models, CVD risk increased almost continuously as the BP category advanced. In disease-specific analyses, the risk of total stroke and coronary heart disease increased similarly as the BP category advanced (see Supplementary Table S3). The PAF estimates indicated that the elimination of normal/non-optimal BP to grade III hypertension could have prevented almost half of the CVD deaths. The results were similar for both sexes, with no statistical evidence of interaction

Table 1 Baseline characteristics of participants according to blood pressure category

	Blood pressure category[a]						
Variable	*Optimal (N = 14764)*	*Normal/non-optimal (N = 13607)*	*High-normal (N = 14325)*	*Grade I hypertension (N = 16729)*	*Grade II hypertension (N = 6079)*	*Grade III hypertension (N = 1805)*	*Total (N = 67309)*
Women, %	66.1	60.0	56.8	55.4	53.6	51.2	58.7
Age, mean (s.d.), years	53.7 (9.7)	55.5 (10.0)	58.0 (10.0)	59.9 (10.0)	61.5 (10.0)	62.1 (10.4)	57.4 (10.3)
Body mass index, mean (s.d.), $kg\,m^{-2}$	22.2 (2.8)	23.0 (2.9)	23.3 (3.0)	23.7 (3.2)	24.0 (3.4)	24.1 (3.6)	23.2 (3.1)
Total cholesterol, mean (s.d.), $mmol\,l^{-1}$[b]	5.05 (0.91)	5.11 (0.93)	5.21 (0.94)	5.23 (0.97)	5.24 (0.99)	5.27 (1.05)	5.16 (0.95)
Smoking							
Never, %	69.5	66.2	64.4	63.1	61.1	58.0	65.1
Past, %	6.7	9.0	10.5	11.6	12.4	12.9	9.9
Current, %	23.8	24.8	25.2	25.3	26.5	29.1	25.1
Drinking							
Never, %	61.5	57.7	55.6	54.8	53.7	51.5	56.8
Past, %	2.7	2.5	2.8	2.8	3.0	3.2	2.8
Current, %	35.8	39.8	41.6	42.4	43.3	45.3	40.4

[a]Blood pressure categories were defined as follows; 'Optimal' as systolic blood pressure <120 mm Hg and diastolic blood pressure <80 mm Hg; the corresponding systolic and diastolic blood pressure values were 120–129 and 80–84 mm Hg for 'Normal/non-optimal,' 130–139 or 85–89 mm Hg (whichever was greater) for 'high-normal,' 140–159 or 90–99 mm Hg for 'grade I hypertension,' 160–179 or 100–109 mm Hg for 'grade II hypertension' and ⩾180 or ⩾110 mm Hg for 'grade III hypertension, respectively.'
[b]The conversion factor for total cholesterol level from $mmol\,l^{-1}$ to $mg\,dl^{-1}$ is 38.67.

(*P* for interaction by sex 0.95) (see Supplementary Table S4 and Supplementary Table S5 for sex-specific results).

The crude death rates, adjusted HRs and PAFs according to BP category for each age group are shown in Table 2. The overall relationship between BP category and CVD risk was positive and graded for all age groups, with a greater strength of association observed in the younger group (*P* value for heterogeneity <0.001). For both the middle-aged and elderly groups, compared with individuals in the optimal BP category, the CVD risk increased significantly for those in the normal/non-optimal BP category and continued to increase overall for those in higher BP categories. For the very elderly group, in contrast, both optimal and normal/non-optimal BP categories appeared to have the lowest CVD risk. The PAFs for CVD death in reference to the optimal BP category tended to be greater for younger groups, accounting for 60, 49 and 23% of all CVD deaths in the middle-aged, elderly and very elderly groups, respectively. There is no statistical evidence that these trends differ according to sex in any of the age groups (*P* values for interaction by sex were 0.23, 0.11 and 0.50 for the middle-aged, elderly and very elderly, respectively). (For sex-specific results by age group, see Supplementary Table S6 and Supplementary Table S7).

The Forest plot by cohort indicated an apparently stronger effect of BP in the YKK workers cohort than in other cohorts (Supplementary Figure S1). However, the confidence interval was wide, and the direction of association was the same as for the other cohorts. Furthermore, exclusion of this cohort did not change the results substantially (data not shown). In the Forest plot, we did not observe a clear difference among methods of BP measurement.

In the first sensitivity analysis, which excluded deaths within the first 3 years, the observed association between the BP category and CVD death became stronger for the very elderly group than it was in the main analysis, such that the CVD risk significantly increased for participants in the high-normal BP category and higher categories (Table 3). The results for other age groups were similar to those in the main analysis. In the second sensitivity analysis, which was restricted to non-users of antihypertensive medication at baseline (29 097 participants, 823 CVD deaths), we observed similar results to the main analysis for all age groups (see Supplementary Table S8). In the third sensitivity analysis, which included DM status in the model, the relationship between BP category and CVD risk was attenuated in both the elderly and very elderly groups, whereas the relationship was slightly strengthened in the middle-aged group (see Supplementary Table S9).

DISCUSSION

This pooled analysis of 10 well-qualified, prospective cohort studies in Japan enabled us to investigate the detailed relationship between BP categories and long-term CVD mortality risk over a broad age range. We found an overall positive relationship for all of the age groups that were studied. In the middle-aged and elderly groups, the risk was lowest for those in the optimal BP category. Importantly, even in the very elderly, the risk appeared to increase from the high-normal BP category to higher BP categories in a graded fashion. The relationship became stronger in this age group when the first 3 years of deaths were excluded. Another important finding of our study is that the impact of elevated BP, as measured by PAF, remained substantial in older groups, suggesting that maintaining optimal BP could have eliminated as many as one-quarter of CVD deaths in the very elderly group and half of those in the elderly group.

In many guidelines, BP categorization involves both SBP and DBP, and the same cutoff values are used irrespective of age.[8–11] However, only a few studies have examined BP category-specific CVD risk in an elderly population. To our knowledge, this is the first observational study that has demonstrated a long-term CVD risk and its impact according to BP category in a group of very elderly (aged ⩾75 years) Asian men and women. From North America/European regions, the FHS showed that major CVD risk increased in a graded fashion with advancing BP category among those aged ⩾80 years.[13] Most other studies from these regions have examined populations aged ⩽75 years.[5,14–16] The FHS observed 336 CVD events among 1932 elderly

Table 2 Cardiovascular death according to blood pressure categories by age group

	Optimal	*Normal/non-optimal*	*High-normal*	*Grade I hypertension*	*Grade II hypertension*	*Grade III hypertension*	*Total*
Very elderly (75–89 years)							
Number at risk	350	483	726	1251	616	241	3667
Person-years	2627	3786	5563	9655	4855	1810	28296
CVD deaths	38	45	105	206	137	60	591
Crude rate[a]	14.46	11.89	18.88	21.34	28.22	33.15	20.89
HR (95% CI)[b]	1	0.83 (0.54–1.28)	1.27 (0.87–1.84)	1.38 (0.97–1.97)	1.46 (1.01–2.12)	1.73 (1.14–2.64)	
PAF (%)[c]	—	−1.6	3.7	9.7	7.3	4.3	23.4
Elderly (65–74 years)							
Number at risk	1880	2227	3105	4290	1735	470	13707
Person-years	16086	19202	26249	38491	15973	4391	120392
CVD deaths	45	96	104	267	146	66	724
Crude rate[a]	2.80	5.00	3.96	6.94	9.14	15.03	6.01
HR (95% CI)[b]	1	1.76 (1.23–2.51)	1.40 (0.99–1.99)	2.20 (1.59–3.03)	2.64 (1.87–3.73)	3.96 (2.67–5.85)	
PAF (%)[c]	—	5.7	4.1	20.1	12.5	6.8	49.3
Middle-aged (40–64 years)							
Number at risk	12534	10897	10494	11188	3728	1094	49935
Person-years	132300	117254	109424	122301	40846	12756	534880
CVD deaths	51	87	102	194	124	71	629
Crude rate[a]	0.39	0.74	0.93	1.59	3.04	5.57	1.18
HR (95% CI)[b]	1	1.77 (1.25–2.51)	1.94 (1.38–2.73)	2.99 (2.17–4.11)	5.23 (3.71–7.35)	8.50 (5.81–12.43)	
PAF (%)[c]	—	6.0	7.9	20.5	15.9	10.0	60.3

Abbreviations: 95% CI, 95% confidence intervals; CVD, cardiovascular disease; HR, hazard ratio; PAF, population attributable fraction.
[a]Crude rate was expressed as per 1000 person-year.
[b]Hazard ratio was adjusted for age, sex, cohort, body mass index ($kg\,m^{-2}$), total cholesterol ($mmol\,l^{-1}$), smoking, and drinking (model 2).
[c]PAF estimate was based on the hazard ratio obtained by model 2.

