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A Combination of Blood Pressure and Total Cholesterol Increases the Lifetime Risk of Coronary Heart Disease Mortality: EPOCH–JAPAN

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Aim: Lifetime risk (LTR) indicates the absolute risk of disease during the remainder of an individual's lifetime. We aimed to assess the LTRs for coronary heart disease (CHD) mortality associated with blood pressure (BP) and total cholesterol levels in an Asian population using a meta-analysis of individual participant data because no previous studies have assessed this risk.

Methods: We analyzed data from 105,432 Japanese participants in 13 cohorts. Apart from grade 1 and 2–3 hypertension groups, we defined "normal BP" as systolic/diastolic BP $<130/<80$ mmHg and "high BP" as 130–139/80–89 mmHg. The sex-specific LTR was estimated while considering the competing risk of death.

Results: During the mean follow-up period of 15 years (1,553,735 person-years), 889 CHD deaths were recorded. The 10-year risk of CHD mortality at index age 35 years was ≤ 0.11%, but the corresponding LTR was ≥ 1.84%. The LTR of CHD at index age 35 years steeply increased with an increase in BP of participants with high total cholesterol levels [≥ 5.7 mmol/L (220 mg/dL)]. This risk was 7.73%/5.77% (95% confidence interval: 3.53%–10.28%/3.83%–7.25%) in men/women with grade 2–3 hypertension and high total cholesterol levels. In normal and high BP groups, the absolute differences in LTRs between the low and high total cholesterol groups were ≤ 0.25% in men and ≤ 0.40% in women.

Conclusions: High total cholesterol levels contributed to an elevated LTR of CHD mortality in hypertensive individuals. These findings could help guide high-risk young individuals toward initiating lifestyle changes or treatments.

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Key words: Blood pressure, Cholesterol, Coronary heart disease, Cohort study, Lifetime risk

Introduction

Hypertension and hyperlipidemia are strongly and independently associated with coronary heart disease (CHD). Individuals with both elevated blood pressure (BP) and elevated total cholesterol (TC) levels have an increased risk of CHD when compared with those with either of the two conditions[1-3]. Using relative risk estimation, we have previously demonstrated the synergic effect of elevated BP and TC levels on the risk of CHD death in an Asian population[4]. However, information regarding the long-term absolute risk of CHD according to BP and TC in Asians is limited.

This synergistic effect is not limited to elderly individuals[4]. As a result, lifestyle interventions or drug initiation early in life may be required[5]. However, most of the guidelines for the management of hypertension or hyperlipidemia in young individuals struggle to identify or explain the absolute cardiovascular risks in this population, as their short-term risks are extremely low[3, 5, 6]. Thus, these guidelines used relative risk as an alternative[3, 5, 6].

The American Heart Association (AHA)/American College of Cardiology (ACC) Guideline on the Management of Blood Cholesterol recommends estimating lifetime risk (LTR) to determine the intensity of primary preventative measures in young adults[7]. LTR is a cumulative assessment of the incidence of disease risk factors from a given age (index age) until the end of life; therefore, it provides an estimation of the absolute risk of CHD during the remainder of an individual's lifetime[8]. As short-term risk (e.g., <10 years) is considerably affected by age, LTR is a suitable index for informing young populations about their current and future risk of CHD. Relative risk indicates the risk ratio relative to status without exposure, whereas LTR shows the concrete risk difference among groups.

The LTR of CHD mortality based on BP values has been examined previously[9-11]. However, prior studies did not evaluate cholesterol levels, which interact with BP to increase CHD risk[4, 12]. Furthermore, irrespective of other factors, the LTR assessment of CHD according to serum cholesterol levels alone is also scarce in Asian populations[13].

Aim

We assessed the LTR of CHD mortality according to the cross-classification by BP and TC in Asian populations through a meta-analysis of individual participant data (IPD) from the Evidence for Cardiovascular Prevention from Observational Cohorts in Japan (EPOCH–JAPAN).

Methods

Study Design and Populations

The EPOCH–JAPAN study is a meta-analysis of individual data from Japanese cohorts[4, 14]. It is based on databases that include an overview of individual participants' data from longitudinal observational studies in Japan. All studies contributing to the EPOCH–JAPAN project received ethical approval from their respective institutional review boards. Moreover, the EPOCH–JAPAN study received ethical approval from the institutional review board of Shiga University of Medical Science (23-125-1) and the Ethics Committee of the Keio University School of Medicine (20110192). The former is a data management center, and the latter is the university in which the primary investigator of EPOCH–JAPAN works.

In 2017, the EPOCH–JAPAN cardiovascular database included 14 Japanese cohorts. Of the 121,003 participants with codes for causes of death, 2,489 participants in the Tanno-Sobetsu cohort[15] were excluded because there was no information on the past history of cardiovascular disease. For the current analyses, 13,082 individuals were excluded because of age [<35 years old throughout the follow-up period ($n=685$)], lack of BP ($n=1,713$) or TC data ($n=2,620$), and lack of data on the history of cardiovascular disease ($n=869$) or a previous history of cardiovascular disease ($n=7,195$). Finally, 105,432 participants without a history of cardiovascular disease from 13 cohorts were analyzed[16-28].

BP Measurement

BP was measured with a mercury sphygmomanometer, with each participant in a seated position, except in the Ohasama study[16], where an automated device was used. Participants rested before any measurement in all the studies, except those in the Ohsaki study[17]. One reading at the examination center was obtained and used in the analysis, except in the cases

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of the Ohasama[16] and Suita[18] studies (two readings) and the Hisayama study[19] (three readings). In one study (JACC[20]), BP was self-recorded after it had been measured at a health check-up. Methods for obtaining other clinical data have been presented previously[4, 29].

On the basis of hypertension guidelines[3, 30] and our previous reports[29, 31], we first set grade (G) 1 hypertension as a systolic/diastolic BP range within 140–159/90–99 mmHg and G2–3 hypertension as a BP of ≥ 160/≥ 100 mmHg[3, 30, 32, 33]. We additionally defined a BP of <130/<80 mmHg as the "normal group" and a BP range within 130–139/80–89 mmHg as the "high BP group," which is defined as stage 1 hypertension by the ACC/AHA Guideline[6]. If systolic and diastolic BP fell within different groups (e.g., systolic high, diastolic normal), participants were assigned to the higher BP category.

Data Collection and Measurement of Serum TC

In all cohorts, a questionnaire was used to obtain detailed information on each participant's drinking and smoking habits. Smoking and drinking (alcohol consumption) habits were categorized into current smoker or nonsmoker and current habitual drinker or nondrinker, respectively, in which the number of cigarettes and the amount of alcohol were not considered. Body mass index was determined by body weight in kilograms divided by height in meters squared. Serum TC was determined by automated enzymatic methods on venous blood samples in all cohorts, with the exception of the NIPPON DATA80 cohort[24], in which TC levels were measured by the Liebermann–Burchard direct method. We divided the participants into groups according to a TC cut-off value of 5.7 mmol/L (220 mg/dL); this TC level is equivalent to an LDL value of 3.6 mmol/L (140 mg/dL), which is the cut-off point for dyslipidemia screening in Japan[34]. For the sensitivity analysis, we also used a TC cut-off point of 6.2 mmol/L (240 mg/dL), which is equivalent to an LDL value of 4.1 mmol/L (160 mg/dL)[34].

