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ORIGINAL RESEARCH

Prediction of Lifetime Risk of Cardiovascular Disease Deaths Stratified by Sex in the Japanese Population

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BACKGROUND: Lifetime risk is an informative estimate for driving lifestyle and behavioral changes especially for young adults. The impact of composite risk factors for cardiovascular disease on lifetime risk stratified by sex has not been investigated in the Japanese population, which has a much lower mortality of coronary heart disease compared with the Western population. We aimed to estimate lifetime risk of death from cardiovascular disease attributable to traditional risk factors.

METHODS AND RESULTS: We analyzed pooled individual data from the Evidence for Cardiovascular Prevention from Observational Cohorts in a Japanese cohort study. A modified Kaplan–Meier approach was used to estimate the remaining lifetime risk of cardiovascular death. In total, 41 002 Japanese men and women with 537 126 person-years of follow-up were included. The lifetime risk at the index-age of 45 years for those with optimal risk factors (total cholesterol <4.65 mmol/L, systolic blood pressure <120 mm Hg, diastolic blood pressure <80 mm Hg, absence of diabetes, and absence of smoking habit) was lower compared with the highest risk profile of ≥2 risk factors (6.8% [95% CI, 0%–11.9%] versus 19.4% [16.7%–21.4%] for men and 6.9% [1.2%–11.5%] versus 15.4% [12.6%–18.1%] for women).

CONCLUSIONS: The magnitude and the number of risk factors were progressively associated with increased lifetime risk even in individuals in early adulthood who tend to have low short-term risk. The degree of established cardiovascular risk factors can be converted into lifetime risk. Our findings may be useful for risk communication in the early detection of future cardiovascular disease risk.

Key Words: blood pressure ■ cardiovascular disease ■ diabetes ■ smoking ■ total cholesterol

Western countries, such as United States, have rapidly growing Asian populations, yet evidence on cardiovascular disease (CVD) in these populations is scarce. More information from the Asian population is needed to understand CVD risks.[1,2] Even among the Asian populations, ethnic differences exist such as higher rates of predisposition to coronary heart disease (CHD) in South Asian compared with

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CLINICAL PERSPECTIVE

What Is New?

- To our knowledge, this is the first study to reveal the impact of composite cardiovascular risk factors on lifetime risk for cardiovascular disease mortality in the Japanese population with one of the highest life expectancies in the world and low coronary heart disease mortality compared with those in Western and South Asian populations.
- As data for lifetime risk in Asian populations is scarce in the United States with its diverse racial and ethnic groups, this study would help further understanding of the differences in lifetime risk across different racial and ethnic groups.

What Are the Clinical Implications?

- When younger individuals had multiple cardiovascular risk factors, lifetime risks were high even though short-term risk was low, which is almost equivalent to the elderly population.
- Therefore, lifetime risks must be a useful communication tool for public health education, especially for those in early adulthood, and could be implemented in relevant guidelines.

Nonstandard Abbreviations and Acronyms

LTR	lifetime risk
TC	total cholesterol

Japanese populations[3] where cardiovascular mortality is relatively low and shows one of the world's highest life expectancies. As recommended in the US guidelines, more evidence is needed to fill the knowledge gaps in the short- and long-term CVD risk in various racial and ethnic groups.[4]

Risk prediction tools can be used by health care professionals in their clinical decision-making process and inform individuals for predicting future CVD risks, which would eventually impact on self-management decisions and behavior changes.[5] Relative risk and 10-year absolute risk for CVD have been estimated based on traditional risk factors to evaluate individual risk and have been considered in current treatment guidelines.[4,6,7] However, these guidelines indicate that younger individuals tend to have low short-term risk (such as within 10 years) despite the presence of significant risk factors. This has led to recommendations for using lifetime risk (LTR) for better risk conversation in public health education, especially among youth.[4,6,7]

The LTR is the probability of developing an event of interest over the remaining lifetime while accounting for competing risks.[8–10] This estimate provides a more comprehensive and intuitive assessment of the general population,[8–10] and it is useful for designing preventative strategies and facilitating health system decision-making.[11] Hypertension, diabetes, hypercholesterolemia, and smoking are established modifiable risk factors, which are collectively responsible for CVD deaths.[12–14] Composite exposure to a combination of these established risk factors has been examined to estimate the LTR in Western populations.[10,15–17] However, to date, there have been no reports on the LTR of CVD deaths based on composite risk factors in the Japanese population, which has one of the highest life expectancies worldwide. Although our research is in the Japanese population with relatively homogeneous diet and cultural background, it may provide an implication for international audiences to increase understanding of ethnicity in CVD risks and contribute to the development of public health strategies in countries with diverse ethnic groups.

Although mortality is influenced by the progress in medical technology as well as the accessibility and quality of health care systems in surveyed populations, high CVD mortality could indicate high CVD incidence and vice versa.[18] Furthermore, risk equations using death as the outcome may be easily recalibrated and updated for application in different populations given the availability and greater reliability of death statistics when compared with the definition of CVD incidence worldwide.

In this study, we used the EPOCH-Japan (Evidence for Cardiovascular Prevention from Observational Cohorts in Japan) study database, which contains pooled individual-level data from multiple cohort studies in Japan.[19–23] The aim of this study was to estimate the LTR of CVD deaths based on composite risk factors.

METHODS

Raw data cannot be made publicly available, as study participants did not consent to have their information freely accessible. Based on these consents, the Ethics Committees of Keio University School of Medicine and each cohort inhibit any public data sharing because data contain potentially identifying or sensitive disease information. Data accession requests may be sent to each administration of the Ethics Committee. The data will be shared after a review of the purpose and with permission from the ethics committees. Data requests can be made to the corresponding author.

Study Population

We used the EPOCH-Japan study database. The details of the study design and entry criteria are described

Table 1. Definition of Risk Factor Profile

Risk factor profile	Definition
All risk factors optimal	TC <4.65 mmol/L, SBP <120 mm Hg, DBP <80 mm Hg, nondiabetic, and nonsmoker
≥1 risk factor not optimal	TC 4.65–5.15 mmol/L, SBP 120–139 mm Hg, or DBP 80–89 mm Hg, nondiabetic, and nonsmoker
≥1 risk factor elevated	TC 5.16–6.18 mmol/L, SBP 140–159 mm Hg, or DBP 90–99 mm Hg, nondiabetic, and nonsmoker
1 major risk factor	Existence of 1 of the following major risk factors: (1) TC ≥6.19 mmol/L, (2) SBP ≥160 mm Hg or DBP ≥100 mm Hg or treated for hypertension, (3) current smoker, (4) diabetes
≥2 major risk factors	Existence of ≥2 of the following major risk factors: (1) TC ≥6.19 mmol/L, (2) SBP ≥160 mm Hg, or DBP ≥100 mm Hg or treated for hypertension, (3) current smoker, (4) diabetes

DBP indicates diastolic blood pressure; SBP, systolic blood pressure; and TC, total cholesterol.

elsewhere.[19–24] Data from 15 major community-based cohort studies in Japan were pooled to generate the EPOCH-Japan database. Each cohort received ethical approval from the ethics committee of the relevant institute. 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). Written informed consent was obtained from the study participants by primary investigators in each cohort. However, in some studies in which baseline surveys were performed by a cross-sectional National Survey (NIPPON DATA80 and 90), we did not take written informed consent for the follow-up surveys. The study designs were published, and all participants could refuse to participate in the follow-up survey.