Table 3 Risk of cardiovascular death in the subgroup with those died in the first 3 years excluded

	Optimal	*Normal/non-optimal*	*High-normal*	*Grade I hypertension*	*Grade II hypertension*	*Grade III hypertension*	*Total*
Very elderly (75–89 years)							
No. at risk	296	429	648	1087	518	190	3168
Person-years	2518	3655	5372	9298	4620	1712	27175
CVD deaths	20	34	81	150	94	40	419
Crude rate[a]	7.94	9.3	15.08	16.13	20.35	23.37	15.42
HR[b]	1	1.17 (0.67–2.04)	1.87 (1.14–3.05)	1.91 (1.19–3.07)	1.83 (1.12–3.01)	2.14 (1.23–3.72)	—
Elderly (65–74 years)							
No. at risk	1829	2141	2980	4136	1655	437	13178
Person-years	15970	18998	25923	38126	15789	4315	119120
CVD deaths	39	78	77	223	117	51	585
Crude rate[a]	2.44	4.11	2.97	5.85	7.41	11.82	4.91
HR[b]	1	1.62 (1.10–2.38)	1.19 (0.81–1.76)	2.01 (1.42–2.85)	2.26 (1.55–3.29)	3.28 (2.13–5.04)	—
Middle-aged (40–64 years)							
No. at risk	12440	10811	10400	11057	3657	1066	49431
Person-years	132096	117053	109187	121997	40667	12700	533700
CVD deaths	40	69	87	155	102	60	513
Crude rate[a]	0.3	0.59	0.8	1.27	2.51	4.72	0.96
HR[b]	1	1.75 (1.19–2.60)	2.08 (1.43–3.05)	2.91 (2.03–4.16)	5.21 (3.55–7.64)	8.39 (5.50–12.8)	—

Abbreviations: CVD, cardiovascular disease; HR, hazard ratio.
[a]Crude rate was expressed as per 1000 person-year.
[b]Hazard ratio (95% confidence interval) adjusted for age (years), sex, cohort, body mass index ($kg\,m^{-2}$), total cholesterol ($mmol\,l^{-1}$), smoking (current, never, past) and drinking (current, never, past).

over a mean of 2.7 years.[13] Compared with the FHS, we observed more than five times as many CVD events among twice as many elderly participants over a mean of 10.2 years. Furthermore, we used six BP categories compared with the four used in the FHS (based on a modified version of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC7) guidelines).[9] Our categorization allows us to show finer BP category-specific CVD risks, such as those for normal/non-optimal BP or high-normal BP categories. Nevertheless, our results were broadly consistent with those in the FHS. There are at least two large-scale meta-analyses with pooled data from individual participants that have studied the association between BP and CVD risk: the Prospective Studies Collaboration (PSC)[2] and the Asia Pacific Cohort Studies Collaboration (APCSC).[28] Although our results

are consistent with the results of these studies, our study differs significantly from both of these studies with respect to BP measurements. The PSC and the APCSC used either continuous DBP or SBP alone, whereas we used BP categories that accounted for both SBP and DBP. Several studies from Japan have reported both BP category-specific risk and/or PAF for CVD events.[29–33] Because of the small sample sizes, however, none of these studies sought detailed estimates for the very elderly population (aged ⩾75 years), unlike the present study. A recent, large, prospective study from China showed both BP category-specific risk and PAF for CVD events.[18] However, this study provided only limited information with regard to BP category-specific risk and impact on the very elderly population because the authors grouped those aged ⩾65 years together and used fewer BP categories (a modified JNC7 categorization similar to the FHS) than did our study.

When excluding the first 3 years of death in the very elderly, we observed a stronger overall relationship between BP category and CVD risk, with a significant increase in risk observed for the high-normal BP category and higher categories. This observation may suggest the presence of reverse causality, in which a poor health condition could have caused a lower BP.[34,35] Exclusion of the first few years of deaths from the analysis was proposed as one way to address reverse causality, particularly when analyzing an elderly population.[26,27,35] Therefore, the lack of difference in CVD risk between the two lowest BP categories in the very elderly group may be attributable to reverse causality. Another possible explanation is that there is an attenuated strength of association between BP and CVD risk in this age group compared with younger age groups.[3,28]

We observed a significant difference in the strength of the association between BP and CVD risk (that is, a difference in the relative risk of CVD) according to age group. Such heterogeneity by age in the effect of BP on CVD risk has been observed consistently in many large observational studies.[18,28,32,36] However, a recent meta-analysis of clinical trials by the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) concluded that there was no evidence of statistical heterogeneity in the effect of BP-lowering therapy on CVD risk between younger and older subjects.[37] We speculate that this discrepancy could be due to differences between observational studies and clinical trials and/or due to a lack of statistical power in the BPLTTC study, as the authors of the study have noted.[37]

Regarding sex-specific differences, we observed that the absolute risk of CVD was generally higher in men than in women in all age groups, whereas the relative risk of CVD according to BP category (expressed as the HR) was similar between men and women (Supplementary Table S4–S7). These findings were consistent with those of previous large observational studies.[18,38]

The PAF estimates calculated in our study imply that, in a Japanese population, BP has a greater impact on CVD risk than does smoking[24,39,40] or elevated cholesterol.[41] Combined with the observed lower CVD risks associated with the lower BP categories, the results endorse maintaining a low BP throughout one's life as an important strategy for CVD prevention, both at an individual level and at the population level. It should be emphasized, however, that our results do not necessarily endorse pharmaceutical treatment for hypertension because the study was an observational study among a general population, and not an interventional study on a group of patients. In fact, recent studies indicate that the use of antihypertensive medication is unlikely to lower the risk of CVD to the same level as the risk for those who remain in low BP categories without such treatment.[42] Furthermore, evidence on pharmaceutical treatment for hypertension in the very elderly is still limited, as stated in the recent consensus document by the American College of Cardiology Foundation and the American Heart Association.[43]

Several limitations need to be considered when interpreting our results. First, we did not take into account the use or non-use of antihypertensive medication in the main analyses because of a substantial amount of missing information. However, the sensitivity analysis that was restricted to non-users of such medication at baseline showed similar results to the main analyses for all three age groups. Thus, it is unlikely that this limitation would materially change our inferences. Second, the study was based on a BP measurement on a single occasion, and it did not account for regression dilution bias.[2] Therefore, the results of the study are likely to underestimate the true association. Third, our estimates in the main analyses were not adjusted for DM. However, we found qualitatively similar results in the sensitivity analysis that adjusted for DM. Therefore, the influence of this limitation on our conclusion would likely be small. One strength of the study is that we pooled data from cohorts with a prospective design with a long follow-up period (over 10 years). Another strength is that the results are likely to be generalizable to a wide age range of adult men and women given that our samples were obtained from across the nation.

In summary, we observed a graded positive trend in CVD mortality risk starting from the high-normal BP category (SBP/DBP > 130/85 mm Hg) continuing up to the higher BP categories among the very elderly group and a significant increase in risk starting from the normal/non-optimal BP category (SBP/DBP > 120/80 mm Hg) up to the higher categories among the middle-aged and elderly groups. The strength of association between the BP category and CVD risk was attenuated but remained positive and graded in the very elderly. PAFs revealed that keeping BP levels low could prevent one-quarter of CVD deaths in the very elderly and one-half of those in the elderly. These findings suggest that maintaining low BP is an important strategy for primary CVD prevention in an elderly population, even among those aged 75–89 years.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

We are grateful to all of the participants in each cohort study. This research was supported by a grant-in-aid from the Ministry of Health, Labour and Welfare, Health and Labor Sciences research grants, Japan (Research on Health Services: H17-Kenkou-007; Comprehensive Research on Cardiovascular Disease and Life-Related Disease: H18-Junkankitou[Seishuu]-Ippan-012; Comprehensive Research on Cardiovascular Disease and Life-Related Disease: H19-Junkankitou [Seishuu]-Ippan-012; Comprehensive Research on Cardiovascular and Life-Style Related Diseases: H20-Junkankitou [Seishuu]-Ippan-013; and Comprehensive Research on Cardiovascular and Life-Style Related Diseases: H23-Junkankitou [Seishuu]-Ippan-005).