Outcomes

In accordance with the Family Registration Law in Japan, all death certificates are forwarded to the Ministry of Health, Labor, and Welfare via the public health center in the area of residence[35]. Registration of death is required by law. Other sources used in some studies included autopsy reports[18, 19], medical records[16, 18, 19], health examinations[16, 17], and questionnaires. The underlying causes of death were coded according to the 9th International Classification of Disease (ICD-9) generated at the end of 1994, and the 10th International Classification of Disease (ICD-10) generated at the beginning of 1995. The cause of death was defined as follows: CHD (410 to 414; I20 to I25).

Statistical Analysis

LTR was calculated using the practical incidence estimator (PIE) macro[8]. Values were adjusted for cause of death other than CHD with a double-decrement approach, taking into consideration the occurrence of the outcome of interest and all-cause mortality[8, 10, 36-38]. We have indicated the schema of methods used to calculate intermediate risk and LTR (**Supplementary Fig. 1**). Age categories began at the age of 35 years, and the highest age category was set at age ≥ 85 years. However, age ≥ 85 years was later changed to 85 years, as the small number of observations in each age group ≥ 85 years caused unstable LTRs. Accordingly, sex-specific LTRs of CHD death at 35, 45, 55, 65, and 75 years were each estimated. Similarly, mortality-adjusted cumulative rates for 10-, 20-, 30-, 40-, and 50-year risks of CHD death were estimated as intermediate-term risks. For sensitivity analysis, we estimated LTRs after excluding two studies[22, 28] based on young workers. We also performed stratified analysis according to the use of antihypertensive drugs using available data from 63,960 individuals. The LTRs and their 95% confidence intervals at the age of 45 years were calculated instead of those at 35 years if LTR was not estimated because of the small sample size. SAS software, version 9.4 (SAS Institute, Cary, NC) was used in our study. Values were expressed as mean ± standard deviation (SD), unless otherwise noted.

Results

Baseline Characteristics

Of the 105,432 participants (42.5% men; mean age, 55.0 ± 12.5 years), 40,901 (38.8%), 29,793 (28.3%), 23,575 (22.4%), and 11,163 (10.6%) showed normal BP, high BP, G1 hypertension, and G2–3 hypertension, respectively, and 28,919 (27.4%) had TC ≥ 5.7 mmol/L. Baseline characteristics according to the BP and TC categories are shown in **Table 1**, and characteristics stratified by cohort are shown in **Supplementary Table 1**.

LTRs and Intermediate-Term Risks of CHD Mortality

During the mean follow-up period of 15 years (1,553,735 person-years), 889 deaths from CHD were recorded. The follow-up person-years according to age group are shown in **Table 2**. In men, the 10-year risk of CHD death at the index age of 35 years was at

Table 1. Baseline Characteristics

TC	Variables	Category: SBP/DBP, mmHg			
		Normal: <130/<80 (*n* = 40,901)	High BP: 130–139/80–89 (*n* = 29,793)	Grade 1 HT: 140–159/90–99 (*n* = 23,575)	Grade 2–3 HT: ≥ 160/≥ 100 (*n* = 11,163)
< 5.7 mmol/L (< 220 mg/dL)	*N*	31,707	21,152	16,152	7,502
	Age, years	50.1 ± 12.5	54.2 ± 12.1	58.8 ± 11.4	61.5 ± 11.2
	Men, %	38.8	49.8	51.5	53.7
	Body mass index, kg/m^2	22.1 ± 2.8	23.0 ± 3.0	23.4 ± 3.2	23.7 ± 3.4
	Current smoking, %	26.8	29.5	28.9	31.0
	Alcohol consumption, %	42.6	49.9	49.8	51.4
	Systolic BP, mmHg	113.0 ± 9.5	129.2 ± 7.3	144.6 ± 7.9	167.5 ± 14.8
	Diastolic BP, mmHg	68.0 ± 6.9	79.8 ± 6.1	85.6 ± 7.9	95.1 ± 11.3
	Total cholesterol, mmol/L	4.6 ± 0.6	4.7 ± 0.6	4.8 ± 0.6	4.7 ± 0.6
≥ 5.7 mmol/L (≥ 220 mg/dL)	*N*	9,194	8,641	7,423	3,661
	Age, years	54.6 ± 10.9	56.7 ± 10.5	59.6 ± 10.2	61.4 ± 10.4
	Men, %	30.2	36.2	32.8	33.5
	Body mass index, kg/m^2	22.9 ± 2.9	23.8 ± 3.1	24.3 ± 3.2	24.8 ± 3.4
	Current smoking, %	20.9	20.3	18.3	18.2
	Alcohol consumption, %	36.5	40.1	37.1	37.5
	Systolic BP, mmHg	114.1 ± 9.1	129.5 ± 7.2	145 ± 7.8	167.4 ± 15.0
	Diastolic BP, mmHg	69.0 ± 6.6	80.2 ± 6.1	85.9 ± 8.0	95.7 ± 11.4
	Total cholesterol, mmol/L	6.3 ± 0.6	6.3 ± 0.6	6.4 ± 0.6	6.4 ± 0.7

A total of 105,432 Japanese individuals from 13 cohorts are included. Data on body mass index, smoking status, alcohol consumption status, and total cholesterol are unavailable in 395, 4,148, and 4,193 individuals, respectively. Data are shown as mean ± SD, unless otherwise stated. BP, blood pressure; HT, hypertension.

Table 2. Number of CHD deaths and the follow-up person-years

Strata	CHD Mortality Rates		
	Number of Deaths	Person-Years	Mortality per 1,000 Person-Years
Men			
35–44	3	64,686	0.05
45–54	19	137,563	0.14
55–64	63	167,670	0.38
65–74	126	157,433	0.80
75–84	197	77,557	2.54
85 ≤	84	31,580	2.66
Women			
35–44	0	70,139	0.00
45–54	3	166,302	0.02
55–64	14	247,515	0.06
65–74	80	253,615	0.32
75–84	175	125,198	1.40
85 ≤	125	54,477	2.29

Data shows the number of CHD death and the follow-up person-years in each age group according to sex. CHD, coronary heart disease. The total number of CHD deaths in men and women are 492 and 397, respectively.

Table 3. Risk Estimates (95% Confidence Intervals) for CHD Mortality in Men at the Index Age of 35

TC, mmol/L	Category: SBP/DBP, mmHg	Intermediate-Term Risk, %					LTR, %
		10-Year	20-Year	30-Year	40-Year	50-Year	
<5.7 (<220 mg/dL)	Normal: <130/<80	0.06 (0.00–0.14)	0.14 (0.02–0.25)	0.27 (0.11–0.42)	0.51 (0.28–0.73)	1.81 (0.97–2.37)	2.90 (1.55–3.71)
	High BP: 130–139/80–89	0.00 (0.00–0.00)	0.12 (0.00–0.24)	0.5 (0.28–0.72)	1.27 (0.89–1.61)	2.66 (1.80–3.26)	3.93 (2.58–4.77)
	G1 hypertension: 140–159/90–99	0.11 (0.00–0.33)	0.26 (0.00–0.55)	0.51 (0.18–0.83)	1.15 (0.72–1.54)	2.75 (1.93–3.34)	4.03 (2.76–4.80)
	G2–3 hypertension: ≥ 160/≥ 100	0.00 (0.00–0.00)	0.79 (0.00–1.60)	1.22 (0.32–2.08)	2.01 (1.02–2.93)	4.20 (2.73–5.31)	5.11 (3.24–6.32)
≥ 5.7 (≥ 220 mg/dL)	Normal: <130/<80	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.42 (0.04–0.79)	0.85 (0.18–1.45)	2.15 (0.23–3.51)	2.65 (0.12–4.32)
	High BP: 130–139/80–89	0.00 (0.00–0.00)	0.10 (0.00–0.30)	0.33 (0.00–0.66)	1.07 (0.40–1.68)	2.65 (1.01–3.87)	3.70 (1.18–5.38)
	G1 hypertension: 140–159/90–99	0.00 (0.00–0.00)	0.26 (0.00–0.63)	0.92 (0.29–1.52)	2.19 (1.19–3.08)	5.06 (2.73–6.66)	6.63 (3.39–8.63)
	G2–3 hypertension: ≥ 160/≥ 100	0.00 (0.00–0.00)	0.35 (0.00–1.03)	1.77 (0.51–2.95)	3.49 (1.79–5.03)	5.76 (3.04–7.82)	7.73 (3.53–10.28)

