Original Article

Calibration between the Estimated Probability of the Risk Assessment Chart of Japan Atherosclerosis Society and Actual Mortality Using External Population: Evidence for Cardiovascular Prevention from Observational Cohorts in Japan (EPOCH-JAPAN)

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Aim: In Japan Atherosclerosis Society guidelines for the prevention of atherosclerotic cardiovascular diseases 2012 (JAS2012), NIPPON DATA80 risk assessment chart (ND80RAC) was adopted to estimate the 10-year probability of coronary artery disease (CAD) mortality. However, there was no comparison between the estimated mortality calculated by ND80RAC and actual mortality in external populations. Accordingly, we used the large pooled database of cohorts in Japan, EPOCH-JAPAN, as an external population.

Methods: The participants of EPOCH-JAPAN without a history of cardiovascular disease (15,091 men and 18,589 women aged 40−74 years) were analyzed based on sex. The probability of a 10-year risk of CAD/stroke mortality was estimated by ND80RAC. The participants were divided into both decile of their estimated mortality and three categories according to JAS2012. The calibration between the mean estimated mortality and the actual mortality was performed by the Hosmer and Lemeshow (H-L) test.

Results: In both sexes, the estimated CAD mortality was higher than the actual mortality, particularly in higher deciles of estimated mortality, and the estimated stroke mortality was almost concordant with the actual mortality in low/moderate deciles of estimated mortality. As for the categories according to JAS2012, the estimated CAD mortality was higher than the actual mortality in both sexes; actual mortality in Category III was lower than that in Category II in women. However, it increased in the ascending order of category when we excluded the presence of diabetes from Category III.

Conclusions: The estimated CAD mortality by ND80RAC tended to be higher than the actual mortality in the population in which the baseline survey was more recently performed.

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Key words: External calibration, Cohort studies, Pooled analysis, Risk assessment Chart, Stroke, Coronary artery disease

Introduction

Cardiovascular disease (CVD) is one of the leading causes of mortality in the world as well as in Japan[1, 2]. To predict individuals at high risk for CVD, several risk prediction tools have been developed[3, 4]. Among them, the Framingham risk score (FRS) was widely accepted in Western countries because of its well-established validity[5-11]. The 2013 American College of Cardiology/American Heart Association recently updated cholesterol guidelines, which recommend the use of Pooled Cohort Equations to estimate the 10-year absolute risk for atherosclerotic cardiovascular disease (ASCVD)[12]. However, because FRS and ASCVD had been established among Caucasians, the risk for coronary artery disease (CAD) may be overestimated in Asians, especially Japanese population, which have extremely lower CAD mortality than the Western population[13].

The Japan Atherosclerosis Society (JAS) proposed comprehensive lipid and risk management guidelines for CAD in 2012. In the guideline, the 10-year absolute risk chart of CAD mortality was established using the National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged 1980 (NIPPON DATA80) Risk Assessment Chart (ND80RAC)[14, 15]. In addition, JAS defined three categories for the prevention of CAD according to the presence of several diseases such as diabetes mellitus (DM). In the previous study, subclinical atherosclerosis of the carotid arteries has been reported to be concordant with the three categories defined by the JAS guidelines 2012[16]. However, there was no calibration study between the estimated mortality calculated by ND80RAC and actual mortality in the external populations and time-period.

The purpose of this study was to investigate the external calibration of ND80RAC using the large pooled database of the cohorts in Japan, the Evidence for Cardiovascular Prevention from Observational Cohorts in Japan (EPOCH-JAPAN).

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Methods

Study Design and Participants

The present study was a part of pooled project called EPOCH-JAPAN, one of the largest cohort dataset, which incorporates 14 both nationwide and regional cohort studies in Japan for meta-analyses. The details of the rationale, study design, and methods of EPOCH-JAPAN have been described elsewhere[17-24]. In brief, the criteria for a cohort recruitment of EPOCH-JAPAN were as follows: (i) collected health examination measures; (ii) had almost 10 years of follow-up; (iii) included >1,000 participants. Quality control of the collected cohort data was performed at the EPOCH-JAPAN study coordinating center. Permission to submit data from each cohort to the EPOCH-JAPAN study coordinating center was obtained from the relevant institutional review boards for ethical issues.