1 Stamler J, Stamler R, Neaton JD. Blood pressure, systolic and diastolic, and cardiovascular risks. US population data. *Arch Intern Med* 1993; **153**: 598–615.
2 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.
3 Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; **360**: 1903–1913.
4 Miura K, Dyer AR, Greenland P, Daviglus ML, Hill M, Liu K, Garside DB, Stamler J. Pulse pressure compared with other blood pressure indexes in the prediction of 25-year

cardiovascular and all-cause mortality rates: The Chicago Heart Association Detection Project in Industry Study. *Hypertension* 2001; **38**: 232–237.
5 Domanski M, Mitchell G, Pfeffer M, Neaton JD, Norman J, Svendsen K, Grimm R, Cohen J, Stamler J. Pulse pressure and cardiovascular disease-related mortality: follow-up study of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA* 2002; **287**: 2677–2683.
6 Okayama A, Kadowaki T, Okamura T, Hayakawa T, Ueshima H. Age-specific effects of systolic and diastolic blood pressures on mortality due to cardiovascular diseases among Japanese men (NIPPON DATA80). *J Hypertens* 2006; **24**: 459–462.
7 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.
8 Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Struijker Boudier HA, Zanchetti A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Erdine S, Kiowski W, Agabiti-Rosei E, Ambrosioni E, Lindholm LH, Manolis A, Nilsson PM, Redon J, Struijker-Boudier HA, Viigimaa M, Adamopoulos S, Bertomeu V, Clement D, Farsang C, Gaita D, Lip G, Mallion JM, Manolis AJ, O'Brien E, Ponikowski P, Ruschitzka F, Tamargo J, van Zwieten P, Waeber B, Williams B. The task force for the management of arterial hypertension of the European Society of H, The task force for the management of arterial hypertension of the European Society of C. 2007 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). *Eur Heart J* 2007; **28**: 1462–1536.
9 Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo Jr. JL, Jones DW, Materson BJ, Oparil S, Wright Jr. JT, Roccella EJ. The Seventh Report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. *JAMA* 2003; **289**: 2560–2572.
10 Ogihara T, Kikuchi K, Matsuoka H, Fujita T, Higaki J, Horiuchi M, Imai Y, Imaizumi T, Ito S, Iwao H, Kario K, Kawano Y, Kim-Mitsuyama S, Kimura G, Matsubara H, Matsuura H, Naruse M, Saito I, Shimada K, Shimamoto K, Suzuki H, Takishita S, Tanahashi N, Tsuchihashi T, Uchiyama M, Ueda S, Ueshima H, Umemura S, Ishimitsu T, Rakugi H. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009). *Hypertens Res* 2009; **32**: 3–107.
11 Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF, Sever PS, Mc GTS. Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004-BHS IV. *J Hum Hypertens* 2004; **18**: 139–185.
12 United_Nations. World population ageing: 1950-2050. In Division_Department_of_Economic_and_Social_Affairs_United_Nations P (ed), The 2002 World Assembly on Ageing. United Nations Publications: New York 2001.
13 Lloyd-Jones DM, Evans JC, Levy D. Hypertension in adults across the age spectrum: current outcomes and control in the community. *JAMA* 2005; **294**: 466–472.
14 Miura K, Daviglus ML, Dyer AR, Liu K, Garside DB, Stamler J, Greenland P. Relationship of blood pressure to 25-year mortality due to coronary heart disease, cardiovascular diseases, and all causes in young adult men: the Chicago Heart Association Detection Project in Industry. *Arch Intern Med* 2001; **161**: 1501–1508.
15 Kshirsagar AV, Carpenter M, Bang H, Wyatt SB, Colindres RE. Blood pressure usually considered normal is associated with an elevated risk of cardiovascular disease. *Am J Med* 2006; **119**: 133–141.
16 Liszka HA, Mainous 3rd AG, King DE, Everett CJ, Egan BM. Prehypertension and cardiovascular morbidity. *Ann Fam Med* 2005; **3**: 294–299.
17 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.
18 He J, Gu D, Chen J, Wu X, Kelly TN, Huang JF, Chen JC, Chen CS, Bazzano LA, Reynolds K, Whelton PK, Klag MJ. Premature deaths attributable to blood pressure in China: a prospective cohort study. *Lancet* 2009; **374**: 1765–1772.
19 Murakami Y. The need for further epidemiologic research on hypertension in Asian regions. *Am J Hypertens* 2009; **22**: 1030.
20 Murakami Y, Hozawa A, Okamura T, Ueshima H. Relation of blood pressure and all-cause mortality in 180,000 Japanese participants: pooled analysis of 13 cohort studies. *Hypertension* 2008; **51**: 1483–1491.
21 Anonymous. Mannual to fill in a death certificate (in Japanese), In The Ministry of Health, Labour, and Welfare (ed), The Ministry of Health, Labour, and Welfare 2010. http://www.mhlw.go.jp/toukei/manual/dl/manual.pdf.
22 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.
23 Yamada S, Koizumi A, Iso H, Wada Y, Watanabe Y, Date C, Yamamoto A, Kikuchi S, Inaba Y, Toyoshima H, Kondo T, Tamakoshi A. Risk factors for fatal subarachnoid hemorrhage: the Japan Collaborative Cohort Study. *Stroke* 2003; **34**: 2781–2787.
24 Murakami Y, Miura K, Okamura T, Ueshima H. Population attributable numbers and fractions of deaths due to smoking: a pooled analysis of 180,000 Japanese. *Prev Med* 2011; **52**: 60–65.
25 Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. *Am J Public Health* 1998; **88**: 15–19.
26 Kikuya M, Ohkubo T, Asayama K, Metoki H, Obara T, Saito S, Hashimoto J, Totsune K, Hoshi H, Satoh H, Imai Y. Ambulatory blood pressure and 10-year risk of cardiovascular and noncardiovascular mortality: the Ohasama study. *Hypertension* 2005; **45**: 240–245.
27 Glynn RJ, Field TS, Rosner B, Hebert PR, Taylor JO, Hennekens CH. Evidence for a positive linear relation between blood pressure and mortality in elderly people. *Lancet* 1995; **345**: 825–829.
28 Lawes CM, Rodgers A, Bennett DA, Parag V, Suh I, Ueshima H, MacMahon S. Blood pressure and cardiovascular disease in the Asia Pacific region. *J Hypertens* 2003; **21**: 707–716.
29 Sairenchi T, Iso H, Irie F, Fukasawa N, Yamagishi K, Kanashiki M, Saito Y, Ota H, Nose T. Age-specific relationship between blood pressure and the risk of total and cardiovascular mortality in Japanese men and women. *Hypertens Res* 2005; **28**: 901–909.
30 Ikeda A, Iso H, Yamagishi K, Inoue M, Tsugane S. Blood pressure and the risk of stroke, cardiovascular disease, and all-cause mortality among Japanese: the JPHC Study. *Am J Hypertens* 2009; **22**: 273–280.
31 Kokubo Y, Kamide K, Okamura T, Watanabe M, Higashiyama A, Kawanishi K, Okayama A, Kawano Y. Impact of high-normal blood pressure on the risk of cardiovascular disease in a Japanese urban cohort: the Suita study. *Hypertension* 2008; **52**: 652–659.
32 Hozawa A, Kuriyama S, Kakizaki M, Ohmori-Matsuda K, Ohkubo T, Tsuji I. Attributable risk fraction of prehypertension on cardiovascular disease mortality in the Japanese population: the Ohsaki Study. *Am J Hypertens* 2009; **22**: 267–272.
33 Iida M, Ueda K, Okayama A, Kodama K, Sawai K, Shibata S, Tanaka S, Keijnkai T, Horibe H, Minowa M, Yanagawa H, Hashimoto T. Impact of elevated blood pressure on mortality from all causes, cardiovascular diseases, heart disease and stroke among Japanese: 14 year follow-up of randomly selected population from Japanese – Nippon data 80. *J Hum Hypertens* 2003; **17**: 851–857.
34 Staessen J, Bulpitt C, Clement D, De Leeuw P, Fagard R, Fletcher A, Forette F, Leonetti G, Nissinen A, O'Malley K *et al.* Relation between mortality and treated blood pressure in elderly patients with hypertension: report of the European Working Party on High Blood Pressure in the Elderly. *BMJ* 1989; **298**: 1552–1556.
35 Greenberg JA. Removing confounders from the relationship between mortality risk and systolic blood pressure at low and moderately increased systolic blood pressure. *J Hypertens* 2003; **21**: 49–56.
36 Cholesterol, diastolic blood pressure, and stroke: 13 000 strokes in 450 000 people in 45 prospective cohorts. Prospective studies collaboration. *Lancet* 1995; **346**: 1647–1653.
37 Turnbull F, Neal B, Ninomiya T, Algert C, Arima H, Barzi F, Bulpitt C, Chalmers J, Fagard R, Gleason A, Heritier S, Li N, Perkovic V, Woodward M, MacMahon S. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. *BMJ* 2008; **336**: 1121–1123.
38 Miura K, Nakagawa H, Ohashi Y, Harada A, Taguri M, Kushiro T, Takahashi A, Nishinaga M, Soejima H, Ueshima H. Four blood pressure indexes and the risk of stroke and myocardial infarction in Japanese men and women: a meta-analysis of 16 cohort studies. *Circulation* 2009; **119**: 1892–1898.
39 Mannami T, Iso H, Baba S, Sasaki S, Okada K, Konishi M, Tsugane S. Cigarette smoking and risk of stroke and its subtypes among middle-aged Japanese men and women: the JPHC Study Cohort I. *Stroke* 2004; **35**: 1248–1253.
40 Baba S, Iso H, Mannami T, Sasaki S, Okada K, Konishi M. Cigarette smoking and risk of coronary heart disease incidence among middle-aged Japanese men and women: the JPHC Study Cohort I. *Eur J Cardiovasc Prev Rehabil* 2006; **13**: 207–213.
41 Woodward M, Martiniuk A, Lee CM, Lam TH, Vanderhoorn S, Ueshima H, Fang X, Kim HC, Rodgers A, Patel A, Jamrozik K, Huxley R. Elevated total cholesterol: its prevalence and population attributable fraction for mortality from coronary heart disease and ischaemic stroke in the Asia-Pacific region. *Eur J Cardiovasc Prev Rehabil* 2008; **15**: 397–401.
42 Asayama K, Ohkubo T, Yoshida S, Suzuki K, Metoki H, Harada A, Murakami Y, Ohashi Y, Ueshima H, Imai Y. Stroke risk and antihypertensive drug treatment in the general population: the Japan arteriosclerosis longitudinal study. *J Hypertens* 2009; **27**: 357–364.
43 Aronow WS, Fleg JL, Pepine CJ, Artinian NT, Bakris G, Brown AS, Ferdinand KC, Forciea MA, Frishman WH, Jaigobin C, Kostis JB, Mancia G, Oparil S, Ortiz E, Reisin E, Rich MW, Schocken DD, Weber MA, Wesley DJ, Harrington RA. ACCF/AHA 2011 expert consensus document on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *Circulation* 2011; **123**: 2434–2506.