Of the 15 cohorts and 147 645 participants in the database, we excluded 6 cohorts because of the lack of baseline information on diabetes and the use of antihypertensive drugs, which resulted in the inclusion of 85 541 participants. In addition, we excluded participants if they had a past history of CVD at baseline, were aged <45 years, and/or had missing data for the variables to be used in the analysis; thus, 41 002 participants were included in the analysis. The flowchart of study participation is presented in Figure S1.

Baseline Variables

The exposures were blood pressure (BP), total cholesterol (TC), diabetes, and smoking. These data were interactively collected from the participants in each cohort. BP was measured by mercury sphygmomanometer in seated position in most cohorts except for the Ohasama study, which used an automated device.[21] The levels of serum TC were enzymatically measured in most of the cohorts except the NIPPON DATA 80 (National Integrated Project for Prospective Observation of Non-Communicable Disease and its Trends in the Aged), in which the Lieberman-Burchard direct method was used.[23,25] The World Health Organization's diagnostic criteria were used for the definition of diabetes. The blood glucose levels were measured in serum in the Radiation Effects Research Foundation and Osaka cohorts, and in plasma in other cohorts.[26] Diabetes was defined as a fasting blood glucose level ≥7.0 mmol/L, a non-fasting blood glucose level ≥11.1 mmol/L, or the use of an anti-diabetic agent as previously defined.[22] Questionnaires or face-to-face interviews were used to obtain smoking history.

Study Outcomes

The Family Registration Law in Japan mandates that all death certificates be forwarded to the Ministry of Health, Labour, and Welfare through the regional public health center.[27] To determine the causes of death, the National Vital statistics of the Ministry of Health, Labour, and Welfare were obtained in all cohorts. Other sources were also used, such as autopsy reports in the Hisayama study,[28] medical records in the Hisayama[28] and Ohasama,[29] and health examination in the Ohasama[29] and Ohsaki studies.[30]

Similar to previous studies in the EPOCH-Japan study, the underlying causes of death were coded based on the *International Classification of Diseases, Ninth Revision* (*ICD-9*), until the end of 1994 or the *International Classification of Diseases, Tenth Revision* (*ICD-10*) from the beginning of 1995. The study outcomes for the present study were death from CVD, which was coded as 390 to 459 in the *ICD-9* and I00 to I99 in the *ICD-10*.

Statistical Analysis

We used a modified version of the Kaplan–Meier analysis to calculate the LTR using the Practical Incidence Estimators macro, as described previously.[9] The differences between standard Kaplan–Meier analysis and the modified one are as follows[9]: (1) This methodology uses survival age (in years) as the time scale instead of survival time that is typically used as the time scale in standard Kaplan–Meier analysis. (2) Data sets were reorganized so that survival age was treated as the time scale and left-truncation was allowed to account for subjects entering a study at different ages. (3) To avoid

overestimation of the remaining LTR, adjustment was made for the competing risk, which was death attributable to causes other than the event of interest, such as death because of cancer. More explanation for the statistical methodology and illustration are provided in Figure S2.

The LTR was estimated for the outcomes of CVD deaths. Participants were stratified into 5 mutually exclusive categories according to the previously reported definition used by the Framingham Heart Study,[17] as follows: (1) all risk factors are optimal, (2) at least 1 risk factor is not optimal, (3) at least 1 risk factor is elevated, (4) 1 high-risk factor exists, and (5) >2 major risk factors exist. The detailed definitions are presented in Table 1. The cut-off points of the categories for BP and TC were in accordance with the Japanese Atherosclerosis Society Guidelines.[7] The LTRs of CVD deaths up to 85 years for the categories were estimated for the participants at the index-ages of 45, 55, 65, and 75 years. The cumulative incidence of CVD deaths is shown in a figure for the index-age of 45 years. SAS statistical software version 9.4 (SAS Institute, Cary, NC, USA) was used for all statistical analyses.

RESULTS

Participant Characteristics

A total of 41 002 participants (18 812 men and 22 190 women) were included in the analysis from 9 cohorts. Both male and female participants having more risk factors were older and had higher BP and TC (Table 2). The percentage of participants with optimal risk factors was higher for women (5.2% [1143 participants]) than for men (2.4% [454 participants]). A higher percentage of men was stratified into the highest risk group compared with women (20.4% [3847 participants] in men and 10.6% [2358 participants] in women). Stratification of participants by baseline age revealed that the prevalence of smoking was higher in men than in women, and this prevalence decreased with age in men (Table S1). The prevalence of diabetes, systolic BP, and diastolic BP increased with age in both men and women. The baseline characteristics of study participants in each cohort is presented in Table S2. Sex-specific distribution of number of CVD deaths and the mean follow-up periods are presented in Table S3.

Competing Risk-Adjusted LTRs for CVD Deaths

A total of 2255 CVD deaths were observed during 537 126 person-years of follow-up. The LTRs of CVD deaths and corresponding 95% CIs are presented in Table 3. LTRs of CVD deaths were higher in men than in women. Individuals with optimal risk factor profiles exhibited the lowest LTRs of CVD deaths (6.8% [95% CI, 0%–11.9%] in men and 6.9% [1.2%–11.5%] in women at the index-age of 45 years). The LTRs increased in a stepwise fashion with having more risk factors. Individuals with >2 risk factors exhibited the highest LTRs of CVD deaths (19.4% [16.7–21.4%] in men and 15.4% [12.6%–18.1%] in women at the index age of 45 years). As shown in the Figure, individuals with ≥2 major risk factors exhibited substantially higher LTRs of CVD deaths, and the cumulative incidence increased more steeply than that for individuals with fewer risk factors.

Short-Term to Intermediate-Term Risks and LTRs of CVD Deaths

The short-term to intermediate-term LTRs and corresponding 95% CIs of CVD deaths are presented in Table 4. The 10-year risk of CVD deaths ranged from 0% to 1.2% across all risk profiles. The 20-year risk of CVD deaths was higher but was still low even for the highest risk factor profile comprising >2 major risk factors (3.4% [2.4%–4.4%] in men and 3.0% [0.9%–5.1%] in women).

Unadjusted LTRs of CVD Deaths

Unadjusted LTRs and corresponding 95% CIs are presented in Table 5. After adjusting for competing risks as aforementioned (Table 3), the LTR was reduced compared with the unadjusted LTRs. At an index-age of 45 years, the competing risk-adjusted LTRs for 2 major risks were 19.4% [16.7%–21.4%] in men and 15.4% [12.6%–18.1%] in women, whereas unadjusted LTRs were 26.1% [23.3%–28.8%] in men and 17.6% [14.8%–20.5%] in women. For favorable risk factor profiles such as optimal levels, the adjusted LTRs were 6.8% [0%–11.9%] in men and 6.9% [1.2%–11.5%] in women, whereas unadjusted LTRs were 9.1% [1.9%–16.4%] in men and 8.2% [2.5%–13.8%] in women.