A total of 44,761 Japanese men from 13 cohorts were included and the total number of observations was 636,489 person-years. Intermediate-term risks were defined as mortality-adjusted cumulative rates for 10-, 20-, 30-, 40-, and 50-year risk of CHD death. CHD, coronary heart disease; DBP, diastolic blood pressure; SBP, systolic blood pressure; LTR, lifetime risk; TC, total cholesterol.

most 0.11% (**Table 3**). The LTR of CHD death was at least 2.65% (**Table 3**). The LTRs increased with incremental increases in BP, and the association of BP with the LTRs was steeper in participants with TC ≥ 5.7 mmol/L than in those with TC <5.7 mmol/L. In hypertensive men, the differences in LTRs between the TC <5.7 mmol/L and ≥ 5.7 mmol/L groups were ≈2.6%. In men with high BP, the LTR in the TC < 5.7 mmol/L group did not differ from that in the TC ≥ 5.7 mmol/L group (3.93% vs 3.70%) (**Table 3**). In women with high BP, although similar results were observed, the difference in the LTR between the TC <5.7 mmol/L and ≥ 5.7 mmol/L groups was only significant in the G2–3 hypertension group (**Table 4**).

Fig. 1 shows summarized data for the LTRs at each index age. The corresponding intermediate-risk and LTR values at the index age of 45 years, 55 years, 65 years, and 75 years are shown in **Supplementary Table 2, Supplementary Table 3, Supplementary Table 4, and Supplementary Table 5,** respectively. Although LTR decreased with age, the association between both BP and TC, and LTR was similar irrespective of the age index (**Fig. 1**). The LTR of CHD mortality at the index age of 75 years in the G2–3 hypertension group with TC ≥ 5.7 mmol/L was 5.71 (1.66–8.49)% in men and 5.19 (3.37–6.71)% in women.

Sensitivity Analyses

Despite excluding two studies on the basis of participant demographics, which could have caused imbalances in participants' characteristics (young workers[22, 28]), the results remained unchanged (**Supplementary Table 6**). We also performed the same analysis after excluding three studies using multiple BP readings, and the highest LTR of CHD mortality was observed in participants with TC ≥ 5.7 mmol/L combined with G2–3 hypertension (**Supplementary Table 7**).

Next, we used a TC of 6.2 mmol/L instead of 5.7 mmol/L as the cut-off value of high TC. In the G2–3 hypertension group, the LTRs at the index age of 45 years were 5.19% (men)/4.00% (women) for the TC <6.2 mmol/L group and 11.08% (men)/6.76% (women) for the TC ≥ 6.2 mmol/L group (**Table 5**). In both men and women of the high BP group aged 45 years, little difference in LTRs between the TC groups was observed (**Table 5**).

Table 4. Risk Estimates (95% Confidence Intervals) for CHD Mortality in Women at the Index Age of 35

TC	Category: SBP/DBP, mmHg	Intermediate-Term Risk, %					LTR, %
		10-Year	20-Year	30-Year	40-Year	50-Year	
<5.7 (<220 mg/dL)	Normal: <130/<80	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.05 (0.00–0.09)	0.14 (0.04–0.23)	0.96 (0.45–1.37)	1.83 (0.94–2.50)
	High BP: 130–139/80–89	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.04 (0.00–0.09)	0.42 (0.21–0.60)	1.40 (0.85–1.86)	3.02 (1.91–3.88)
	G1 hypertension: 140–159/90–99	0.00 (0.00–0.00)	0.06 (0.00–0.18)	0.06 (0.00–0.18)	0.34 (0.13–0.54)	1.63 (1.03–2.12)	3.55 (2.48–4.36)
	G2–3 hypertension: ≥ 160/≥ 100	0.00 (0.00–0.00)	0.20 (0.00–0.59)	0.26 (0.00–0.67)	0.68 (0.15–1.17)	1.96 (1.06–2.71)	3.78 (2.34–4.82)
≥ 5.7 (≥ 220 mg/dL)	Normal: <130/<80	0.00 (0.00–0.00)	0.05 (0.00–0.16)	0.08 (0.00–0.20)	0.18 (0.01–0.34)	1.30 (0.43–2.01)	1.84 (0.67–2.78)
	High BP: 130–139/80–89	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.08 (0.00–0.18)	0.36 (0.14–0.57)	1.60 (0.87–2.24)	2.62 (1.42–3.60)
	G1 hypertension: 140–159/90–99	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.46 (0.20–0.70)	1.51 (0.88–2.04)	2.79 (1.70–3.64)
	G2–3 hypertension: ≥ 160/≥ 100	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.58 (0.00–1.16)	1.34 (0.57–2.07)	3.73 (2.4–4.85)	5.77 (3.83–7.25)

A total of 60,671 Japanese individuals from 13 cohorts were included and the total number of observations was 917,246 person-years, considering the mean follow-up period of 15 years. Intermediate-term risks were defined as mortality-adjusted cumulative rates for 10-, 20-, 30-, 40-, and 50-year risk of CHD death. CHD, coronary heart disease; DBP, diastolic blood pressure; SBP, systolic blood pressure; LTR, lifetime risk; TC, total cholesterol.

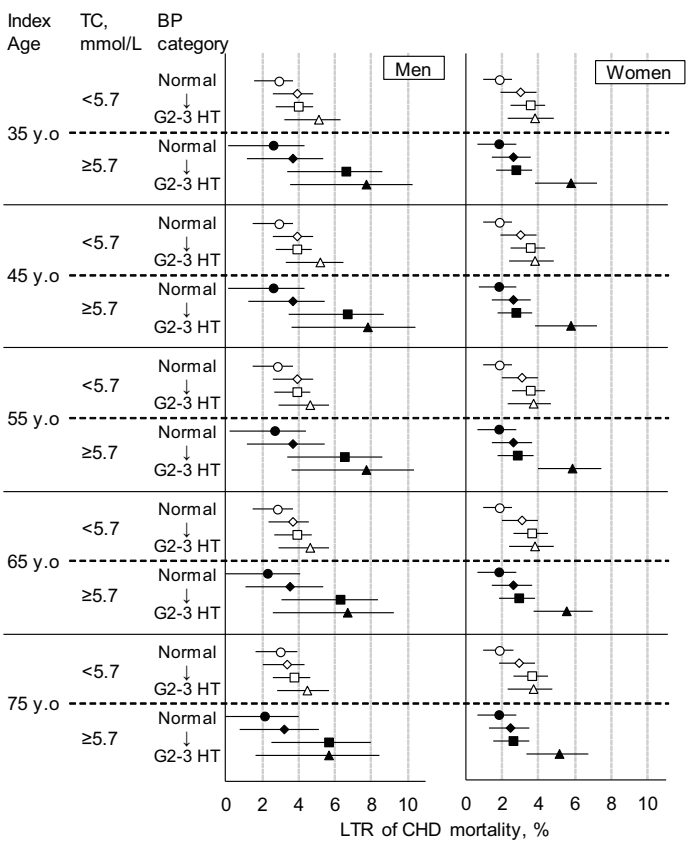

Fig. 1. Sex- and blood pressure-specific lifetime risk of CHD mortality after stratification of the total cholesterol level across five age groups

A total of 105,432 Japanese individuals from 13 cohorts were included, and the mean follow-up period was 15 years (1,553,735 person-years). Open and closed symbols indicate the TC <5.7 mmol/L and ≥ 5.7 mmol/L groups, respectively. CHD, coronary heart disease; DBP, diastolic blood pressure; SBP, systolic blood pressure; LTR, lifetime risk.