Supplementary Information accompanies the paper on Hypertension Research website (http://www.nature.com/hr)

APPENDIX

The EPOCH-JAPAN Research Group

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); Executive committee: Hirotsugu Ueshima (Shiga University of Medical Science), Yutaka Imai (Tohoku University Graduate School of Pharmaceutical Sciences), Fujiko Irie (Ibaraki Prefecture), Hiroyasu Iso (Osaka University Graduate School of Medicine), Yutaka Kiyohara (Kyushu University Graduate School of Medicine), Katsuyuki Miura, Yoshitaka Murakami (Shiga University of Medical Science), Hideaki Nakagawa (Kanazawa Medical University), Takeo Nakayama (Kyoto University School of Public Health), Tomonori Okamura (Keio University), Akira Okayama (Japan Anti-Tuberculosis Association), Toshimi Sairenchi (Dokkyo Medical University), Shigeyuki Saitoh (Sapporo Medical University), Kiyomi Sakata (Iwate Medical University), Akiko Tamakoshi (Aichi Medical University), Ichiro Tsuji (Tohoku University Graduate School of Medicine) and Michiko Yamada (Radiation Effects Research Foundation).

Journal of the American Heart Association
OPEN ACCESS

American Heart Association | American Stroke Association

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

Sin-ya Nagasawa, Tomonori Okamura, Hiroyasu Iso, Akiko Tamakoshi, Michiko Yamada, Makoto Watanabe, Yoshitaka Murakami, Katsuyuki Miura, Hirotsugu Ueshima and for the Evidence for Cardiovascular Prevention from Observational Cohorts in Japan (EPOCH-JAPAN) Research Group

J Am Heart Assoc. 2012;1:e001974; originally published October 12, 2012;
doi: 10.1161/JAHA.112.001974
The *Journal of the American Heart Association* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Online ISSN: 2047-9980

ORIGINAL RESEARCH

American Heart Association | American Stroke Association.

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

Sin-ya Nagasawa, MD, PhD; Tomonori Okamura, MD, PhD; Hiroyasu Iso, MD, PhD; Akiko Tamakoshi, MD, PhD; Michiko Yamada, MD, PhD; Makoto Watanabe, MD, PhD; Yoshitaka Murakami, PhD; Katsuyuki Miura, MD, PhD; Hirotsugu Ueshima, MD, PhD; for the Evidence for Cardiovascular Prevention from Observational Cohorts in Japan (EPOCH-JAPAN) Research Group

Background—The relation between serum total cholesterol (TC) and cardiovascular disease in women and in the elderly is unclear, especially in Asian populations.

Methods and Results—We examined this relation in the largest-scale pooled analysis of the Japanese population, the Evidence for Cardiovascular Prevention from Observational Cohorts in Japan (EPOCH-JAPAN) study. A total of 65 594 participants who were 40 to 89 years of age and did not have a past history of cardiovascular disease were examined. Cox proportional-hazards models were used to estimate hazard ratios for death from total stroke, cerebral infarction, intracranial cerebral hemorrhage, or coronary heart disease. The mean follow-up period was 10.1 years, with the number of deaths from total stroke, cerebral infarction, cerebral hemorrhage, and coronary heart disease being 875, 457, 212, and 374, respectively. The participants were divided into 2 age groups: middle-aged (40 to 69 years; mean age 55 years) and elderly (70 to 89 years; mean age 75 years). In men, the multivariate-adjusted hazard ratios for coronary heart disease in the highest TC category (≥6.21 mmol/L) compared with the lowest category (<4.14 mmol/L) were 2.52 (95% confidence interval: 1.15–5.07) in middle-aged participants and 2.77 (1.09–7.03) in elderly participants. In women, the hazard ratios of the highest TC category (≥6.72 mmol/L) compared with the lowest category (<4.66 mmol/L) were 3.20 (1.44–7.09) in middle-aged participants and 1.02 (0.42–2.49) in elderly participants. TC levels were not associated with cerebral infarction in any age or sex group and were associated negatively with total stroke and cerebral hemorrhage.

Conclusion—High serum TC levels are associated with coronary heart disease in middle-aged Japanese men and women, but evidence in elderly Japanese individuals is still limited. (***J Am Heart Assoc.* 2012;1:e001974 doi: 10.1161/JAHA.112.001974**)

Key Words: cholesterol • coronary heart disease • pooled analysis • stroke

From the Department of Epidemiology and Public Health, Kanazawa Medical University, Ishikawa, Japan (S.N.); the Department of Preventive Medicine and Public Health, Keio University, Tokyo, Japan (T.O.); the Department of Social and Environmental Medicine, Osaka University Graduate School of Medicine, Osaka, Japan (H.I.); the Department of Public Health, Aichi Medical University School of Medicine, Aichi, Japan (A.T.); the Department of Clinical Studies, Radiation Effects Research Foundation, Hiroshima, Japan (M.Y.); Department of Preventive Cardiology, National Cerebral and Cardiovascular Center, Suita, Japan (M.W.); and the Department of Medical Statistics (Y.M.), Department of Health Science (K.M.), and Life-Related Disease Prevention Center (H.U.), Shiga University of Medical Science, Otsu, Japan.

Dr. Tamakoshi is now located at the Department of Public Health, Hokkaido University Graduate School of Medicine, Hokkaido, Japan.

Correspondence to: Shin-ya Nagasawa, MD, PhD, Department of Epidemiology and Public Health, Kanazawa Medical University, Uchinadamachi Daigaku 1-1, Ishikawa, 920-0293, Japan. E-mail nagasawa@kanazawa-med.ac.jp

Received May 9, 2012; accepted August 7, 2012.

Hypercholesterolemia is a well-documented and established risk factor for coronary heart disease (CHD).[1,2] However, evidence of this association is mainly from middle-aged or relatively young elderly men <70 years of age, whereas evidence from women or the elderly, especially in Asian populations, is scarce. One large meta-analysis based on observational studies found that high levels of serum total cholesterol (TC) were associated with an increased CHD mortality rate in both men and women.[3] However, this study was stratified only by age and sex and was not adjusted for other confounders. Another meta-analysis based on observational studies showed a weaker association between TC and CHD in women and in participants ≥75 years of age.[4] To our knowledge, no observational study has demonstrated a clear positive relation between serum TC levels and death from CHD in women and the elderly specific to Asian populations.[1] Furthermore, less evidence is available on the influence of serum TC on stroke than on CHD.

We therefore investigated the associations between serum TC level and death due to cardiovascular disease (CVD), such as CHD and stroke, after stratification by sex and age in the largest-scale pooled analysis carried out in the Japanese population. Our a priori hypothesis is that a high serum TC level is a risk factor for CVD in Japanese after stratification by both sex and age.

Methods

Study Design

This study was part of a pooled project called EPOCH-JAPAN (Evidence for Cardiovascular Prevention from Observational Cohorts in Japan), which incorporates a meta-analysis of individual participant data from 13 cohorts across Japan. The project was designed to conduct pooled analyses and examine the relation between cause-specific mortality rate and various exposures, including laboratory measures and lifestyle factors. The guidelines for a cohort recruitment of EPOCH-JAPAN were as follows: collection of health examination measures, >1000 participants, and >10 years of follow-up (although each cohort's collaborator had discretion to choose the size of his or her data set for pooling). Both nationwide and regional cohort studies were included. We have reported the detailed characteristics of each cohort previously.[5]

Study Population

Of the 13 cohorts, 10 provided data on the cause of death (n=90 528).[5] The people who were (1) <40 or ≥90 years of age (n=10 528), (2) had past history of CVD (n=7422), and (3) lacked data on TC level (n=2122) at the baseline survey were removed. Moreover, 4862 participants were removed because of missing data for at least one of the following covariates: sex, age, body mass index, blood pressure, and smoking and drinking status. Finally, a total of 65 594 participants were included in the analysis. The levels of serum TC were measured enzymatically in all the cohorts, with the exception of the NIPPON DATA80 cohort, in which TC was measured by the Lieberman-Burchard direct method.