Sensitivity Analysis

Sensitivity analysis was performed by excluding 2 cohorts (YKK and Aichi workers), which were primarily young workers. In addition, Aichi workers had the shortest follow-up periods among the cohorts as baseline examination was started in 2002 (Table S2). After excluding these 2 cohorts, the total number of participants was 35 848. As shown in Table S4, the results of LTRs were almost stable. For instance, the competing risk adjusted LTR for optimal risk factor level in men was 6.1% [0.0%–11.1%] in the sensitivity analysis whereas it was 6.8% [0.0%–11.9%] in the main analysis. The LTR for 2 major risks in men was 19.8% [17.0%–21.9%] in the sensitivity analysis while it was 19.4% [16.7%–21.4%] in the main analysis. In addition, the Ohasama cohort was excluded for sensitivity analysis because the prevalence of diabetes was high (23.7%) compared

Table 2. Baseline Characteristics of Participants

	Optimal	1 risk not optimal	1 risk elevated	1 major risk	2 major risks	Total
Men						
N (%)	454 (2.4)	4325 (23.0)	1106 (5.9)	9080 (48.3)	3847 (20.4)	18 812
Age, y	58.5±9.2	58.6±9.3	58.4±9.6	59.0±9.3	60.5±9.2	59.2±9.3
BMI, kg/m^2	21.8±2.5	23.2±2.7	23.0±2.8	22.9±2.9	23.4±3.0	23.0±2.9
SBP, mm Hg	108.3±7.4	130.3±11.0	130.3±20.0	133.2±19.0	147.8±22.7	134.7±19.8
DBP, mm Hg	67.6±6.8	80.2±8.1	78.9±12.9	80.7±11.8	87.5±13.2	81.5±11.9
Serum total cholesterol, mmol/L	4.1±0.4	4.9±0.7	5.2±0.7	5.0±0.9	5.4±1.2	5.0±0.9
Smoking, n (%)				5999 (66.1)	3241 (84.2)	9240
Diabetes, n (%)				340 (3.7)	1012 (26.3)	1352
Women						
N(%)	1143 (5.2)	8343 (37.6)	2610 (11.8)	7736 (34.9)	2358 (10.6)	22 190
Age, y	55.4±8.6	58.9±9.1	59.1±9.0	62.3±9.2	64.0±9.0	60.5±9.3
BMI, kg/m^2	22.0±2.9	23.1±3.2	22.9±3.2	23.9±3.5	24.3±3.7	23.4±3.4
SBP, mm Hg	107.6±7.8	129.0±12.4	123.3±20.0	141.0±22.4	149.2±23.2	133.6±21.0
DBP, mm Hg	66.0±6.8	77.6±8.5	73.6±11.7	82.4±12.3	85.3±13.1	79.0±11.8
Serum total cholesterol, mmol/L	4.2±0.4	5.1±0.6	5.5±0.5	5.7±1.0	6.3±1.0	5.4±0.9
Smoking, n (%)				780 (10.1)	585 (24.8)	1365
Diabetes, n (%)				344 (4.4)	795 (33.7)	1139

Continuous variables are presented as the mean±SD and categorical variables are presented as a percentage. "Optimal" was defined as total cholesterol <4.65 mmol/L, systolic blood pressure (BP) <120 mm Hg, diastolic BP <80 mm Hg, nondiabetic, and nonsmoker. "1 Risk Not Optimal" was defined as individuals who did not have diabetes, were nonsmokers, and had total cholesterol of 4.65 to 5.15 mmol/L, systolic BP of 120 to 139 mm Hg, or diastolic BP of 80 to 89 mm Hg. "1 Risk Elevated" was defined as individuals who did not have diabetes, were nonsmokers, and had total cholesterol of 5.16 to 6.18 mmol/L, systolic BP of 140 to 159 mm Hg, or diastolic BP of 90 to 99 mm Hg. Major risk factors were defined as having a (1) total cholesterol ≥6.19 mmol/L, (2) systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg or treated for hypertension, (3) current smoker, and (4) diabetes. "1 Major Risk" was defined as the existence of one of the defined major risk factors. "2 Major Risks" was defined as the existence of ≥2 of the defined major risk factors. BMI indicates body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; and TC, total cholesterol.

with other cohorts as shown in Table S2. Especially, the measurement of blood glucose was performed only for those individuals who were detected as having a high-risk for diabetes development by public health nurses. As presented in Table S5, the results remained unchanged; in men, the LTR for the optimal risk factor level was 6.9% [0.0%–12.0%] and the LTR for 2 major risks was 19.4% [16.7%-21.4%].

DISCUSSION

In this study, we estimated the LTR of CVD deaths according to composite risk factor profiles. Several notable findings were observed in this large Japanese cohort study with long-term follow-up. We showed index-age starting from 45 to 75 years to demonstrate that having multiple cardiovascular risk factors increased the LTR of CVD deaths regardless of the index-age, indicating that even younger individuals exhibited remaining LTRs of CVD deaths. In contrast, individuals with the absence of traditional risk factors had the lowest LTRs. The LTRs tended to be lower in women than in men across all index-ages. Short- to intermediate-term risks were extremely low at the index-age of 45 years even for the highest risk factor profile comprising >2 major risk factors, indicating that individuals developed CVD at an older age. To avoid overestimation, a modified Kaplan–Meier approach was used to allow for adjusting competing risk, which is death attributable to causes other than CVD. LTR was more strongly influenced by competing risks for less favorable risk factor levels than for more favorable risk factor levels, and the effects were greater in men than in women. These findings agree with previous reports.[10] These results suggest that the burden of CVD may be managed despite population aging if the population is shifted towards having optimal risk factor levels, which would lead to the compression of morbidity.[17,31]

Previous studies have reported the LTR according to multiple risk factor profiles of developing CVD,[15,17,32] and of CVD deaths.[10,16] In an American study, the LTR of developing CVD exceeded 50% in both men and women for those with >2 major risk factors at an index-age >45 years.[15,17] In a Chinese study, the LTR of CVD up to 80 years of age was 51.1% in men and 38.6% in women for those with ≥2 major risk factors.[32] These