Table 5. Sex- and Blood Pressure-Specific Lifetime Risk (95% Confidence Intervals) for CHD Mortality After Stratification of Total Cholesterol Level of 6.2 mmol/L (240 mg/dL)

Strata	LTR at each Index Age, %				
	35 Years Old	45 Years Old	55 Years Old	65 Years Old	75 Years Old
Men					
TC < 6.2 mmol/L					
Normal	2.95 (1.69–3.72)	2.92 (1.66–3.69)	2.90 (1.64–3.68)	2.83 (1.57–3.64)	2.89 (1.64–3.79)
High BP	3.81 (2.57–4.58)	3.82 (2.59–4.60)	3.78 (2.55–4.57)	3.57 (2.35–4.38)	3.22 (2.02–4.11)
Grade 1 HT	4.25 (3.04–4.98)	4.20 (3.01–4.92)	4.17 (2.99–4.90)	4.16 (2.98–4.91)	3.92 (2.76–4.76)
Grade 2–3 HT	5.11 (3.41–6.20)	5.19 (3.49–6.31)	4.77 (3.17–5.71)	4.63 (3.06–5.60)	4.28 (2.74–5.35)
TC ≥ 6.2 mmol/L					
Normal	1.92 (0.00–4.32)	1.93 (0.00–4.33)	1.96 (0.00–4.41)	2.05 (0.00–4.61)	1.84 (0.00–4.56)
High BP	4.99 (0.00–8.23)	5.01 (0.03–8.27)	5.11 (0.12–8.43)	5.09 (0.11–8.50)	4.53 (0.00–8.26)
Grade 1 HT	7.70 (1.80–11.18)	7.70 (1.80–11.18)	7.36 (1.48–10.87)	6.86 (0.97–10.53)	6.82 (0.93–10.90)
Grade 2–3 HT	10.95 (3.11–15.47)	11.08 (3.24–15.65)	11.08 (3.28–15.75)	9.79 (1.97–14.53)	10.00 (2.18–15.48)
Women					
TC < 6.2 mmol/L					
Normal	1.75 (0.99–2.34)	1.76 (1.00–2.35)	1.78 (1.02–2.38)	1.78 (1.01–2.38)	1.79 (1.03–2.43)
High BP	2.66 (1.77–3.36)	2.67 (1.78–3.37)	2.70 (1.81–3.41)	2.72 (1.83–3.44)	2.49 (1.62–3.24)
Grade 1 HT	3.35 (2.44–4.03)	3.37 (2.46–4.05)	3.38 (2.47–4.07)	3.48 (2.58–4.19)	3.38 (2.48–4.12)
Grade 2–3 HT	3.98 (2.72–4.92)	4.00 (2.74–4.94)	3.93 (2.71–4.83)	3.89 (2.68–4.80)	3.78 (2.60–4.74)
TC ≥ 6.2 mmol/L					
Normal	2.21 (0.41–3.67)	2.24 (0.44–3.70)	2.13 (0.34–3.59)	2.11 (0.33–3.60)	2.07 (0.29–3.61)
High BP	3.71 (1.64–5.37)	3.71 (1.64–5.37)	3.75 (1.68–5.42)	3.81 (1.73–5.53)	3.68 (1.62–5.47)
Grade 1 HT	2.91 (1.43–4.08)	2.91 (1.43–4.08)	2.93 (1.46–4.11)	3.01 (1.53–4.22)	2.67 (1.24–3.91)
Grade 2–3 HT	No data*	6.76 (3.94–8.88)	6.89 (4.07–9.04)	6.76 (3.99–8.92)	6.19 (3.49–8.45)

*LTR was not calculated as there were no participants within the index age.
BP, blood pressure; CHD, coronary heart disease; HT, hypertension; LTR, lifetime risk. TC, total cholesterol.

We confirmed that 8,712 subjects were treated with antihypertensive therapy, whereas 55,248 participants were not. The results in untreated participants were similar to the main results (**Table 6**). However, this was not true in treated participants. The LTRs at the index age of 45 years in treated men/women with G2–3 hypertension were 7.87%/7.29% for the TC < 5.7 mmol/L group and 8.43%/6.15% for the TC ≥ 5.7 mmol/L group, respectively, resulting in little difference in the LTRs of CHD mortality between the low and high TC groups (**Table 6**).

Discussion

The present study assessed the LTR of CHD mortality according to BP levels after stratification of TC levels, by considering the threshold for hypertension determined by the ACC/AHA Guideline. There was a greater LTR of CHD mortality with the presence of hypertension in the TC ≥ 5.7 mmol/L and TC ≥ 6.2 mmol/L groups than at lower TC values. LTR was highest in men and women with G2–3 hypertension and high TC. In the high BP group, the absolute differences in LTR between low and high TC were 0.23% (low TC, 3.93%; high TC, 3.70%) in men and 0.40% (low TC, 3.02%; high TC, 2.62%) in women.

There are few studies assessing the LTR of CHD in Asian populations[11, 36]. This is primarily due to the large number of subjects and extensive data collection necessary to detect LTRs, as the number of CHD events is limited in Asian populations[11, 36]. The Suita study is the only study reporting the LTR of CHD events according to hypertension status[10] or hypercholesterolemia[13] in an Asian population. According to this study, the LTR of CHD was 26.95% for Japanese hypertensive men and 14.85% for Japanese hypertensive women[10]. Similarly, a raised cholesterol level was associated with an elevated LTR of CHD[13]. The LTRs of CHD in the Suita study were higher than those in our study, which is likely because LTR was estimated based on incidence and not mortality[10]. However, as their Suita study included only 5,834 participants with 204 CHD events, a detailed stratification analysis according to both hypertension and

Table 6. Sex- and Blood Pressure- Specific Lifetime Risk (95% Confidence Intervals) for CHD Mortality at the Index Age of 45 After Stratification of the Usage of Antihypertensive Treatment