Ascertainment of Death

The causes of death were sought in great detail from the available sources in each cohort study. In most studies, death certificates were reviewed or the National Vital Statistics were used after permission had been obtained. Other sources used in some studies included autopsy reports, medical records, health examinations, and questionnaires. The underlying cause of death was coded according to the *International Classification of Diseases* (*ICD*) for National Vital Statistics based on the criteria proposed by the World Health Organization.[6] These classifications were based on the *ICD-9* until the end of 1994 and on the *ICD-10* from the beginning of 1995. The respective classification codes for *ICD-9* and *ICD-10* used in the study were as follows: death from CVD (390 to 459; I00 to I99), total stroke (TS) (410 to 414 or 430 to 438; I20 to I25 or I60 to I69), cerebral infarction (433 or 434 or 437.8; I63 or I69.3), intracranial cerebral hemorrhage (431 to 432; I61 or I69.1), and CHD (410 to 414; I20 to I25).

Statistical Methods

Sex-specific analysis was performed. TC was categorized into 7 categories (<4.14, 4.14 to 4.65, 4.66 to 5.16, 5.17 to 5.68, 5.69 to 6.20, 6.21 to 6.71, and ≥6.72 mmol/L) in accordance with a previous Japanese cohort study,[7] which had provided key evidence for the guidelines of the Japan Atherosclerosis Society for diagnosis and prevention of atherosclerotic CVD for Japanese.[8] However, because only a small number of participants had TC levels ≥6.72 mmol/L in men and <4.14 mmol/L in women, with the number of events in these participants being limited, we decided to combine these TC levels into the adjacent category (6.21 to 6.71 mmol/L in men and 4.14 to 4.65 mmol/L in women). The lowest level in both sexes (men, <4.14 mmol/L; women, <4.65 mmol/L) served as the reference group.

The study population was divided into 2 age groups in both men and women: middle-aged (40 to 69 years; mean age 55 years) and elderly (70 to 89 years; mean age 75 years). Age group– and sex-specific analyses were performed. Cox proportional-hazards models stratified by cohorts[9] were used to estimate the hazard ratios (HRs) for cardiovascular outcomes according to baseline TC. Deaths from CHD and from TS and its subtypes (cerebral infarction and cerebral hemorrhage) were used in the analysis. In the Cox model, age, body mass index, systolic blood pressure, smoking status (current smoker, ex-smoker, never-smoker), and drinking status (current drinker, ex-drinker, never-drinker) were used as confounding variables.

All confidence intervals were estimated at the 95% level, and the significance level was set at P=0.05. All the statistical analyses were performed in Statistical Analysis System release 9.13 (SAS Institute, Inc., Cary, NC).

Results

The baseline characteristics of the participants in the 10 cohorts are shown in Table 1. Each baseline survey was performed between 1977 and 1990, with the number of participants ranging from 1608 in the Tanno-Sobetsu cohort

Table 1. Baseline Characteristics of the Study Participants in Each Cohort

Cohort Name	Geographic Location (Prefecture)	Year of Baseline Survey	Follow-Up Periods, y, Average ±SD	No. Participants	Age at Study Entry, y, Average±SD	Serum Total Cholesterol, mmol/L, Average±SD	Systolic Blood Pressure, mm Hg, Average±SD	Diastolic Blood Pressure, mm Hg, Average± SD	Body Mass Index, kg/m^2, Average± SD	Smoking*Status			Drinking† Status		
										Never	Ex-	Current	Never	Ex-	Current
Men															
Tanno-Sobetsu	Hokkaido	1977	18.5±3.7	742	50.5±6.9	4.81±1.06	131±19	82±10	23.1±2.7	226	0	516	212	0	530
Osaki	Miyagi	1994	6.0±1.4	6142	62.1±10.0	5.02±0.88	132±17	80±11	23.6±2.9	1335	1811	2996	966	473	4703
Ohasama	Iwate	1987	9.9±2.6	877	59.4±10.9	4.84±0.88	134±17	76±11	23.1±2.8	435	0	442	341	0	536
Oyabe	Ishikawa	1988	9.6±2.1	1461	60.4±10.3	4.71±0.85	131±20	79±11	22.6±2.7	661	0	800	374	0	1087
YKK workers	Toyama	1990	10.7±2.8	1970	47.3±5.4	5.22±0.88	121±16	76±12	22.7±2.6	545	303	1122	359	30	1581
RERF cohort	Hiroshima	1986	15.4±3.5	619	54.5±10.8	5.12±0.88	122±13	80±8	21.7±2.7	95	182	342	112	35	472
Hisayama	Fukuoka	1988	10.7±2.8	1106	58.3±11.6	5.10±1.06	135±20	81±11	22.8±3.0	226	327	553	369	69	668
JACC study	Nationwide‡	1988–1990	9.4±2.1	8988	57.9±9.9	4.86±0.91	135±19	81±11	22.8±2.8	2048	2163	4777	1760	436	6792
NIPPON DATA80	Nationwide‡	1980	16.5±4.7	2737	55.5±10.7	4.84±0.88	142±21	85±12	22.5±2.9	492	556	1689	556	164	2017
NIPPON DATA90	Nationwide‡	1990	9.4±1.9	2412	57.0±11.3	5.15±0.96	140±20	85±12	23.0±3.0	524	597	1291	820	156	1436
Total			9.9±4.1	27 054	57.7±10.7	4.95±0.91	134±19	81±12	23.0±2.9	6587	5939	14 528	5869	1363	19 822
Women															
Tanno-Sobetsu	Hokkaido	1977	18.7±3.6	866	50.3±6.7	5.02±0.91	133±20	82±10	24.2±3.4	801	0	65	790	0	76
Osaki	Miyagi	1994	6.0±1.5	6612	61.2±9.2	5.48±0.88	130±18	78±11	24.1±3.2	6195	106	311	5049	183	1380
Ohasama	Iwate	1987	10.7±2.2	1363	58.4±9.3	5.30±0.93	129±16	73±11	23.9±3.3	1329	0	34	1280	0	83
Oyabe	Ishikawa	1988	10.1±1.4	3166	58.0±9.5	5.22±0.93	126±20	75±11	23.2±3.1	3085	0	81	2729	0	437
YKK workers	Toyama	1990	11.0±2.6	1036	47.2±5.4	5.30±0.96	117±16	72±12	22.3±2.7	1025	2	9	825	2	209
RERF cohort	Hiroshima	1986	16.2±2.6	1342	57.3±9.9	5.56±0.98	121±14	76±9	22.3±3.3	1168	35	139	803	17	522
Hisayama	Fukuoka	1988	11.3±2.2	1513	59.4±11.8	5.53±1.06	133±22	76±11	22.9±3.3	1378	31	104	1363	17	133
JACC study	Nationwide‡	1988–1990	9.6±1.9	15 952	56.5±9.5	5.25±0.93	132±19	78±11	23.3±3.2	15 213	182	557	12 800	155	2997
NIPPON DATA80	Nationwide‡	1980	17.3±4.0	3415	55.8±10.7	5.04±0.88	138±22	81±12	23.1±3.4	3052	73	290	2753	42	620
NIPPON DATA90	Nationwide‡	1990	9.6±1.5	3275	56.8±11.5	5.48±0.98	137±20	81±12	23.1±3.3	2925	72	278	3055	26	194
Total			10.3±3.9	38 540	57.2±10.1	5.33±0.96	131±20	78±11	23.4±3.2	36 171	501	1868	31 447	442	6651

*In the studies of Tanno-Sobetsu, Ohasama, and Oyabe, ex-smokers were classified as nonsmokers.
†In the studies of Tanno-Sobetsu, Ohasama, and Oyabe, ex-drinkers were classified as nondrinkers.
‡In this nationwide cohort study, the participants were from all areas of Japan.

DOI: 10.1161/JAHA.112.001974

to 24 940 in the Japan Collaborative Cohort (JACC) study. Mean age ranged from 47 years in the YKK cohort to 61 years in the Osaki cohort.

The number of total participants was 65 594 (27 054 men and 38 540 women), and the mean age was 57 years. The mean ± standard deviation (SD) serum TC level of the total participants was 4.95±0.91 mmol/L for men and 5.33±0.96 mmol/L for women. The levels were lowest in the Oyabe cohort for men (4.71 mmol/L) and in the Tanno-Sobetsu cohort for women (5.02 mmol/L) and were highest in the YKK cohort for men (5.22 mmol/L) and in the Radiation Effects Research Foundation (RERF) cohort for women (5.56 mmol/L). The mean follow-up period was ≈10.1 years, with the number of deaths from TS, cerebral infarction, cerebral hemorrhage, and CHD being 875, 457, 212, and 374, respectively.

In the Cox regression models, the relation between serum TC levels and CHD death was continuous and positive overall, with the exception of elderly women. However, when TC level was treated as a continuous variable, the relation was not significant in elderly men (Table 2). In middle-aged men, the multivariate-adjusted HR of the highest TC category (≥6.21 mmol/L) for CHD was 2.52 (95% confidence interval [CI]: 1.15–5.07) compared with the lowest TC category (<4.14 mmol/L), and the multivariate-adjusted HR for a 1-SD increment in serum TC level (0.98 mmol/L) was 1.26 (95% CI: 1.11–1.42). In elderly men, the multivariate-adjusted HR of the highest TC category for CHD was 2.77 (95% CI: 1.09–7.03) compared with the lowest TC category. The multivariate-adjusted HR for a 1-SD increment in serum TC level in these participants was 1.23 (95% CI: 0.96–1.56).