Table 3. Lifetime Risk of Cardiovascular Deaths Adjusted for Competing Risks

Index-age of lifetime risk, y	Lifetime risks, %				
	Optimal	1 risk not optimal	1 risk elevated	1 major risk	2 major risks
Men					
45	6.8 (0–11.9)	8.1 (6.1–9.8)	11.8 (6.9–15.8)	12.2 (10.5–13.5)	19.4 (16.7–21.4)
55	6.9 (0–12.0)	8.0 (6.0–9.7)	11.3 (6.5–15.2)	12.1 (10.4–13.4)	19.2 (16.5–21.2)
65	6.6 (0–11.9)	7.6 (5.5–9.3)	11.1 (6.3–15.0)	11.5 (9.8–12.8)	18.1 (15.4–20.2)
75	7.4 (0.2–13.3)	6.4 (4.4–8.1)	10.3 (5.6–14.4)	10.4 (8.7–11.9)	15.6 (12.8–17.8)
Women					
45	6.9 (1.2–11.5)	7.0 (5.7–8.2)	7.5 (5.0–9.7)	11.0 (9.6–12.2)	15.4 (12.6–18.1)
55	6.7 (1.1–11.3)	7.0 (5.7–8.1)	7.6 (5.0–9.8)	10.6 (9.3–11.8)	14.6 (12.2–16.6)
65	6.5 (0.9–11.2)	6.9 (5.6–8.0)	7.4 (4.9–9.6)	9.9 (8.6–11.1)	13.3 (11.1–15.4)
75	6.2 (0.6–11.1)	6.0 (4.7–7.1)	6.8 (4.3–9.0)	8.7 (7.5–9.9)	11.3 (9.1–13.3)

The lifetime risks are presented as percentages and 95% CIs. The lifetime risks were adjusted for competing risks. "Optimal" was defined as total cholesterol <4.65 mmol/L, systolic blood pressure (BP) <120 mm Hg, diastolic BP <80 mm Hg, nondiabetic, and nonsmoker. "1 Risk Not Optimal" was defined as individuals who did not have diabetes, were nonsmokers, and had total cholesterol of 4.65 to 5.15 mmol/L, systolic BP of 120 to 139 mm Hg, or diastolic BP of 80 to 89 mm Hg. "1 Risk Elevated" was defined as individuals who did not have diabetes, were nonsmokers, and had total cholesterol of 5.16 to 6.18 mmol/L, systolic BP of 140 to 159 mm Hg, or diastolic BP of 90 to 99 mm Hg. Major risk factors were defined as having a (1) total cholesterol ≥6.19 mmol/L, (2) systolic BP ≥160 mm Hg, or diastolic BP ≥100 mm Hg or treated for hypertension, (3) current smoker, and (4) diabetes. "1 Major Risk" was defined as the existence of one of the defined major risk factors. "2 Major Risks" was defined as the existence of ≥2 of the defined major risk factors.

studies reported higher LTRs than those reported in our study because the estimates were based on incidence, whereas we used CVD deaths as the outcome. With regards to the outcomes of CVD deaths, the LTR was 32.5% in men and 21.9% in women at the index-age of 45 years for the highest risk factor profile in an American study.[10] In contrast, our results demonstrated that the LTR was 19.4% [16.7%–21.4%] in men and 15.4% [12.6–18.1%] in women for the highest risk factor level (Table 3). Although baseline risk factor levels were similar between our study (Table S1) and the American study,[10] the LTR was higher in the American study because the number of CVD deaths was 5912 in 731 615 person-years of follow-up (8.1 mortality per 1000 person-years) in the American study.[10] In contrast, 2255 CVD deaths in 537 126 person-years follow-up (4.2 mortality per 1000 person-years) were observed in our study. This is mainly because of the low mortality attributable to CHD and a dramatic decline in stroke mortality over almost half a century in Japan.[33]

Additionally, a previous study reported that the Western risk model, such as the Systematic Coronary Risk Evaluation risk chart or Framingham risk score, was unsatisfactory in Japan because their baseline hazards for CVD are quite different.[34] Thus, we developed the 10-year risk estimation that is based on the Japanese population.[35] In this study, we have estimated lifetime risk that is suitable for the general Japanese population including young adults, and this information would also help understand ethnic differences in the United States or other countries with diverse ethnicities.

Communicating health risks and knowledge transformation are critical to increase awareness and educate individuals in an accessible way about the magnitude of risks they may face in the future.[36,37] To prevent CVD, risk prediction has become pivotal for the purpose of enhancing a healthy lifestyle and reducing the prevalence of CVD risk factors.[5] Younger individuals tend to have low short- to intermediate-term risks, which may not be suitable estimates for motivating lifestyle modifications at an early stage. To provide effective public health education to prevent CVD and implement basic preventative strategies, LTRs provide more intuitively comprehensive estimates and are more useful given their particular relevance for young individuals.[8] For this purpose, LTRs have been already implemented in the guidelines[4] and online tools for the estimation of cardiovascular prognosis; however, designing and performing studies to directly assess these prediction tools may not be feasible.[5] As European Society of Cardiology Prevention of CVD Programme has been planning to develop a mobile app for CVD risk assessment,[5] using electronic health would be one way to elicit behavioral changes especially for young individuals who are more comfortable using digital tools compared with older people. A previous study reported that a work health program incorporating digital health interventions has successfully reduced CVD risk factors such as blood pressure and lipids.[38] The LTR estimates for Japanese population could be thus implemented in digital health as a CVD risk prediction tool to motivate behavioral changes as a first approach for their lifestyle modification to prevent future CVD.