Of the 14 cohorts, two cohorts were excluded from the present analysis because of the absence of cause of death information and 12 cohorts were included (Tanno-Sobetsu, Ohsaki, Ohasama, Oyabe, YKK workers, Suita, RERF cohort, Hisayama, JACC, NIPPON DATA80, NIPPON DATA90 and Osaka). From 101,977 total participants, the participants of NIPPON DATA80 (n=9,442), the participants who had a history of cardiovascular disease at baseline (n=7,029) and who were <40 years or >75 years (n=13,747) were excluded. In addition, those with the missing values or outliers on systolic blood pressure, serum total cholesterol, blood glucose, and smoking status (n=38,079) were excluded. In this process, the dataset of 2 cohorts (Oyabe and JACC) were completely excluded due to the missing values of blood glucose. Finally, the remaining participants of 33,680 (15,091 men and 18,589 women) were included in the present study.

Risk Factors

Information of each participant's medical history and drinking/smoking status was obtained throughout questionnaires. Blood pressure was measured in the sitting position with a standard mercury sphygmomanometer, except for the Ohasama study in which the validated automatic monitor was used. The participants rested before measurement except in the Ohsaki study. Two (Ohasama and Suita studies) or three (Hisayama study) consecutive values, or otherwise one reading at the examination center was used in the analysis[17, 18, 24-26]. Non-fasting serum total cholesterol and blood glucose level were determined by automated enzymatic methods on venous blood samples.

Endpoints

The details of determining the endpoints in EPOCH-JAPAN have been reported elsewhere[19]. Shortly, a primary underlying cause of death was sought in great detail from the available sources such as death certificates, the National Vital Statistics, autopsy reports as well as medical records in each cohort study and coded according to the ninth revision of the International Classification of Disease (ICD-9) for National Vital Statistics based on the criteria proposed by the World Health Organization[27]. In the present study, the endpoints were mortality from CAD (ICD-9 codes 410-414, ICD-10 codes I-20-I25) and stroke (ICD-9 codes 430-438, ICD-10 codes I60-I69) during the 10 year follow-up.

NIPPON DATA80 Risk Assessment Charts

Risk charts for the probability over a 10-year period of mortality from CAD/stroke were constructed on the basis of a nationwide cohort study called NIPPON DATA80 and cited in the JAS guidelines 2012[14, 15]. The participants of NIPPON DATA80 were those in the National Survey on Circulatory Disorders 1980 and all household members aged ≥30 years in 300 randomly selected census tracts across Japan who agreed to cooperate in the survey.

Statistical Methods

Sex-specific analyses were performed. From the risk assessment charts in JAS guidelines 2012, the equation $1-S(10:x)=1-[S_0(10:\bar{x})]^{\exp(\beta(\bar{x}-x))}$ estimated the probability of the 10-year risk for CAD/stroke mortality, where x: risk factors at baseline in EPOCH-JAPAN, $\bar{x}$: mean values of risk factors at baseline in NIPPON DATA80, β: regression coefficients for the risk factors of NIPPON DATA80, and $S_0(10:\bar{x})$: the survival probability of 10-year risk with risk factors $\bar{x}$. The risk factors in this model were as follows: age, systolic blood pressure (SBP), total cholesterol, smoke status (current or not), and casual glucose level (≥200 mg/dL or <200 mg/dL)[15]. To calibrate the mean estimated CAD/stroke mortality in ND80RAC and the actual cumulative mortality in EPOCH-JAPAN, the participants were divided into decile of their estimated probability, and the mean estimated probability was calculated in each decile. Furthermore, the actual cumulative mortality of CAD/stroke in each decile was calculated as the number of deceased participants divided by the number of all participants in the decile. Hosmer and Lemeshow test was conducted to perform the difference between the estimate CAD/stroke mortality and the actual cumulative mortality.