In middle-aged women, the multivariate-adjusted HR of the highest TC category (≥6.72 mmol/L) for CHD was 3.20 (95% CI: 1.44–7.09) compared with the lowest TC category (<4.66 mmol/L), whereas the multivariate-adjusted HR for a 1-SD increment in serum TC (0.98 mmol/L) was 1.36 (95% CI: 1.12–1.66). However, in elderly women, the multivariate-adjusted HR of the highest TC level for CHD was 1.02 (95% CI: 0.42–2.49), and the multivariate-adjusted HR for a 1-SD increment in serum TC was 1.02 (95% CI: 0.82–1.27).

On the other hand, serum TC levels were not associated with cerebral infarction in any age or sex group and were associated negatively with cerebral hemorrhage and TS. The multivariate-adjusted HRs for cerebral infarction for a 1-SD increment in serum TC were 0.92 (95% CI: 0.74–1.14) in middle-aged men, 1.04 (95% CI: 0.87–1.24) in elderly men, 1.08 (95% CI: 0.83–1.39) in middle-aged women, and 0.97 (95% CI: 0.80–1.16) in elderly women. The multivariate-adjusted HR for cerebral hemorrhage for a 1-SD increment in serum TC was 0.84 (95% CI: 0.72–0.97) in the combined participants. The multivariate-adjusted HR for TS for a 1-SD increment in serum TC was 0.93 (95% CI: 0.862–0.997) in the combined participants. The Figure 1 summarizes the associations with CHD and cerebral infarction by sex and age groups.

Although 52% (n=34 379) of the participants in the present study had information on antihypertensive medication, the relations between TC and death from CVD (HRs) did not change substantially when use of hypertension medication (16%) was added as a covariate. In the subgroup analysis of participants with information on self-reported diabetes (n=28 793) or casual blood glucose (n=32 384), the relations between TC and death from CVD also were not altered when diabetes was added as a covariate. Because it is likely that there were time period differences in CVD event rates, we reanalyzed the data excluding 2 cohorts with earlier baseline surveys (Tanno-Sobetsu [1977] and NIPPON DATA80 [1980] cohorts). This analysis showed that the relations between TC and death from CVD (HRs) did not change substantially (data not shown).

Discussion

In this large cohort study in Japan, we found a positive relation between serum TC level and CHD death in both middle-aged women and middle-aged men. We also observed that the highest TC group (≥6.21 mmol/L) had an increased risk for CHD in elderly men, although the multivariate-adjusted HR did not reach a statistically significant level when TC level was treated as a continuous variable. There was also no relation between TC and CHD in elderly women. Except for elderly women, our results are similar to those reported in 2 previous large-scale studies.[3,4] To our knowledge, this is the first finding from a large-scale study specific to an Asian population that demonstrates a positive relation between hypercholesterolemia and CHD in middle-aged women with a mean age of 55 years. On the other hand, serum TC levels were not associated with cerebral infarction in any age or sex group and were associated negatively with TS and cerebral hemorrhage death.

The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) study, which included participants between 70 and 82 years of age with prior vascular disease (mean age 75 years), showed that pravastatin reduced the risk of CHD events.[10] In addition, the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) study showed that pravastatin reduced the risk of CHD in Japanese participants ≥60 years of age without a history of CHD or stroke.[11] The Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study also showed that rosuvastatin reduced the incidence of major cardiovascular events, including CHD, in people ≥70 years of age without prior vascular disease who had an elevated high-sensitivity C-reactive protein without apparent hyperlipidemia.[12] However, observational studies on

Table 2. The Number of Deaths, Crude Mortality Rate, and Multivariate-Adjusted HRs for CVD Death According to Total Cholesterol Levels

	Age Category, years		Total Cholesterol, mmo/L							
			<4.14	4.14 to 4.65	4.66 to 5.16	5.17 to 5.68	5.69 to 6.20	6.21 to 6.71	≥6.72	For 1 SD* Increasing
Men										
Coronary heart disease	40 to 69	Number of participants	3956	4805	5339	4276	2597	2111		
		Number of deaths	16	30	24	25	19	17		
		Crude mortality rate†	0.39	0.60	0.44	0.57	0.72	0.82		
		HR (95% CI)‡	1	1.56 (0.85 to 2.87)	1.20 (0.64 to 2.28)	1.71 (0.91 to 3.24)	2.26 (1.14 to 4.45)	2.52 (1.15 to 5.07)		1.26 (1.11 to 1.42)
	70 to 89	Number of participants	871	860	892	694	380	273		
		Number of deaths	11	21	18	11	10	8		
		Crude mortality rate†	1.70	3.18	2.69	2.11	3.45	5.08		
		HR (95% CI)‡	1	1.95 (0.93 to 4.06)	1.73 (0.81 to 3.67)	1.49 (0.64 to 3.48)	2.31 (0.96 to 5.53)	2.77 (1.09 to 7.03)		1.23 (0.96 to 1.56)
Cerebral infarction	40 to 69	Number of participants	3956	4805	5339	4276	2597	2111		
		Number of deaths	16	34	25	14	9	7		
		Crude mortality rate†	0.39	0.67	0.45	0.32	0.34	0.32		
		HR (95% CI)‡	1	1.78 (0.98 to 3.23)	1.26 (0.67 to 2.37)	1.05 (0.51 to 2.16)	1.13 (0.49 to 2.59)	1.11 (0.45 to 2.73)		0.92 (0.74 to 1.14)
	70 to 89	Number of participants	871	860	892	694	380	273		
		Number of deaths	37	32	43	28	14	8		
		Crude mortality rate†	5.73	4.85	6.43	5.38	4.82	6.47		
		HR (95% CI)‡	1	0.85 (0.53 to 1.38)	1.25 (0.80 to 1.96)	1.25 (0.76 to 2.07)	0.94 (0.50 to 1.77)	0.78 (0.36 to 1.69)		1.04 (0.87 to 1.24)
Women										
Coronary heart disease	40 to 69	Number of participants	8566		7230	7240	5359	3159	2502	
		Number of deaths	12		16	15	15	8	15	
		Crude mortality rate†	0.13		0.21	0.20	0.28	0.25	0.59	
		HR (95% CI)‡	1		1.37 (0.65 to 2.90)	1.21 (0.56 to 2.61)	1.56 (0.72 to 3.36)	1.45 (0.58 to 3.59)	3.20 (1.44 to 7.09)	1.36 (1.12 to 1.66)
	70 to 89	Number of participants	945		884	968	789	482	416	
		Number of deaths	20		19	17	11	9	7	
		Crude mortality rate†	2.37		2.46	2.02	1.64	2.15	1.92	
		HR (95% CI)‡	1		1.08 (0.57 to 2.03)	0.95 (0.49 to 1.82)	0.83 (0.40 to 1.75)	1.06 (0.48 to 2.37)	1.02 (0.42 to 2.49)	1.02 (0.82 to 1.27)

Continued

DOI: 10.1161/JAHA.112.001974

Table 2. Continued

	Age Category, years		Total Cholesterol, mmo/L							
			<4.14	4.14 to 4.65	4.66 to 5.16	5.17 to 5.68	5.69 to 6.20	6.21 to 6.71	≥6.72	For 1 SD* Increasing
Cerebral infarction	40 to 69	Number of participants	8566		7230	7240	5359	3159	2502	
		Number of deaths	13		13	9	14	8	8	
		Crude mortality rate†	0.14		0.17	0.12	0.26	0.25	0.32	
		HR (95% CI)‡	1		0.97 (0.45 to 2.10)	0.61 (0.26 to 1.44)	1.12 (0.52 to 2.42)	1.11 (0.45 to 2.74)	1.28 (0.51 to 3.22)	1.08 (0.83 to 1.39)
	70 to 89	Number of participants	945		884	968	789	482	416	
		Number of deaths	35		21	27	29	6	7	
		Crude mortality rate†	4.16		2.72	3.21	4.32	1.43	1.92	
		HR (95% CI)‡	1		0.70 (0.41 to 1.21)	0.89 (0.54 to 1.48)	1.39 (0.84 to 2.29)	0.45 (0.19 to 1.07)	0.69 (0.30 to 1.58)	0.97 (0.80 to 1.16)
Men and Women										
Total stroke	40 to 89	Number of participants	8449	11 554	14 345	13 178	9125	5100	3843	
		Number of deaths	147	183	182	160	103	45	55	
		Crude mortality rate†	1.70	1.52	1.25	1.21	1.14	0.89	1.45	
		HR (95% CI)‡	1	0.95 (0.76 to 1.18)	0.82 (0.65 to 1.02)	0.83 (0.66 to 1.05)	0.78 (0.60 to 1.02)	0.60 (0.42 to 0.84)	0.99 (0.72 to 1.37)	0.93 (0.862 to 0.997)
Cerebral hemorrhage	40 to 89	Number of participants	8449	11 554	14 345	13 178	9125	5100	3843	
		Number of deaths	44	41	47	38	15	12	15	
		Crude mortality rate†	0.51	0.34	0.32	0.29	0.17	0.24	0.39	
		HR (95% CI)‡	1	0.71 (0.46 to 1.09)	0.69 (0.46 to 1.05)	0.63 (0.41 to 0.99)	0.37 (0.20 to 0.68)	0.51 (0.27 to 0.99)	0.85 (0.46 to 1.58)	0.84 (0.72 to 0.97)

HR indicates hazard ratio; CVD, cardiovascular disease.