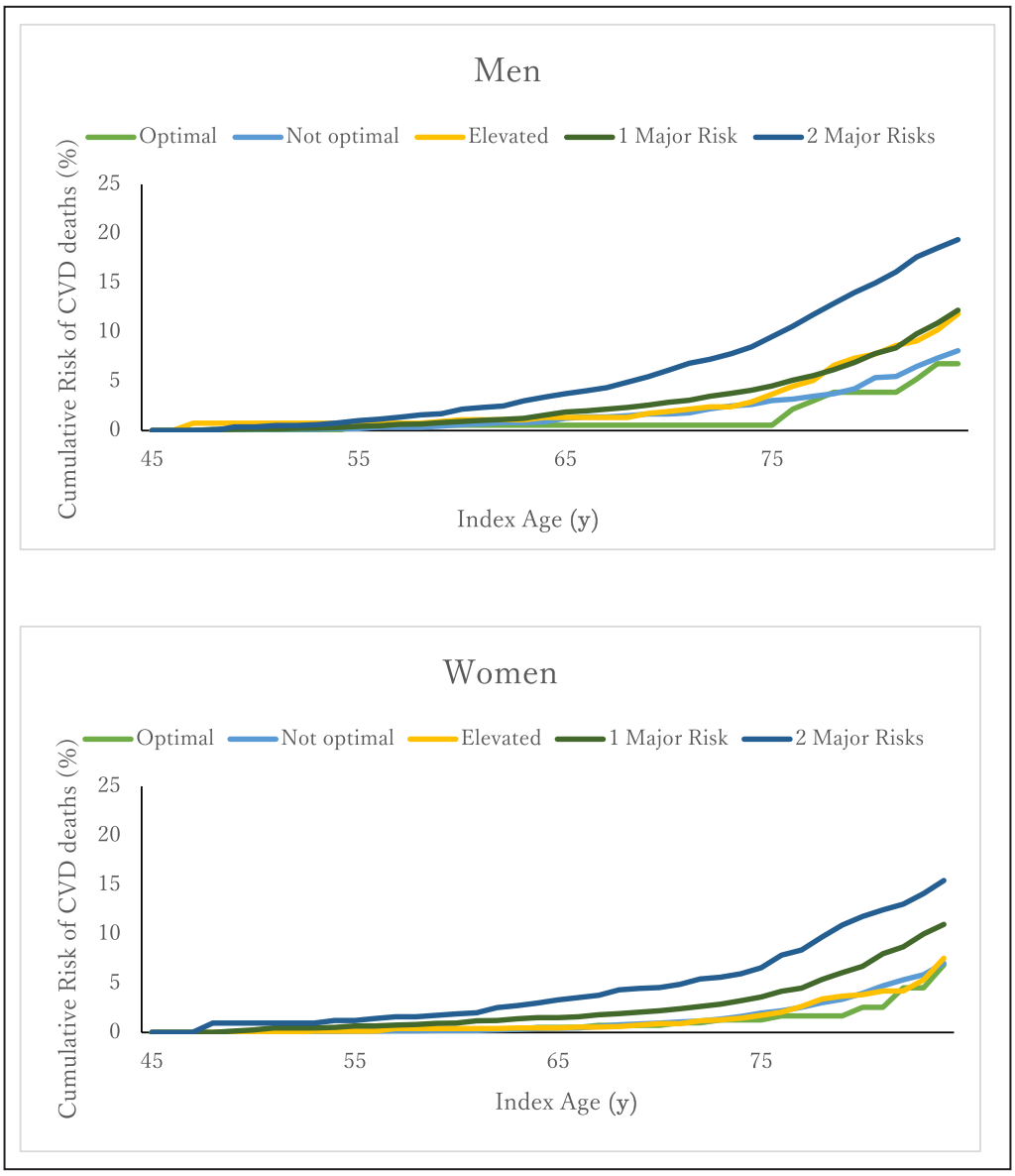

Figure. Cumulative incidence of cardiovascular disease deaths adjusted for competing risk factors at index-ages of 45 to 85 years according to risk factor level.
"Optimal" was defined as total cholesterol<4.65 mmol/L, systolic blood pressure (BP) <120 mm Hg, diastolic BP<80 mm Hg, nondiabetic, and nonsmoker. "1 Risk Not Optimal" was defined as individuals who did not have diabetes, were nonsmokers, and had total cholesterol of 4.65 to 5.15 mmol/L, systolic BP of 120 to 139 mm Hg, or diastolic BP of 80 to 89 mm Hg. "1 Risk Elevated" was defined as individuals who did not have diabetes, were nonsmokers, and had total cholesterol of 5.16 to 6.18 mmol/L, systolic BP of 140 to 159 mm Hg, or diastolic BP of 90 to 99 mm Hg. Major risk factors were defined as having a (1) total cholesterol ≥6.19 mmol/L, (2) systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg or being treated for hypertension, (3) being a current smoker, and (4) being diabetic. "1 Major Risk" was considered as the existence of 1 major risk factor as defined above. "2 Major Risks" was considered as the existence of ≥2 of the major risk factors defined above. CVD indicates cardiovascular disease.

Our study has several limitations. First, as the prevalence of risk factors changed over the long follow-up time and our pooled data included various cohorts with study design such as different baseline, and follow-up years (Table S2), baseline exposure may not have persisted because of modifications in lifestyle and treatment status, which could lead to misclassification. Second, although data stratified by age, sex, and risk factors were considered in the analysis, this analysis methodology does not allow for adjustment by confounders. Therefore, there may have been residual

Table 4. Short-Term to Intermediate-Term Risks of Cardiovascular Death at an Index-Age of 45 Years

	Short-term to intermediate-term risks, %				
	Optimal	1 risk not optimal	1 risk elevated	1 major risk	2 major risks
Men					
10-y risk	0.0 (0.0–0.0)	0.2 (0.0–0.5)	0.7 (0.0–2.2)	0.3 (0.1–0.5)	0.8 (0.1–1.4)
20-y risk	0.5 (0.0–1.6)	0.9 (0.4–1.4)	1.3 (0.0–2.9)	1.6 (1.2–2.0)	3.4 (2.4–4.4)
Women					
10-y risk	0.2 (0.0–0.6)	0.1 (0.0–0.2)	0.1 (0.0–0.4)	0.5 (0.0–1.0)	1.2 (0.0–3.1)
20-y risk	0.5 (0.0–1.1)	0.4 (0.2–0.6)	0.5 (0.0–0.9)	1.5 (0.9–2.1)	3.0 (0.9–5.1)

The short-term to intermediate-term risks are presented as percentages and 95% CIs. "Optimal" was defined as total cholesterol <4.65 mmol/L, systolic blood pressure (BP) <120 mm Hg, diastolic BP <80 mm Hg, nondiabetic, and nonsmoker. "1 Risk Not Optimal" was defined as individuals who did not have diabetes, were nonsmokers, and had total cholesterol of 4.65 to 5.15 mmol/L, systolic BP of 120 to 139 mm Hg, or diastolic BP of 80 to 89 mm Hg. "1 Risk Elevated" was defined as individuals who did not have diabetes, were nonsmokers, and had total cholesterol of 5.16 to 6.18 mmol/L, systolic BP of 140 to 159 mm Hg, or diastolic BP of 90 to 99 mm Hg. Major risk factors were defined as having a (1) total cholesterol ≥6.19 mmol/L, (2) systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg or treated for hypertension, (3) current smoker, and (4) diabetes. "1 Major Risk" was defined as the existence of 1 of the defined major risk factors. "2 Major Risks" was defined as the existence of ≥2 of the defined major risk factors.

confounding factors such as socioeconomic status and regional differences. We performed a sensitivity analysis by excluding the cohorts that could have impacted the results and confirmed that the results were similar with main LTR analysis. Third, information on CVD incidence was not available for our LTR assessment. However, risk equations using death as the outcome could be easily recalibrated and updated for application in different populations since death statistics are usually more readily available and reliable than data on global CVD incidence. Furthermore, it is often difficult to use common incidence surveillance methods between different countries.

CONCLUSIONS

To our knowledge, this is the first study to reveal the LTRs according to composite risk factors in the Japanese population where mortality for CHD is low compared with Western populations. Our study would be useful not only for the Japanese population but also for other countries with diverse ethnic groups for understanding the ethnic differences in CVD risks. The presence of elevated CVD risk factors remarkably increased the LTRs even for young individuals. Knowledge of LTRs may be useful for risk communication in public health education and implemented in the relevant guideline.