The participants were also categorized according to the JAS guidelines 2012 with four exceptions: (i) none of the study participants had a history of non-cardiogenic cerebral infarction because a history of any type of stroke was excluded from the cohort; (ii) a family history of premature CAD was not assessed because we have not been collected; (iii) there was no information about HDL (high density lipoprotein) cholesterol; and (iv) there was also no information about chronic kidney disease (CKD). Finally, the participants were defined in three categories: Category I (low risk, probability of CAD mortality <0.5%), Category II (intermediate risk, probability of CAD mortality ≥0.5% and <2.0%), and Category III (high risk, probability of CAD mortality ≥2.0% or having DM)[14]. In addition, the participants were classified into three risk categories according to the probability of CAD mortality mentioned above, without considering the presence of DM in Category III.

The analyses were performed using the SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

The mean age of the participants was 56 years (standard deviation: 10 years) and the mean follow-up period was 9.4 years. During the 10-year follow-up, we observed 120 deaths from CAD and 186 deaths from stroke (cerebral infarction: 65, hemorrhagic stroke: 42 and subarachnoidal hemorrhage: 39).

Table 1 shows the baseline characteristics of the participants defined by the three categories of JAS guidelines 2012. Category III accounted for a majority of the CAD/stroke mortality.

Fig. 1 shows the mean estimated CAD mortality and its actual cumulative mortality according to the decile of estimated CAD mortality. In men, the actual mortality increased as the mean estimated mortality increased. In lower decile groups, the mean estimated mortality fairly predicted the actual mortality. Meanwhile, in higher decile groups, the mean estimated mortality was predicted to be higher than the actual mortality, especially in the 8th, 9th, and 10th decile. In women, the results were almost similar with those in men, while the number of CAD mortality in women was fewer than that in men. In the 10th decile, the mean estimated mortality was particularly higher than the actual mortality. Homer and Lemeshow test showed the significant difference in both men ($p<0.001$) and women ($p<0.001$).

Fig. 2 shows the mean estimated stroke mortality and its actual cumulative mortality according to the decile of estimated stroke mortality. In men, the actual mortality increased as the estimated mortality

Table 1. Baseline Characteristics of EPOCH-JAPAN distinguished by Japan Atherosclerosis Society (JAS) classification

	Category for LDL-c management proposed by JAS Guidelines 2012[1]					
	Men			Women		
	I	II	III	I	II	III
Age, years (SD)	46 (5)	58 (6)	57 (10)	51 (7)	67 (3)	58 (10)
Person year (SD)	9.8 (0.9)	9.5 (1.5)	9.3 (2.0)	9.8 (0.9)	9.6 (1.5)	9.4 (2.0)
Systolic blood pressure, mmHg (SD)	121 (15)	131 (18)	133 (19)	126 (19)	137 (20)	131 (20)
Total cholesterol, mg/dL (SD)	186 (30)	200 (34)	199 (36)	210 (37)	227 (38)	213 (37)
Blood glucose, mg/dL (SD)	96 (13)	101 (19)	106 (32)	95 (13)	102 (19)	103 (28)
% of those having glucose ≥ 200 mg/dL	0	0	2.2	0	0	1.7
Current Smoker (%)	56.6	55.4	53.0	8.3	11.5	6.7
Number of Stroke	0	8	81	4	8	85
Number of Ischemic Stroke	0	2	33	1	4	25
Number of Hemorrhagic Strokes	0	2	24	1	3	12
Number of Subarachnoid hemorrhage	0	3	13	0	1	22
Number of Coronary Artery Disease	1	10	69	1	8	31

1) Category I: < 0.5%, Category II: ≥ 0.5% < 2.0%, Category III: ≥ 2.0% or Diabetes Mellitus

increased. In low/moderate decile groups, the mean estimated mortality fairly predicted the actual mortality. Meanwhile, in the higher decile group, the mean estimated mortality was predicted to be higher than the actual mortality, particularly in the 9th and 10th decile. In women, the results were almost similar with those in men. In the 9th and 10th decile, the mean estimated mortality was particularly higher than the actual mortality. Homer and Lemeshow test showed the significant difference in both men ($p<0.001$) and women ($p<0.001$).