*One SD of total cholesterol was 0.98 mmol/L.

†Crude mortality rate was expressed as per 1000 person-years.

‡HR was adjusted for age, systolic blood pressure, body mass index, smoking categories, and drinking categories. All analyses were stratified by cohort.

DOI: 10.1161/JAHA.112.001974

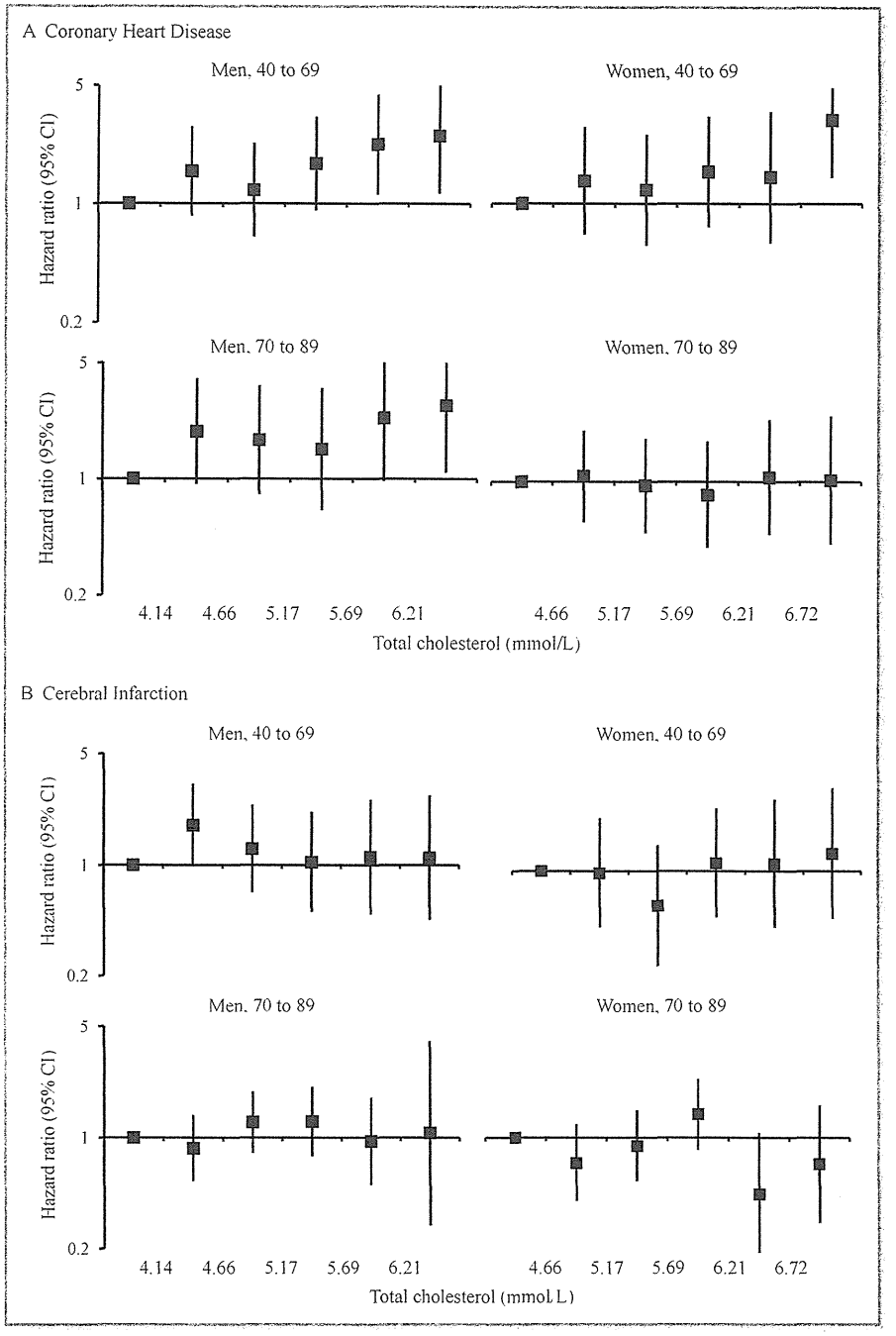

Figure 1. Multivariate-adjusted hazard ratios for death from (A) coronary heart disease and (B) cerebral infarction according to total cholesterol levels. Hazard ratio was adjusted for cohort, age, systolic blood pressure, body mass index, and smoking and drinking categories. CI indicates confidence interval.

elderly people at low risk or in the primary care setting are very rare, and there is little evidence of a sex difference. Moreover, elderly people, especially elderly women, are the dominant population in the currently aging societies of developed countries. Therefore, the sex-specific findings we observed in elderly community dwellers are important and suggest an increased risk for CHD in the highest TC group (≥6.21 mmol/L) in elderly men. However, this relation was not significant when TC level was treated as a continuous variable.

The Seven Countries Study showed that Japan had the lowest CHD mortality rate among developed countries, which was attributed largely to remarkably low serum TC

levels in the 1950s.[13] However, changes in lifestyle toward a Westernized pattern in Japan have resulted in a continuous increase in dietary fat intake and serum TC levels. Moreover, it was reported recently that Japanese born after World War II had serum TC levels similar to those of white men[14] and that the incident rate of CHD in Japan is increasing in some areas.[15,16] In the Western population, a positive relation between TC and CHD was observed in both sexes and in all age groups, although its association was attenuated in the elderly.[3] The weak association or lack of association between serum TC and CHD in elderly Japanese participants could be due to relatively less exposure to hypercholesterolemia in their young and middle-aged periods before the baseline, a time when mean serum TC level was known to be very low.[17,18] Although we do not have information on serum TC levels before the baseline measurements in the present study, elderly Japanese, even those with hypercholesterolemia, might not have had higher serum TC levels throughout their entire lives. Especially for elderly women, the exposure period to high serum TC could be shorter than for men, as serum TC levels in women before menopause are considerably lower than in men. This could be one reason for the lack of relation between serum TC levels and CHD in elderly women. Furthermore, our findings could be explained by survivor bias.[19] In other words, elderly participants in the present study might have some beneficial characteristics that helped them avoid CHD due to hypercholesterolemia.

In the present study, serum TC levels were not associated with cerebral infarction in any age or sex group. This finding is different from several other large-scale cohort studies in Western populations, which showed a weak but positive association between serum TC and cerebral infarction,[3,4,20,21] but is similar to previous cohort studies in Japan and some Western countries.[2,22–25] These discrepancies could be due to differences in the prevalence of subtypes of cerebral infarction. Cerebral infarction consists of 3 major pathological subtypes—namely lacunar, atherothrombotic, and cardioembolic infarctions. In some Western populations, atherothrombotic infarctions account for approximately one half of cerebral infarctions,[26] whereas in some Japanese populations, it accounts for only approximately one quarter of cerebral infarctions. Furthermore, cardioembolic infarction is more common than atherothrombotic infarction, accounting for 23% to 38% of cerebral infarctions.[27–30] The Hisayama study in a Japanese community showed that serum low-density lipoprotein cholesterol was associated positively with only atherothrombotic infarctions, whereas it was associated negatively with cardioembolic infarction and showed no association with lacunar infarction.[27] One possible mechanism for the inverse association between low TC and cardioembolic infarction is that low TC increases the occurrence of atrial fibrillation,[31] which is the predominant risk factor for cardioembolic infarction. The aforementioned heterogeneity in pathological background of cerebral infarction might be a major reason for the variation in findings observed among cohort studies.

In the present study, serum TC levels were associated negatively with risk of cerebral hemorrhage death. This result is similar to previous studies in Japan and the United States.[20,32,33] Low serum TC can induce angionecrosis, possibly in coexistence with hypertension. Experimental evidence from one study showed that a hypercholesterolemic diet given to spontaneously hypertensive rats reduced angionecrosis of smooth muscle cells in intracerebral arteries, leading to the occurrence of hemorrhagic stroke.[34] Low serum TC also can reflect nutritional status, which is known to be related to death after onset. Further basic, clinical, and epidemiological studies on these associations are required. Consequently, because TC can be associated inversely with the cardioembolic type of cerebral infarction in addition to cerebral hemorrhage, it is not unexpected that TC was associated inversely with TS death in the present study, similar to another recent report from Japan.[35]

Several limitations need to be considered when these results are interpreted. First, we did not take into account the use or nonuse of cholesterol-lowering therapy, including statins, the main drug used to treat hypercholesterolemia. However, baseline surveys in 7 cohorts of EPOCH-JAPAN were performed before the introduction of the first statin in Japan (1989).[36] Another 3 cohorts were also started around 1990, and therefore it is likely that only a few participants were taking statins at baseline. Consequently, it is not likely that this limitation would have changed our inferences substantially. Second, the results were based on single health examinations and were likely to have underestimated the true association because of regression dilution bias. Third, the participants in the study volunteered to receive their health examinations, and for that reason their characteristics could be somewhat different from those of nonparticipants or the general population. This would influence the absolute measure of effect (mortality rate) and could therefore underestimate the risk. However, these differences have little effect on relative measures of effect, such as HRs. Fourth, the number of deaths from CHD in the study might not be sufficient in elderly women to estimate the association with serum TC.