Table 5. Unadjusted Lifetime Risk of Cardiovascular Deaths

Index age of lifetime risk, y	Lifetime risks, %				
	Optimal	1 risk not optimal	1 risk elevated	1 major risk	2 major risks
Men					
45	9.1 (1.9–16.4)	9.7 (7.6–11.7)	14.3 (9.4–19.3)	16.3 (14.5–18.0)	26.1 (23.3–28.8)
55	9.1 (1.9–16.4)	9.5 (7.4–11.5)	13.7 (8.9–18.5)	16.0 (14.2–17.7)	25.5 (22.8–28.2)
65	8.6 (1.5–15.8)	8.8 (6.8–10.9)	13.2 (8.4–18.0)	14.9 (13.1–16.6)	23.4 (20.6–26.1)
75	8.6 (1.5–15.8)	7.1 (5.1–9.1)	11.6 (6.9–16.4)	12.3 (10.6–14.1)	18.3 (15.6–21.0)
Women					
45	8.2 (2.5–13.8)	7.9 (6.6–9.2)	8.8 (6.2–11.3)	12.4 (11.1–13.8)	17.6 (14.8–20.5)
55	8.0 (2.3–13.6)	7.8 (6.5–9.1)	8.6 (6.1–11.2)	12.0 (10.7–13.3)	16.6 (14.2–19.0)
65	7.7 (2.0–13.3)	7.6 (6.3–8.9)	8.3 (5.8–10.8)	11.1 (9.8–12.4)	15.1 (12.8–17.3)
75	6.9 (1.3–12.6)	6.4 (5.1–7.6)	7.3 (4.8–9.8)	9.4 (8.1–10.7)	12.2 (10.0–14.4)

The lifetime risks are presented as percentages and 95% CIs. "Optimal" was defined as total cholesterol<4.65 mmol/L, systolic blood pressure (BP) <120 mm Hg, diastolic BP <80 mm Hg, nondiabetic, and nonsmoker. "1 Risk Not Optimal" was defined as individuals who did not have diabetes, were nonsmokers, and had total cholesterol of 4.65 to 5.15 mmol/L, systolic BP of 120 to 139 mm Hg, or diastolic BP of 80 to 89 mm Hg. "1 Risk Elevated" was defined as individuals who did not have diabetes, were nonsmokers, and had total cholesterol of 5.16 to 6.18 mmol/L, systolic BP of 140 to 159 mm Hg, or diastolic BP of 90 to 99 mm Hg. Major risk factors were defined as having a (1) total cholesterol ≥6.19 mmol/L, (2) systolic BP ≥160 mm Hg or diastolic BP≥100 mm Hg or treated for hypertension, (3) current smoker, and (4) diabetes. "1 Major Risk" was defined as the existence of one of the defined major risk factors. "2 Major Risks" was defined as the existence of ≥2 of the defined major risk factors.

APPENDIX

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ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Tables S1–S5
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Baseline risk factors by baseline age group.

	45 years	55 years	65 years	75 years	85 years
Men					
N	7,037	6,268	4,273	1,162	72
SBP (mmHg)	130.0 ± 17.6	136.0 ± 19.9	138.0 ± 20.2	143.2 ± 22.4	152.8 ± 25.4
DBP (mmHg)	81.3 ± 12.1	82.7 ± 11.9	80.9 ± 11.6	79.6 ± 11.3	76.7 ± 11.8
Serum Total Cholesterol (mmol/L)	5.2 ± 0.9	5.0 ± 0.9	4.9 ± 0.9	4.8 ± 0.9	4.7 ± 0.8
Diabetes (n(%))	363 (5.2)	522 (8.3)	354 (8.3)	104 (9.0)	9 (12.5)
Current Smoking (n(%))	3,579 (50.9)	3,180(50.7)	2,006 (46.9)	452 (38.9)	23 (31.9)
Women					
N	6,503	8,452	5,509	1,547	179
SBP (mm Hg)	127.3 ± 19.1	132.9 ± 20.3	138.1 ± 20.9	145.5 ± 22.4	153.0 ± 24.3
DBP (mm Hg)	77.8 ± 11.8	79.8 ± 11.6	79.4 ± 11.7	78.3 ± 12.1	79.5 ± 11.8
Serum Total Cholesterol (mmol/L)	5.2 ± 1.0	5.5 ± 0.9	5.5 ± 0.9	5.4 ± 1.0	5.1 ± 1.0
Diabetes (n(%))	159 (2.4)	454 (5.4)	370 (6.7)	142 (9.2)	14 (7.8)
Current Smoking (n(%))	450 (6.9)	504 (6.0)	292 (5.3)	110 (7.1)	9 (5.0)

SBP: systolic blood pressure, DBP: diastolic blood pressure.

45 years included participants with their baseline risk factors measured between 45 and 50 years of age.

55 years included participants with their baseline risk factors measured between 50 and 60 years of age.

65 years included participants with their baseline risk factors measured between 60 and 70 years of age.

75 years included participants with their baseline risk factors measured between 70 and 80 years of age.

Continuous variables are presented as the mean ± standard deviation and categorical variables are presented as a percentage. SI conversion factors: To convert cholesterol to mmol/L, multiply by 0.0259.

Table S2. Baseline characteristics of study participants according to cohort.

Cohort	N	Baseline Year	Geographic location	Men (%)	Age (Year)	BMI (kg/m^2)	SBP (mm Hg)	DBP (mm Hg)	TC (mg/dL)	Smoking (%)	Diabetes (%)	Number of CVD deaths	Follow up periods
Ohsaki	10,465	1994	Miyagi	47.6	62.8 (8.7)	23.9 (3.1)	131.8 (17.5)	79.5 (10.8)	204.5 (35.2)	25.4	5.8	320	11.1 (3.6)
Ohasama	778	1987	Iwate	33.2	60.1 (8.4)	25.2 (3.6)	132.7 (16.5)	75.3 (10.8)	203.7 (36.6)	15.8	23.7	27	12.7 (3.2)
YKK	1,603	1990	Toyama	67.2	50.7 (4.1)	22.7 (2.6)	121.3 (16.8)	75.6 (12.6)	206.5 (36.3)	38.1	3.9	13	17.8 (5.8)
RERF cohort	3,542	1986	Hiroshima	27.8	63.5 (10.2)	22.7 (3.5)	135.7 (22.5)	82.5 (12.0)	213.0 (39.1)	21.8	14.0	339	16.6 (5.8)
Hisayama	2,332	1988	Fukuoka	41.2	61.3 (10.9)	22.8 (3.2)	135.1 (21.9)	77.8 (11.3)	207.5 (42.5)	24.1	9.4	170	12.4 (3.4)
ND80	5,664	1980	Nationwide	43.4	58.9 (9.8)	22.8 (3.2)	142.3 (21.9)	83.4 (12.2)	193.0 (34.6)	31.6	2.4	870	19.6 (6.6)
ND90	4,642	1990	Nationwide	42.8	60.1 (10.1)	23.1 (3.2)	141.1 (20.5)	83.3 (11.9)	207.9 (38.5)	26.6	5.2	295	13.5 (3.4)
JMS	8,425	1992	Tochigi	38.1	59.8 (7.7)	23.1 (3.0)	131.6 (20.9)	78.5 (12.1)	195.3 (34.7)	20.3	3.2	204	10.7 (2.4)
Aichi workers	3,551	2002	Aichi	81.3	52.1 (4.5)	23.1 (2.7)	128.4 (16.0)	79.4 (11.5)	212.7 (34.9)	32.4	7.8	17	8.8 (3.1)

A total of 41,002 participants were included. Continuous variables are presented as means (standard deviations) and categorical variables are presented as percentage. BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, TC: total cholesterol, YKK: Yoshida Kogyo Kabushikigaisha, RERF: Radiation Effects Research Foundation, ND: Nippon Data (National Integrated Project for Prospective Observation of Noncommunicable Disease And its Trends in the Aged), JMS: Jichi Medical School. SI conversion factors: To convert cholesterol to mmol/L, multiply by 0.0259.