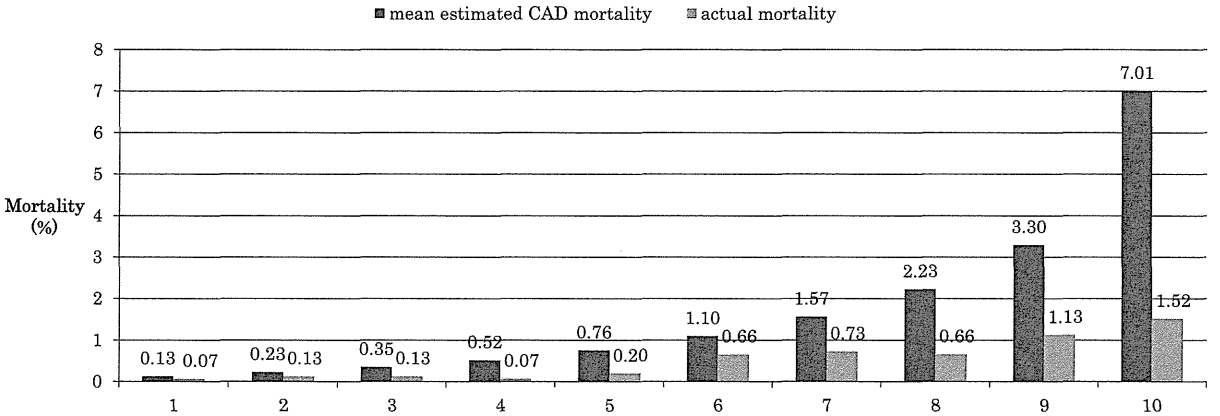
Supplemental Figures show the cohort-specific analysis between the mean estimated CAD/stroke mortality and its actual mortality by the quintile of estimated mortality. Based on their sample size and actual mortality, Suita cohort and Osaki cohort were selected as a representative of high and low age-adjusted CAD mortality rate (Suita: 474, Osaki: 273/100,000 population), respectively. In addition, NIPPON DATA90 was selected because it was performed under the similar protocol (sampling scheme of study participants) 10 years after NIPPON DATA80. In both men and women, the actual CAD/stroke mortality increased as the estimated morality increased. In higher quintile groups, i.e., 4th and 5th quintile, the mean estimated CAD/stroke mortality was higher than its actual mortality. These results were similar to the above-mentioned whole population analysis (**Fig. 1** and **2**).

Fig. 3 shows the mean estimated CAD mortality and its actual mortality according to the three categories of JAS guidelines 2012. The mean estimated mortality was higher than its actual mortality in all categories. In men, while the mean estimated mortality increased in the ascending order of category, its actual mortality in Category III did not increase significantly from that in Category II. The mean estimated mortality was higher than its actual mortality in Category III. In women, both the mean estimated mortality and actual mortality in Category III were lower than those in Category II. The Homer and Lemeshow test showed the significant difference in both men ($p<0.001$) and women ($p<0.001$).

Fig. 4 shows the mean estimated CAD mortality and its actual mortality according to the three categories of JAS guidelines 2012, without considering the presence of DM in risk classification. The mean estimated mortality was higher than its actual mortality in all categories. Compared to **Fig. 3**, the mean estimated mortality was higher than its actual mortality in Category III in **Fig. 4**. In men, both the mean estimated mortality and actual mortality increased in the ascending order of category, and the mean estimated mortality was higher than its actual mortality in Category III. In women, the results were almost the same as those in men. The Homer and Lemeshow test showed the significant difference in both men ($p<0.001$) and women ($p<0.001$).