Sex	Strata	LTR at the Index Age of 45 Years*, % Untreated with Antihypertensive Medication (CHD death/ *n*=353/ 55,248)	LTR at the Index Age of 45 Years*, % Treated with Antihypertensive Medication (CHD death/ *n*=160/ 8,712)
Men			
	TC<5.7 mmol/L		
	Normal	2.39 (0.45–3.55)	6.97 (0.00–11.67)
	High BP	4.30 (2.07–5.67)	2.19 (0.00–4.19)
	Grade 1 HT	4.71 (2.48–6.02)	3.63 (0.44–5.49)
	Grade 2–3 HT	3.67 (1.31–5.33)	7.87 (2.97–11.44)
	TC ≥ 5.7 mmol/L		
	Optimal	2.25 (0.00–4.80)	2.96 (0.00–8.69)
	High BP	4.61 (0.00–7.86)	2.24 (0.00–5.31)
	Grade 1 HT	5.05 (0.66–7.71)	9.43 (0.00–15.54)
	Grade 2–3 HT	7.88 (0.28–12.19)	8.43 (0.14–13.79)
Women			
	TC<5.7 mmol/L		
	Normal	2.57 (0.99–3.75)	3.59 (0.00–7.20)
	High BP	3.86 (1.85–5.42)	4.51 (0.94–7.17)
	Grade 1 HT	3.39 (1.57–4.68)	3.30 (0.74–5.13)
	Grade 2–3 HT	2.51 (0.40–3.86)	7.29 (2.83–11.09)
	TC ≥ 5.7 mmol/L		
	Normal	1.82 (0.00–3.38)	0.88 (0.00–2.61)
	High BP	2.23 (0.43–3.69)	2.81 (0.00–5.46)
	Grade 1 HT	3.19 (1.22–4.72)	2.46 (0.00–4.37)
	Grade 2–3 HT	6.12 (2.48–8.70)	6.15 (2.02–9.42)

*Because of the small sample size, the LTRs at the age of 45 years were calculated instead of those at 35 years. BP, blood pressure; LTR, lifetime risk; HT, hypertension; TC, total cholesterol.

hypercholesterolemia could not be performed[10, 13]. The present study estimated the BP- and TC- specific LTRs of CHD death based on 105,432 individuals. The participants were followed up for 15 years, resulting in 1,553,735 person-years. The 10-year risk of CHD mortality at the index age of 35 years was ≤ 0.11% regardless of sex, BP, or TC. The LTRs were higher than the 10-year risks and clearly increased with an increase in BP levels, as we have reported previously[9]. The LTRs of CHD mortality in men aged 35 years with G1 and G2–3 hypertension increased from 4.03% and 5.11% in the TC <5.7 mmol/L group to 6.63% and 7.73% in the TC ≥ 5.7 mmol/L group, respectively (**Table 3**). A similar increase in LTR on stratification based on high TC was also observed in women, although only in the G2–3 hypertension group (**Table 4**). The LTR of CHD mortality in hypertensive individuals with TC ≥ 6.2 mmol/L (240 mg/dL) appears to be higher than in those with TC ≥ 5.7 mmol/L (**Table 5**). In our previous study, we noted that the LTRs of CHD mortality at the age of 35 years in men and women with G2–3 hypertension were 5.3%–7.2% and 4.0%–6.9%, respectively[9]. These results suggest that high TC contributes to an elevation in LTR of CHD death in hypertensive individuals. These results are supported by the response-to-injury hypothesis[39] and the inflammation hypothesis, in which the combination of hypertension and hypercholesterolemia contributes to long-term mortality rates[40].

The ACC/AHA Guideline for the Prevention, Detection, Evaluation and Management of High BP in Adults lowered the diagnostic threshold for hypertension from ≥ 140/≥ 90 mmHg to ≥ 130/≥ 80 mmHg (systolic/diastolic)[6]. The use of BP-lowering medications is indicated when patients are presented with a BP of 130–139/80–89 mmHg, in the presence of a ≥ 10% atherosclerotic cardiovascular disease risk. TC has been noted as one of the significant risk factors for atherosclerotic cardiovascular disease[6]. However, whether this recommendation should be adopted in Asian populations is still controversial. In the present

study, the LTR of CHD mortality did not differ based on TC levels in the high BP group, which is defined as stage 1 hypertension by the ACC/AHA Guideline[6]. Although high TC is likely to increase the adjusted risk ratio of CHD mortality[4], our findings suggest that the impact of high TC on the LTR of CHD mortality is low in Asian populations.

The LTR of CHD mortality in those with G2–3 hypertension in the presence of high TC levels decreased with age in this study. We estimated the LTR to be 7.73% for men (**Table 3**) and 5.77% for women in the 35-year-old group (**Table 4**) and only 5.71% for men and 5.19% for women in the 75-year-old group (**Supplementary Table 5**). Thus, our data suggest that in individuals with hypertension and hyperlipidemia, it is important to intervene early in life, especially for men. As the short-term absolute CHD risk in younger populations is quite low[9, 10], it is often difficult to implement and maintain healthy lifestyles in young high-risk individuals. LTR is far easier to comprehend for patients than a relative risk estimation[41], and patients prefer health risks to be indicated in absolute terms[42]. Thus, the estimated LTR in the present study could help encourage young, high-risk individuals to make lifestyle changes or begin treatments, which in turn could lead to lower rates of CHD mortality.

The LTRs in untreated participants in this study were almost identical to the overall main findings (**Table 6**). In treated G2–3 hypertensive men and women, the LTR of CHD mortality at the age of 45 years was 7.87% and 7.29% in the TC $<$5.7 mmol/L group, respectively, which was similar to the results observed in the TC $\geq$ 5.7 mmol/L group in the same BP level group (**Table 6**). Patients undergoing treatment who still presented with G2–3 hypertension could have pharmacologically resistant hypertension, which has previously been shown to be related to cardiovascular complications[3, 43]. Therefore, the LTRs of CHD mortality in treated patients with G2–3 hypertension may have already increased irrespective of current TC levels. In normotensive men undergoing treatment, the LTR of CHD mortality at the age of 45 years was 6.97%, even though the corresponding 95% confidence interval ranged from 0.00% to 11.67%. Although a limited number of observations may have caused the high LTR observed in this group, it may also partly reflect a J-curve relationship between BP, cardiovascular risk, and LTR in these patients[44]. In treated women with G2–3 hypertension, the TC $<$ 5.7 mmol/L group had a slightly higher LTR of CHD mortality than the TC $\geq$ 5.7 mmol/L group (7.29% vs 6.15% in **Table 6**). We previously reported that only TC $\geq$ 6.72 mmol/L was significantly associated with the higher relative risk of CHD mortality in women aged 40–69 years[45]. The cut-off point of a higher TC level may change this inverse association of TC with LTR of CHD mortality in women with uncontrolled BP, because the present study could not perform further stratified analysis according to a high TC cut-off point such as TC $\geq$ 6.7 mmol/L due to the limited number of CHD deaths.

The present findings must be interpreted within the context of their potential limitations. First, although our findings demonstrated the impact of BP and TC on long-term absolute CHD mortality risk, no direct inference can be made regarding the benefit of antihypertensive treatment because of the observational study design. Second, our findings cannot be generalized to Western populations where the rate of CHD and total cardiovascular disease is substantially higher. The Cooper Center Longitudinal Study in the United States reported that the LTRs of CHD mortality were 13.7% in men with a family history of premature CHD and 8.9% in men without a family history[46]. Because the highest LTR of CHD mortality in 45-year-old men was 7.8% in the present study (**Supplementary Table 2**) even in the hypertension groups, the Japanese population can have a lower LTR of CHD than the United States population. Third, the model estimating LTR assumed that the exposure related to the risks remained stable. For example, patients with G3 hypertension at baseline are assumed to maintain the same BP levels even if they are treated with antihypertensive medication during follow-up. However, the intensity or presence of hypertension could have changed due to lifestyle modifications and/or treatment initiation over the follow-up period. As such, our findings could underestimate the LTR according to hypertension or high TC levels, although this limitation exists in other studies[10, 37, 47]. Furthermore, the model for the estimation of LTR was not adjusted for confounding factors in this study. There is a possibility that some other confounding factors affected the association of TC and BP with the LTR of CHD. Participants in the cohort study were generally volunteers, who may have different characteristics compared with nonparticipants. This could also cause an underestimation of LTR in the present study. Fourth, a cholesterol-lowering therapy was not considered because this information was only available for a small portion of the participants (28,576 participants, 27.1%). However, statin use in Japan began only in the late 1980s, and because baseline surveys in EPOCH–JAPAN were primarily performed around the year 1989, it is unlikely that the use of statins at baseline affected the present findings. Furthermore, the Framingham[48] and Japanese[49] risk score for car-

diovascular disease and the atherosclerotic cardiovascular disease risk estimator[50] do not consider statin therapy because statin therapy appears not to alter the impact of TC on cardiovascular risk. Finally, the classification system for death certificate diagnosis was changed from ICD-9 to ICD-10 in 1995 in Japan, which caused a decrement of heart failure death and an increment of CHD death[51]. This may lead to the underestimation of CHD mortality that occurred before 1995. We cannot assess the effect of changing the ICD code on our findings because the present database does not include baseline year in each participant's data. However, this effect could be limited because the mean follow-up duration was 15 years and most CHD deaths occurred after 1995.