Table S3. Sex-specific distribution of number of CVD deaths and mean follow-up period.

	Optimal	1 Risk Not Optimal	1 Risk Elevated	1 Major Risk	2 Major Risks
Men					
N	454	4,325	1,106	9,080	3,847
Number of CVD deaths	9	136	47	484	387
Follow-up periods	12.1 ± 4.8	12.5 ± 5.0	12.4 ± 5.2	12.7 ± 5.5	12.2 ± 5.5
Mortality per 1,000 person-years	1.64	2.52	3.43	4.20	8.25
Women					
N	1,143	8,343	2,610	7,736	2,358
Number of CVD deaths	17	287	93	547	248
Follow-up periods	13.1 ± 5.2	13.8 ± 5.4	13.5 ± 5.3	13.5 ± 5.4	13.5 ± 5.4
Mortality per 1,000 person-years	1.14	2.49	2.64	5.24	7.79

Follow-up periods indicate mean person-years. Continuous variables are presented as means ± standard deviations. TC: total cholesterol, SBP: systolic blood pressure, DBP: diastolic blood pressure, CVD: cardiovascular disease. “Optimal” was defined as TC < 4.65 mmol/L, SBP < 120 mmHg, DBP < 80 mmHg, nondiabetic, and non-smoker. “1 Risk Not Optimal” was defined as individuals who did not have diabetes, were non-smokers, and had TC of 4.65–5.15 mmol/L, SBP of 120–139 mmHg, or DBP of 80–89 mmHg. “1 Risk Elevated” was defined as individuals who did not have diabetes, were non-smokers, and had TC of 5.16–6.18 mmol/L, SBP of 140–159 mmHg, or DBP of 90–99 mmHg. Major risk factors were defined as having a 1) TC ≥ 6.19 mmol/L, 2) SBP ≥ 160 mmHg or DBP ≥ 100 mmHg or treated for hypertension, 3) current smoker, and 4) diabetic. “1 Major Risk” was defined as the existence of one of the defined major risk factors. “2 Major Risks” was defined as the existence of two or more of the defined major risk factors.

Table S4. Sensitivity analysis of lifetime risk of cardiovascular deaths (Excluding YKK and Aichi workers).

	Lifetime Risks (%)				
Index Age of Lifetime Risk	**Optimal**	**1 Risk Not Optimal**	**1 Risk Elevated**	**1 Major Risk**	**2 Major Risks**
Men					
45 years	6.1 (0.0–11.1)	8.4 (6.3–10.1)	13.0 (7.3–17.9)	12.2 (10.4–13.5)	19.8 (17.0–21.9)
55 years	6.3 (0.0–11.3)	8.2 (6.2–9.9)	11.6 (6.7–15.5)	12.2 (10.4–13.5)	19.8 (17.0–21.8)
65 years	6.5 (0.0–11.8)	7.6 (5.5–9.3)	11.2 (6.4–15.2)	11.6 (9.9–13.0)	18.4 (15.7–20.5)
75 years	7.4 (0.2–13.4)	6.4 (4.4–8.1)	10.4 (5.6–14.5)	10.5 (8.7–11.9)	15.6 (12.9–17.9)
Women					
45 years	6.9 (1.3–11.5)	7.1 (5.8–8.2)	7.6 (5.1–9.8)	11.1 (9.7–12.4)	15.7 (12.7–18.4)
45 years	6.7 (1.1–11.3)	7.0 (5.7–8.2)	7.7 (5.1–9.8)	10.7 (9.4–11.9)	14.7 (12.2–16.8)
55 years	6.5 (0.9–11.2)	6.9 (5.6–8.1)	7.4 (4.9–9.6)	10.0 (8.7–11.1)	13.4 (11.1–15.4)
65 years	6.2 (0.6–11.1)	6.0 (4.7–7.1)	6.8 (4.3–9.1)	8.8 (7.5–9.9)	11.3 (9.1–13.3)

The lifetime risks are presented as percentages and 95% confidence intervals. The lifetime risks were adjusted for competing risks. The total number of participants for this sensitivity analysis were 35,848 participants after excluding two cohorts (YKK and Aichi workers). TC: total cholesterol, SBP: systolic blood pressure, DBP: diastolic blood pressure. “Optimal” was defined as TC < 4.65 mmol/L, SBP < 120 mmHg, DBP < 80 mmHg, nondiabetic, and non-smoker. “1 Risk Not Optimal” was defined as individuals who did not have diabetes, were non-smokers, and had TC of 4.65–5.15 mmol/L, SBP of 120–139 mmHg, or DBP of 80–89 mmHg. “1 Risk Elevated” was defined as individuals who did not have diabetes, were non-smokers, and had TC of 5.16–6.18 mmol/L, SBP of 140–159 mmHg, or DBP of 90–99 mmHg. Major risk factors were defined as having a 1) TC ≥ 6.19 mmol/L, 2) SBP ≥ 160 mmHg or DBP ≥ 100 mmHg or treated for hypertension, 3) current smoker, and 4) diabetic. “1 Major Risk” was defined as the existence of one of the defined major risk factors. “2 Major Risks” was defined as the existence of two or more of the defined major risk factors

Table S5. Sensitivity analysis of lifetime risk of cardiovascular deaths (excluding the Ohasama cohort).

	Lifetime Risks (%)				
Index Age of Lifetime Risk	**Optimal**	**1 Risk Not Optimal**	**1 Risk Elevated**	**1 Major Risk**	**2 Major Risks**
Men					
45 years	6.9 (0.0–12.0)	8.1 (6.0–9.8)	11.9 (6.9–16.0)	12.3 (10.5–13.6)	19.4 (16.7–21.4)
55 years	6.9 (0.0–12.2)	8.0 (6.0–9.7)	11.4 (6.5–15.3)	12.2 (10.5–13.5)	19.2 (16.5–21.2)
65 years	6.6 (0.0–12.0)	7.6 (5.6–9.3)	11.4 (6.4–15.4)	11.6 (9.8–12.9)	18.2 (15.5–20.3)
75 years	7.4 (0.2–13.4)	6.4 (4.4–8.2)	10.6 (5.7–14.8)	10.6 (8.8–12.0)	15.7 (12.9–18.0)
Women					
45 years	6.9 (1.2–11.5)	7.2 (5.8–8.3)	7.5 (4.9–9.7)	11.0 (9.7–12.3)	15.5 (12.6–18.2)
45 years	6.8 (1.1–11.4)	7.1 (5.8–8.3)	7.5 (5.0–9.7)	10.8 (9.4–11.9)	14.6 (12.2–16.7)
55 years	6.6 (0.9–11.3)	7.0 (5.7–8.2)	7.4 (4.8–9.6)	10.1 (8.8–11.2)	13.3 (11.0–15.4)
65 years	6.2 (0.6–11.2)	6.1 (4.8–7.3)	6.7 (4.2–9.0)	8.9 (7.6–10.1)	11.2 (9.0–13.3)