Discussion

In the present study, we calibrated ND80RAC using one of the largest pooled cohort study, EPOCH-JAPAN. For CAD, in low mortality groups, the abso-

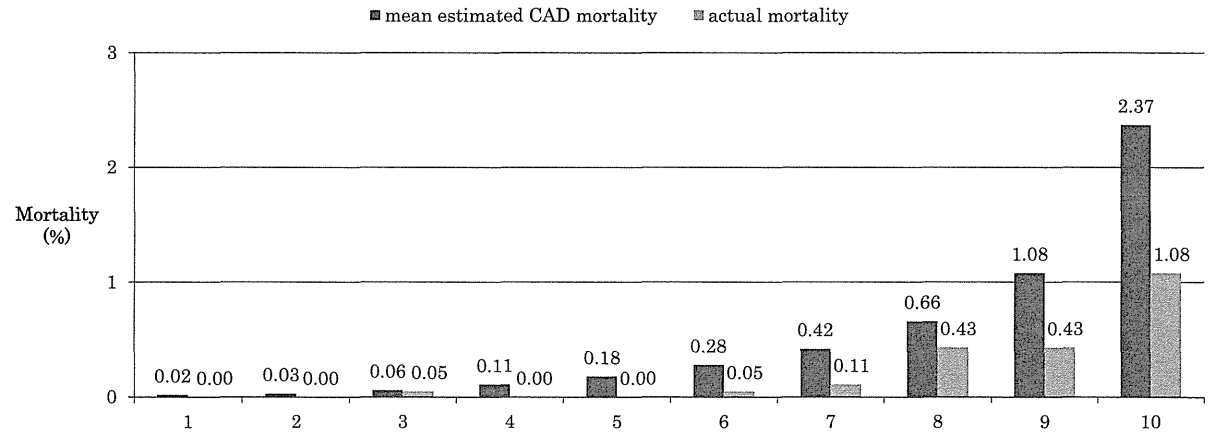


	1	2	3	4	5	6	7	8	9	10
Difference between two mortality [2]	0.06	0.10	0.22	0.45	0.56	0.44	0.84	1.57	2.17	5.49
Number of participants	1509	1509	1509	1509	1509	1509	1509	1508	1508	1512
Number of deaths	1	2	2	1	3	10	11	10	17	23

1) Estimated from NIPPON DATA80 risk chart

2) Calculated the difference between the mean estimated CAD mortality and the actual cumulative mortality in each decile

Fig. 1A. Decile of mean estimated CAD mortality of men in NIPPON DATA80 and actual mortality of men in EPOCH-JAPAN.[1] Hosmer–Lemeshow test (χ^2 statistic=134.18 d.f.=8, $P<0.001$)

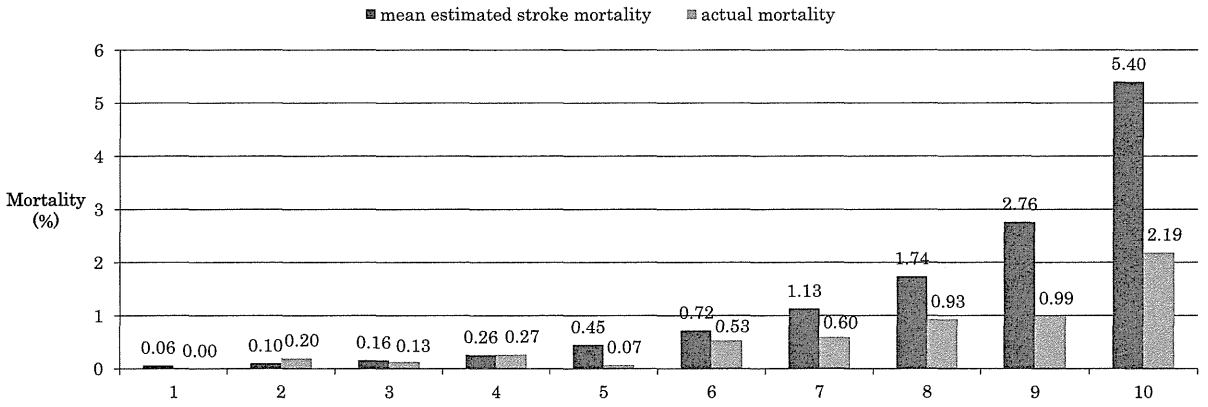


	1	2	3	4	5	6	7	8	9	10
Difference between two mortality [2]	0.02	0.03	0.01	0.11	0.18	0.23	0.31	0.23	0.65	1.29
Number of participants	1858	1859	1859	1859	1859	1859	1859	1859	1859	1859
Number of deaths	0	0	1	0	0	1	2	8	8	20