Perspectives

BP was found to be strongly associated with the LTR of CHD mortality in those with high TC. This suggests that even in nonelderly hypertensive individuals, high TC contributes to an elevated LTR of CHD mortality. Further, the LTR of CHD mortality in participants with elevated BP and TC was higher in nonelderly individuals than in elderly individuals. The LTR estimated in the present study could be a useful tool to inform the general public about the dangers of hypertension and hyperlipidemia. These findings on LTR could help guide high-risk young individuals toward initiating lifestyle changes or treatments.

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Disclosures/ Conflicts of Interest

The authors have declared that no competing interests exist.

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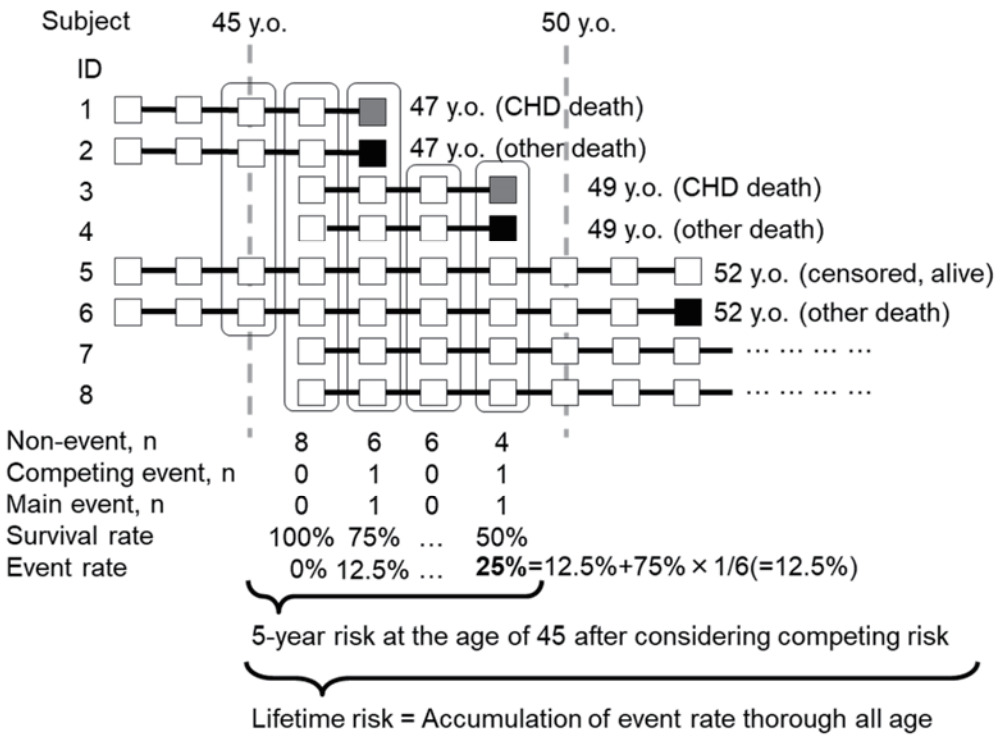

Supplementary Fig. 1. Schema of intermediate- and lifetime risk calculation
CHD, coronary heart disease.

Supplementary Table 1. Characteristics of Study Participants in Each Cohort: EPOCH–JAPAN

Cohorts	Baseline Year	*N*	Men, %	Age, years	Systolic BP, mmHg	Diastolic BP, mmHg	Total Cholesterol, mmol/L	CHD Death, *n*
Ohsaki[1)]	1994	15,551	42.0	62.2 ± 9.4	131.2 ± 17.7	78.6 ± 11.0	5.3 ± 0.9	107
Ohasama[2)]	1987	2,617	39.1	55.8 ± 12.1	129.4 ± 16.7	73.3 ± 11.1	5.1 ± 0.9	25
Oyabe[3)]	1988	5,124	30.8	56.8 ± 11.3	126.5 ± 19.9	75.5 ± 11.2	5.0 ± 0.9	28
YKK workers[4)]	1990	6,507	63.8	38.7 ± 9.7	118.7 ± 14.7	71.4 ± 11.8	4.9 ± 0.9	5
Suita[5)]	1989	6,241	47.2	55.0 ± 13.3	127.1 ± 22.1	77.4 ± 12.3	5.4 ± 1.0	79
RERF cohort[6)]	1986	4,243	31.9	61.6 ± 12.2	134.2 ± 22.5	82.2 ± 11.9	5.4 ± 1.0	68
Hisayama[7)]	1988	2,636	42.1	59.1 ± 11.9	133.8 ± 21.4	77.8 ± 11.3	5.3 ± 1.1	22
JACC study[8)]	1988	26,454	35.9	57.1 ± 9.6	133.0 ± 19.3	79.1 ± 11.3	5.1 ± 0.9	260
NIPPON DATA 80[9)]	1980	9,173	43.8	50.7 ± 13.2	135.9 ± 21.3	81.3 ± 12.2	4.9 ± 0.9	177
NIPPON DATA 90[10)]	1990	7,125	41.6	52.3 ± 13.7	135.1 ± 20.6	81.2 ± 11.9	5.2 ± 1.0	61
Osaka[11)]	1985	3,613	32.9	51.2 ± 12.0	125.6 ± 16.6	78.2 ± 10.3	5.4 ± 1.0	9
JMS[12)]	1992	10,744	38.6	55.5 ± 11.0	129.3 ± 20.9	77.4 ± 12.2	5.0 ± 0.9	45
Aichi workers[13)]	2002	5,404	78.5	48.0 ± 7.1	126.2 ± 15.5	77.7 ± 11.5	5.4 ± 0.9	3

A total of 105,432 Japanese individuals from 13 cohorts were included. BP, blood pressure; CHD, coronary heart disease; JACC, Japan Collaborative Cohort; JMS, Jichi Medical School; NIPPON DATA, National Integrated Project for Prospective Observation of Non–communicable Disease And its Trends in the Aged; RERF, Radiation Effects Research Foundation; YKK, Yoshida Kogyo Kabushikigaisya.