The lifetime risks are presented as percentages and 95% confidence intervals. The lifetime risks were adjusted for competing risks. The total number of participants for this sensitivity analysis were 40,224 participants after excluding Ohasama cohort. TC: total cholesterol, SBP: systolic blood pressure, DBP: diastolic blood pressure. “Optimal” was defined as TC < 4.65 mmol/L, SBP < 120 mmHg, DBP < 80 mmHg, nondiabetic, and non-smoker. “1 Risk Not Optimal” was defined as individuals who did not have diabetes, were non-smokers, and had TC of 4.65–5.15 mmol/L, SBP of 120–139 mmHg, or DBP of 80–89 mmHg. “1 Risk Elevated” was defined as individuals who did not have diabetes, were non-smokers, and had TC of 5.16–6.18 mmol/L, SBP of 140–159 mmHg, or DBP of 90–99 mmHg. Major risk factors were defined as having a 1) TC ≥ 6.19 mmol/L, 2) SBP ≥ 160 mmHg or DBP ≥ 100 mmHg or treated for hypertension, 3) current smoker, and 4) diabetic. “1 Major Risk” was defined as the existence of one of the defined major risk factors. “2 Major Risks” was defined as the existence of two or more of the defined major risk factors.

Figure S1. Flowchart of the study participants: EPOCH-JAPAN, the Evidence for Cardiovascular Prevention from Observational Cohorts in Japan.

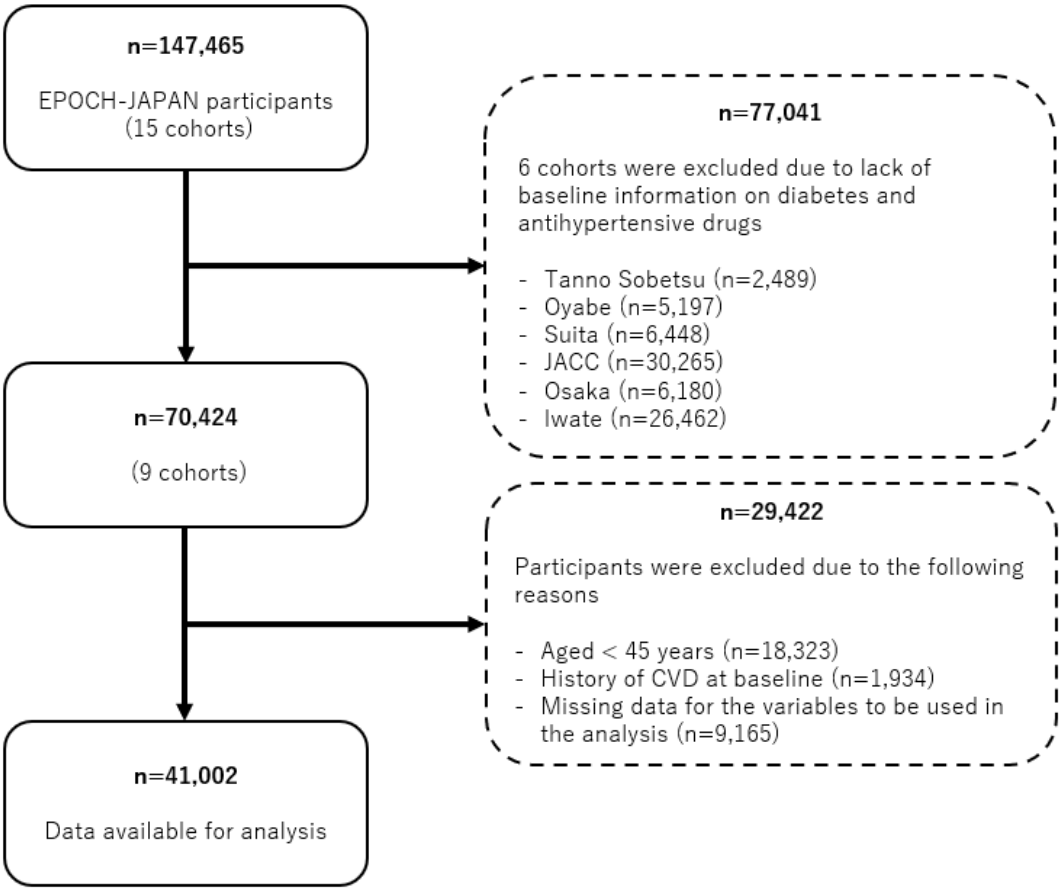
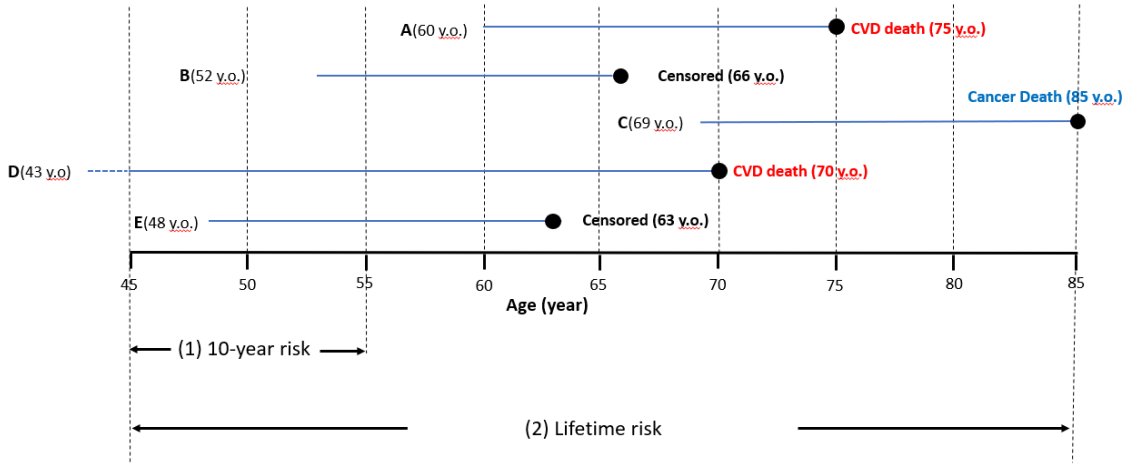


Figure S2. Illustration of 10-year risk and lifetime risk.



Modified Kaplan-Meier analysis uses survival age as time scale as illustrated above. Above 5 participants (A, B, C, D and E) contribute the lifetime estimation starting from index-age 45 and 55 years. For index-age of 65 years, A, B, C and D contribute the estimation. Person C (Cancer Death) is treated as competing risk.

Cumulative incidence of CVD death adjusting for competing risk at index age of A is denoted as following formula:

$$F_A = \sum_{A_{min}}^{A_{max}} h_A U_{A-1}$$

Where h_A is the hazard failing from CVD death at age A, U_{A-1} is the probability of survival beyond age A-1 years free of CVD death adjusted for competing risk.

(1) 10-year risk at age 45 adjusting for competing risk is the summation from age=45 to age=55

(2) Lifetime risk at age 45 adjusting for competing risk is the summation from age=45 to age=85