In conclusion, this largest-scale pooled analysis specific to Asians found a significant positive relation between serum TC and CHD in both middle-aged men and middle-aged women who were 40 to 69 years of age and did not have a past history of CVD, although a similar relation in elderly participants was not confirmed. Further research is therefore warranted in elderly men and women.

Acknowledgments

We are grateful to all the participants who took part in each of the cohort studies.

EPOCH-JAPAN Research Group: *Chair:* Hirotsugu Ueshima (Shiga University of Medical Science); *Writing Committee:* Sin-ya Nagasawa, Tomonori Okamura, Hiroyasu Iso, Akiko Tamakoshi, Michiko Yamada, Makoto Watanabe, Yoshitaka Murakami, Katsuyuki Miura, and Hirotsugu Ueshima; *Executive Committee:* Hirotsugu Ueshima (Shiga University of Medical Science), Yutaka Imai (Tohoku University Graduate School of Medicine), Hiroyasu Iso (Osaka University Graduate School of Medicine), Yutaka Kiyohara (Kyushu University Graduate School of Medicine), Michiko Yamada (Radiation Effects Research Foundation), Hideaki Nakagawa (Kanazawa Medical University), Takeo Nakayama (Kyoto University School of Public Health), Tomonori Okamura (Keio University), Yoshihiro Miyamoto (National Cerebral and Cardiovascular Center), Akira Okayama (Japan Anti-Tuberculosis Association), Shigeyuki Saitoh (Sapporo Medical University), Akiko Tamakoshi (Hokkaido University), Ichiro Tsuji (Tohoku University Graduate School of Medicine), and Fujiko Irie (Ibaraki Prefecture).

Sources of Funding

This research was supported by Grants-in-Aid from the Ministry of Health, Labor and Welfare, Health and Labor Sciences Research Grants, Japan (Research on Health Services: H17-Kenkou-007; Comprehensive Research on Cardiovascular and Life-Style Related Diseases: H18-Junkankitou [Seishuu]-Ippan-012; Comprehensive Research on Life-Style Related Diseases including Cardiovascular Diseases and Diabetes Mellitus: H20-Junkankitou [Seishuu]-Ippan-013 and Comprehensive Research on Life-Style Related Diseases including Cardiovascular Diseases and Diabetes Mellitus: H23-Junkankitou [Seishuu]-Ippan-005).

Disclosures

None.

References

1. Ueshima H. 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.
2. Tanabe N, Iso H, Okada K, Nakamura Y, Harada A, Ohashi Y, Ando T, Ueshima H. Serum total and non-high-density lipoprotein cholesterol and the risk prediction of cardiovascular events—the JALS-ECC. *Circ J.* 2010;74:1346–1356.
3. 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.
4. Zhang X, Patel A, Horibe H, Wu Z, Barzi F, Rodgers A, MacMahon S, Woodward M. Cholesterol, coronary heart disease, and stroke in the Asia Pacific region. *Int J Epidemiol.* 2003;32:563–572.
5. Murakami Y, Miura K, Okamura T, Ueshima H. Population attributable numbers and fractions of deaths due to smoking: a pooled analysis of 180,000 Japanese. *Prev Med.* 2011;52:60–65.
6. Manual to fill in a death certificate (in Japanese). Tokyo, Japan: Ministry of Health, Labour, and Welfare; 2010.
7. Okamura T, Tanaka H, Miyamatsu N, Hayakawa T, Kadowaki T, Kita Y, Nakamura Y, Okayama A, Ueshima H. The relationship between serum total cholesterol and all-cause or cause-specific mortality in a 17.3-year study of a Japanese cohort. *Atherosclerosis.* 2007;190:216–223.
8. Teramoto T, Sasaki J, Ueshima H, Egusa G, Kinoshita M, Shimamoto K, Daida H, Biro S, Hirobe K, Funahashi T, Yokote K, Yokode M. Executive summary of Japan Atherosclerosis Society (JAS) guideline for diagnosis and prevention of atherosclerotic cardiovascular diseases for Japanese. *J Atheroscler Thromb.* 2007;14:45–50.
9. Woodward M. *Epidemiology: Study Design and Data Analysis*. 2nd ed. Boca Raton, FL: Chapman & Hall/CRC Press; 2005.
10. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, Ford I, Gaw A, Hyland M, Jukema JW, Kamper AM, Macfarlane PW, Meinders AE, Norrie J, Packard CJ, Perry IJ, Stott DJ, Sweeney BJ, Twomey C, Westendorp RG. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet.* 2002;360:1623–1630.
11. Nakamura H, Arakawa K, Itakura H, Kitabatake A, Goto Y, Toyota T, Nakaya N, Nishimoto S, Muranaka M, Yamamoto A, Mizuno K, Ohashi Y. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. *Lancet.* 2006;368:1155–1163.
12. Glynn RJ, Koenig W, Nordestgaard BG, Shepherd J, Ridker PM. Rosuvastatin for primary prevention in older persons with elevated C-reactive protein and low to average low-density lipoprotein cholesterol levels: exploratory analysis of a randomized trial. *Ann Intern Med.* 2010;152:488–496, W174.
13. Nichaman MZ, Hamilton HB, Kagan A, Grier T, Sacks T, Syme SL. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California: distribution of biochemical risk factors. *Am J Epidemiol.* 1975;102:491–501.
14. Woodward M, Huxley H, Lam TH, Barzi F, Lawes CM, Ueshima H. A comparison of the associations between risk factors and cardiovascular disease in Asia and Australasia. *Eur J Cardiovasc Prev Rehabil.* 2005;12:484–491.
15. Rumana N, Kita Y, Turin TC, Murakami Y, Sugihara H, Morita Y, Tomioka N, Okayama A, Nakamura Y, Abbott RD, Ueshima H. Trend of increase in the incidence of acute myocardial infarction in a Japanese population: Takashima AMI Registry, 1990–2001. *Am J Epidemiol.* 2008;167:1358–1364.
16. Kitamura A, Sato S, Kiyama M, Imano H, Iso H, Okada T, Ohira T, Tanigawa T, Yamagishi K, Nakamura M, Konishi M, Shimamoto T, Iida M, Komachi Y. Trends in the incidence of coronary heart disease and stroke and their risk factors in Japan, 1964 to 2003: the Akita-Osaka study. *J Am Coll Cardiol.* 2008;52:71–79.
17. 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.
18. Iso H. Changes in coronary heart disease risk among Japanese. *Circulation.* 2008;118:2725–2729.
19. Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology*. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.
20. 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.
21. Ebrahim S, Sung J, Song YM, Ferrer RL, Lawlor DA, Davey Smith G. Serum cholesterol, haemorrhagic stroke, ischaemic stroke, and myocardial infarction: Korean national health system prospective cohort study. *BMJ.* 2006;333:22.
22. Nakayama T, Date C, Yokoyama T, Yoshiike N, Yamaguchi M, Tanaka H. A 15.5-year follow-up study of stroke in a Japanese provincial city: the Shibata Study. *Stroke.* 1997;28:45–52.
23. Tanizaki Y, Kiyohara Y, Kato I, Iwamoto H, Nakayama K, Shinohara N, Arima H, Tanaka K, Ibayashi S, Fujishima M. Incidence and risk factors for subtypes of cerebral infarction in a general population: the Hisayama study. *Stroke.* 2000;31:2616–2622.
24. Cui R, Iso H, Toyoshima H, Date C, Yamamoto A, Kikuchi S, Kondo T, Watanabe Y, Koizumi A, Inaba Y, Tamakoshi A. Serum total cholesterol levels and risk of mortality from stroke and coronary heart disease in Japanese: the JACC study. *Atherosclerosis.* 2007;194:415–420.
25. Hart CL, Hole DJ, Smith GD. Risk factors and 20-year stroke mortality in men and women in the Renfrew/Paisley study in Scotland. *Stroke.* 1999;30:1999–2007.
26. Warlow CP, Dennis MS, van Gijn J. What caused this transient or persisting ischaemic event? In: Warlow CP, Dennis MS, van Gijn J, Sandrock PA, Bamford JM, Wardlaw J, eds. *Stroke: A Practical Guide to Management*. 2nd ed. Oxford, England: Blackwell Science Ltd; 2001:223–300.
27. 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.