Supplementary Table 2. Sex- and Blood Pressure-Specific Risk Estimates (95% Confidence Intervals) for Coronary Heart Disease Mortality at the Index Age of 45 After Stratification of Total Cholesterol Level

Strata	Intermediate-Term Risk, %				LTR, %
	10-Year Risk	20-Year Risk	30-Year Risk	40-Year Risk	
Men					
TC < 5.7 mmol/L					
Normal	0.08 (0.00–0.16)	0.21 (0.08–0.34)	0.46 (0.24–0.66)	1.76 (0.93–2.32)	2.86 (1.51–3.67)
High BP	0.12 (0.00–0.24)	0.51 (0.28–0.72)	1.27 (0.89–1.62)	2.67 (1.81–3.28)	3.95 (2.59–4.80)
Grade 1 HT	0.15 (0.00–0.34)	0.40 (0.15–0.65)	1.05 (0.68–1.38)	2.66 (1.87–3.22)	3.96 (2.70–4.71)
Grade 2–3 HT	0.80 (0.00–1.63)	1.24 (0.34–2.12)	2.04 (1.05–2.99)	4.27 (2.80–5.41)	5.20 (3.32–6.44)
TC ≥ 5.7 mmol/L					
Optimal	0.00 (0.00–0.00)	0.42 (0.04–0.80)	0.85 (0.18–1.46)	2.16 (0.24–3.54)	2.67 (0.14–4.35)
High BP	0.10(0.00–0.30)	0.34 (0.00–0.67)	1.08 (0.41–1.69)	2.67 (1.02–3.89)	3.72 (1.20–5.41)
Grade 1 HT	0.27 (0.00–0.64)	0.93 (0.30–1.54)	2.21 (1.22–3.11)	5.11 (2.79–6.73)	6.70 (3.46–8.72)
Grade 2–3 HT	0.35 (0.00–1.04)	1.79 (0.54–2.99)	3.53 (1.84–5.10)	5.83 (3.11–7.92)	7.83 (3.64–10.41)
Women					
TC < 5.7 mmol/L					
Normal	0.00 (0.00–0.00)	0.05 (0.00–0.09)	0.14 (0.04–0.23)	0.96 (0.46–1.37)	1.83 (0.95–2.51)
High BP	0.00 (0.00–0.00)	0.04 (0.00–0.09)	0.42 (0.22–0.61)	1.41 (0.85–1.87)	3.04 (1.93–3.90)
Grade 1 HT	0.06 (0.00–0.18)	0.06 (0.00–0.18)	0.34 (0.13–0.54)	1.64 (1.04–2.13)	3.57 (2.49–4.38)
Grade 2–3 HT	0.20 (0.00–0.59)	0.26 (0.00–0.68)	0.68 (0.15–1.18)	1.97 (1.07–2.72)	3.80 (2.36–4.84)
TC ≥ 5.7 mmol/L					
Normal	0.05 (0.00–0.16)	0.08 (0.00–0.20)	0.18 (0.01–0.34)	1.30 (0.44–2.03)	1.85 (0.69–2.80)
High BP	0.00 (0.00–0.00)	0.08 (0.00–0.18)	0.36 (0.14–0.57)	1.60 (0.87–2.24)	2.62 (1.42–3.60)
Grade 1 HT	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.46 (0.21–0.70)	1.52 (0.89–2.05)	2.81 (1.72–3.66)
Grade 2–3 HT	0.00 (0.00–0.00)	0.58 (0.00–1.16)	1.34 (0.57–2.07)	3.73 (2.40–4.85)	5.77 (3.83–7.25)

Normal, high BP, grade (G) 1 hypertension and G2–3 hypertension was defined as systolic/diastolic BPs < 130/< 80 mmHg, 130–139/80–89, 140–159/90–99, ≥ 160/≥ 100 mmHg, respectively. BP, blood pressure; CHD, coronary heart disease; LTR, lifetime risk; TC, total cholesterol.

Supplementary Table 3. Sex- and Blood Pressure-Specific Risk Estimates (95% Confidence Intervals) for Coronary Heart Disease Mortality at the Index Age of 55 After Stratification of Total Cholesterol Level

Strata	Intermediate-Term Risk, %			LTR, %
	10-Year Risk	20-Year Risk	30-Year Risk	
Men				
TC < 5.7 mmol/L				
Normal	0.13 (0.02–0.23)	0.38 (0.18–0.57)	1.71 (0.88–2.27)	2.83 (1.48–3.65)
High BP	0.39 (0.20–0.58)	1.18 (0.82–1.51)	2.61 (1.76–3.22)	3.92 (2.57–4.78)
Grade 1 HT	0.26 (0.08–0.42)	0.91 (0.59–1.21)	2.57 (1.80–3.12)	3.91 (2.66–4.65)
Grade 2–3 HT	0.47 (0.12–0.79)	1.32 (0.76–1.81)	3.68 (2.42–4.52)	4.66 (2.94–5.65)
TC ≥ 5.7 mmol/L				
Optimal	0.43 (0.04–0.81)	0.86 (0.20–1.48)	2.19 (0.27–3.59)	2.70 (0.18–4.41)
High BP	0.24 (0.00–0.51)	1.00 (0.36–1.59)	2.62 (0.99–3.85)	3.69 (1.18–5.41)
Grade 1 HT	0.68 (0.17–1.18)	1.99 (1.07–2.84)	4.96 (2.66–6.58)	6.59 (3.36–8.63)
Grade 2–3 HT	1.49 (0.44–2.52)	3.30 (1.74–4.77)	5.69 (3.04–7.75)	7.76 (3.60–10.35)
Women				
TC < 5.7 mmol/L				
Normal	0.05 (0.00–0.09)	0.14 (0.04–0.23)	0.97 (0.47–1.39)	1.85 (0.97–2.54)
High BP	0.04 (0.00–0.09)	0.42 (0.22–0.61)	1.42 (0.87–1.89)	3.07 (1.96–3.94)
Grade 1 HT	0.00 (0.00–0.00)	0.29 (0.11–0.45)	1.61 (1.02–2.09)	3.57 (2.50–4.39)
Grade 2–3 HT	0.07 (0.00–0.19)	0.49 (0.14–0.81)	1.82 (1.00–2.48)	3.70 (2.30–4.69)
TC ≥ 5.7 mmol/L				
Normal	0.03 (0.00–0.09)	0.12 (0.00–0.25)	1.26 (0.41–1.98)	1.82 (0.65–2.77)
High BP	0.08 (0.00–0.18)	0.36 (0.14–0.57)	1.62 (0.88–2.26)	2.64 (1.45–3.63)
Grade 1 HT	0.00 (0.00–0.00)	0.47 (0.21–0.71)	1.54 (0.91–2.08)	2.84 (1.75–3.70)
Grade 2–3 HT	0.59 (0.00–1.19)	1.38 (0.61–2.12)	3.82 (2.49–4.97)	5.91 (3.97–7.42)

Normal, high BP, grade (G) 1 hypertension and G2–3 hypertension were defined as systolic/diastolic BPs < 130/< 80 mmHg, 130–139/80–89, 140–159/90–99, ≥ 160/≥ 100 mmHg, respectively. BP, blood pressure; CHD, coronary heart disease; LTR, lifetime risk; TC, total cholesterol.