1) Estimated from NIPPON DATA80 risk chart

2) Calculated the difference between the mean estimated CAD mortality and the actual cumulative mortality in each decile

Fig. 1B. Decile of mean estimated CAD mortality of women in NIPPON DATA80 and actual mortality of women in EPOCH-JAPAN.[1] Hosmer–Lemeshow test (χ^2 statistic=36.38, d.f.=8, $P<0.001$)

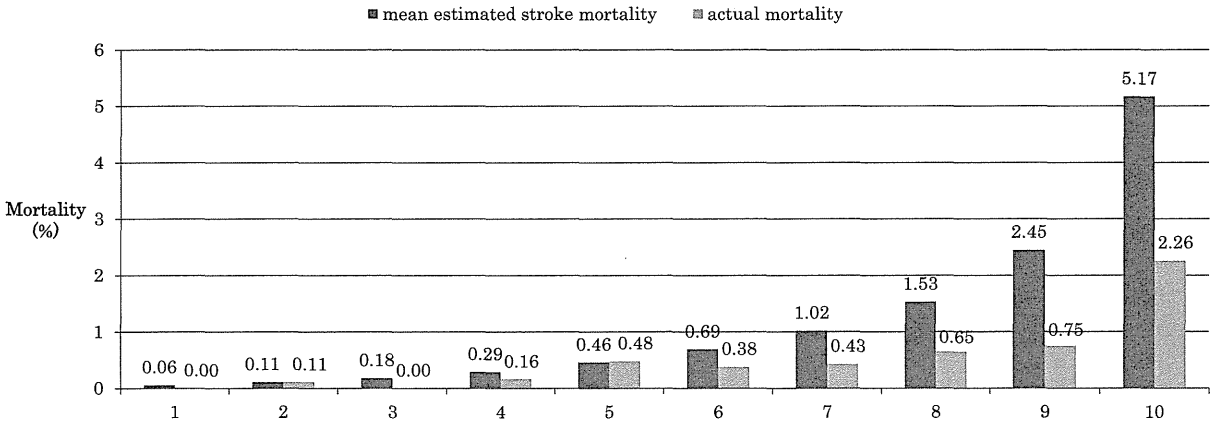


Difference between two mortality [2]	0.06	0.10	0.03	0.01	0.38	0.19	0.53	0.81	1.77	3.21
Number of participants	1509	1509	1509	1509	1509	1509	1509	1509	1509	1509
Number of deaths	0	3	2	4	1	8	9	14	15	33

1) Estimated from NIPPON DATA80 risk chart

2) Calculated the difference between the mean estimated stroke mortality and the actual cumulative mortality in each decile

Fig. 2A. Decile of mean estimated stroke mortality of men in NIPPON DATA80 and actual mortality of men in EPOCH-JAPAN.[1] Hosmer–Lemeshow test (χ^2 statistic=65.87, d.f.=8, $P<0.001$)