Supplementary Table 4. Sex- and Blood Pressure-Specific Risk Estimates (95% Confidence Intervals) for Coronary Heart Disease Mortality at the Index Age of 65 After Stratification of Total Cholesterol Level

Strata	Intermediate-Term Risk, %		LTR, %
	10-Year Risk	20-Year Risk	
Men			
TC < 5.7 mmol/L			
Normal	0.27 (0.09–0.43)	1.67 (0.85–2.25)	2.85 (1.50–3.71)
High BP	0.83 (0.52–1.11)	2.33 (1.50–2.95)	3.71 (2.36–4.59)
Grade 1 HT	0.71 (0.43–0.97)	2.48 (1.73–3.04)	3.91 (2.67–4.69)
Grade 2–3 HT	0.94 (0.50–1.35)	3.55 (2.33–4.40)	4.64 (2.93–5.66)
TC ≥ 5.7 mmol/L			
Optimal	0.45 (0.00–0.96)	1.83 (0.00–3.23)	2.37 (0.00–4.10)
High BP	0.79 (0.21–1.33)	2.46 (0.85–3.71)	3.57 (1.07–5.33)
Grade 1 HT	1.40 (0.61–2.13)	4.55 (2.28–6.19)	6.28 (3.06–8.38)
Grade 2–3 HT	1.94 (0.74–3.07)	4.48 (1.99–6.41)	6.70 (2.58–9.27)
Women			
TC < 5.7 mmol/L			
Normal	0.09 (0.01–0.17)	0.94 (0.44–1.37)	1.84 (0.96–2.54)
High BP	0.39 (0.20–0.58)	1.42 (0.87–1.90)	3.11 (2.00–4.00)
Grade 1 HT	0.30 (0.12–0.46)	1.66 (1.07–2.16)	3.69 (2.62–4.53)
Grade 2–3 HT	0.45 (0.12–0.75)	1.84 (1.02–2.51)	3.79 (2.40–4.82)
TC ≥ 5.7 mmol/L			
Normal	0.10 (0.00–0.21)	1.26 (0.41–1.99)	1.82 (0.66–2.79)
High BP	0.29 (0.10–0.48)	1.58 (0.85–2.23)	2.63 (1.44–3.64)
Grade 1 HT	0.48 (0.22–0.73)	1.58 (0.94–2.13)	2.91 (1.82–3.79)
Grade 2–3 HT	0.82 (0.34–1.29)	3.37 (2.17–4.41)	5.56 (3.69–7.02)

Normal, high BP, grade (G) 1 hypertension and G2–3 hypertension were defined as systolic/diastolic BPs < 130/< 80 mmHg, 130–139/80–89, 140–159/90–99, ≥ 160/≥ 100 mmHg, respectively. BP, blood pressure; CHD, coronary heart disease; LTR, lifetime risk; TC, total cholesterol.

Supplementary Table 5. Sex- and Blood Pressure-Specific Risk Estimates (95% Confidence Intervals) for Coronary Heart Disease Mortality at the Index Age of 75 after Stratification of Total Cholesterol Level

Strata	Intermediate-Term Risk, %	
	10-Year Risk	LTR, %
Men		
TC < 5.7 mmol/L		
Normal	1.60 (0.79–2.23)	2.94 (1.60–3.90)
High BP	1.75 (0.96–2.38)	3.34 (2.02–4.31)
Grade 1 HT	2.10 (1.39–2.69)	3.79 (2.57–4.66)
Grade 2–3 HT	3.19 (2.03–4.11)	4.51 (2.84–5.67)
TC ≥ 5.7 mmol/L		
Optimal	1.55 (0.00–3.01)	2.15 (0.00–4.01)
High BP	1.92 (0.40–3.21)	3.20 (0.73–5.11)
Grade 1 HT	3.65 (1.48–5.37)	5.65 (2.47–7.95)
Grade 2–3 HT	3.05 (0.79–4.94)	5.71 (1.66–8.49)
Women		
TC < 5.7 mmol/L		
Normal	0.90 (0.41–1.35)	1.86 (0.98–2.60)
High BP	1.09 (0.58–1.57)	2.90 (1.80–3.83)
Grade 1 HT	1.47 (0.91–1.97)	3.65 (2.59–4.54)
Grade 2–3 HT	1.53 (0.78–2.19)	3.69 (2.33–4.78)
TC ≥ 5.7 mmol/L		
Normal	1.22 (0.37–1.97)	1.81 (0.65–2.82)
High BP	1.35 (0.64–2.00)	2.45 (1.27–3.48)
Grade 1 HT	1.17 (0.59–1.70)	2.60 (1.53–3.50)
Grade 2–3 HT	2.80 (1.68–3.81)	5.19 (3.37–6.71)

Normal, high BP, grade (G) 1 hypertension and G2–3 hypertension were defined as systolic/diastolic BPs < 130/< 80 mmHg, 130–139/80–89, 140–159/90–99, ≥ 160/≥ 100 mmHg, respectively. BP, blood pressure; CHD, coronary heart disease; LTR, lifetime risk; TC, total cholesterol.

Supplementary Table 6. Sex- and Blood Pressure- Specific Lifetime Risk (95% Confidence Intervals) for Coronary Heart Disease Mortality at the Index Age of 35 After Excluding 2 Studies Based Young Workers

Sex	Strata	LTR at the Index Age of 35 Years, %
Men		
	TC < 5.7 mmol/L	
	Normal	3.02 (1.65–3.84)
	High BP	3.98 (2.62–4.83)
	Grade 1 HT	3.92 (2.66–4.67)
	Grade 2–3 HT	5.29 (3.35–6.59)
	TC ≥ 5.7 mmol/L	
	Optimal	2.59 (0.04–4.24)
	High BP	3.81 (1.26–5.49)
	Grade 1 HT	6.71 (3.45–8.74)
	Grade 2–3 HT	8.13 (3.87–10.8)
Women		
	TC < 5.7 mmol/L	
	Normal	1.83 (0.95–2.50)
	High BP	3.02 (1.91–3.87)
	Grade 1 HT	3.56 (2.48–4.36)
	Grade 2–3 HT	3.78 (2.33–4.82)
	TC ≥ 5.7 mmol/L	
	Optimal	1.86 (0.69–2.80)
	High BP	2.62 (1.43–3.60)
	Grade 1 HT	2.80 (1.70–3.65)
	Grade 2–3 HT	5.78 (3.83–7.26)

After excluding the YKK workers study[4] and the Aichi workers study[13], 93,521 Japanese people were included in this analysis. BP, blood pressure; LTR, lifetime risk; HT, hypertension; TC, total cholesterol.

Supplementary Table 7. Sex- and Blood Pressure- Specific Lifetime Risk (95% Confidence Intervals) for Coronary Heart Disease Mortality at the Index Age of 35 After Excluding 3 Studies using multiple BP readings

Sex	Strata	LTR at the Index Age of 35 Years, %
Men		
	TC < 5.7 mmol/L	
	Normal	2.99 (1.06–4.18)
	High BP	4.07 (2.07–5.28)
	Grade 1 HT	4.38 (2.53–5.49)
	Grade 2–3 HT	4.98 (2.61–6.49)
	TC ≥ 5.7 mmol/L	
	Optimal	1.81 (0.00–3.87)
	High BP	3.50 (0.03–5.81)
	Grade 1 HT	6.26 (1.62–8.93)
	Grade 2–3 HT	8.25 (2.48–11.68)
Women		
	TC < 5.7 mmol/L	
	Normal	2.49 (1.06–3.57)
	High BP	3.94 (2.22–5.26)
	Grade 1 HT	3.51 (2.00–4.60)
	Grade 2–3 HT	4.30 (2.23–5.74)
	TC ≥ 5.7 mmol/L	
	Optimal	1.52 (0.05–2.71)
	High BP	1.82 (0.57–2.86)
	Grade 1 HT	2.85 (1.32–4.03)
	Grade 2–3 HT	5.52 (3.01–7.40)

After excluding the Ohasama[2], Suita studies (two readings)[5] and the Hisayama study (three readings)[7], 67,484 Japanese people were included in this analysis. BP, blood pressure; LTR, lifetime risk; HT, hypertension; TC, total cholesterol.

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