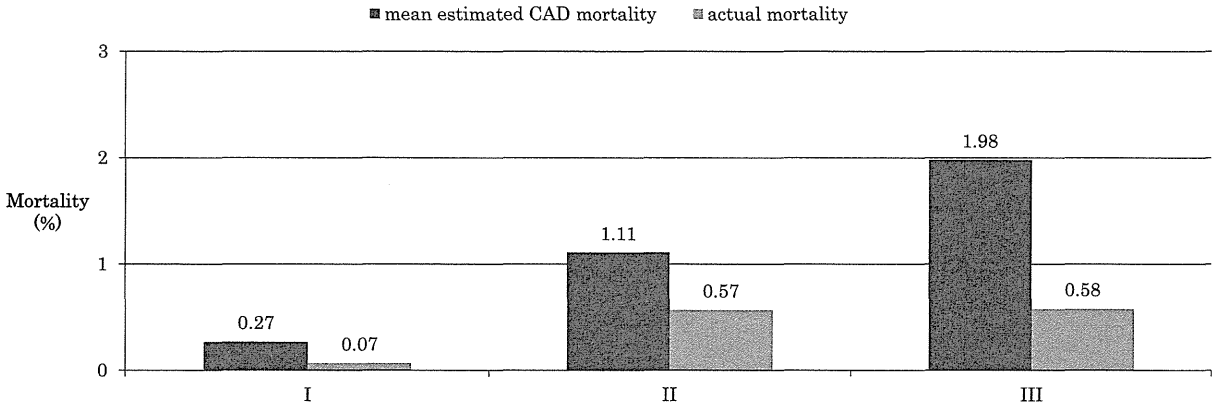


Difference between two mortality [2]	0.06	0.00	0.18	0.13	0.02	0.31	0.59	0.88	1.70	2.91
Number of participants	1858	1858	1860	1859	1859	1859	1859	1859	1857	1861
Number of deaths	0	2	0	3	9	7	8	12	14	42

1) Estimated from NIPPON DATA80 risk chart

2) Calculated the difference between the mean estimated stroke mortality and the actual cumulative mortality in each decile

Fig. 2B. Decile of mean estimated stroke mortality of women in NIPPON DATA80 and actual mortality of women in EPOCH-JAPAN.[1] Hosmer–Lemeshow test (χ^2 statistic=78.84, d.f.=8, $P<0.001$)

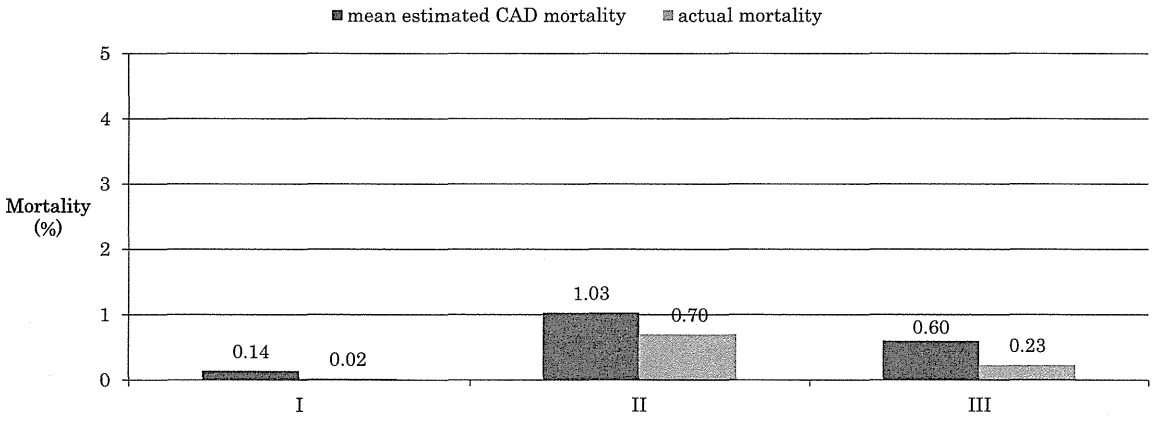


	I	II	III
Difference between two mortality [2]	0.20	0.54	1.40
Number of participants	1387	1765	11939
Number of death	1	10	69

1) Category I:<0.5%, Category II: ≥0.5% <2.0%, Category III: ≥2.0% or DM

2) Calculated the difference between the mean estimated CAD mortality and the actual cumulative mortality in each category

Fig. 3A. Mean estimated CAD mortality of men in NIPPON DATA80 and actual mortality of men in EPOCH-JAPAN according to the JAS Guidelines 2012.[1] Hosmer–Lemeshow test (χ^2 statistic=127.69, d.f.=1, $P<0.001$)

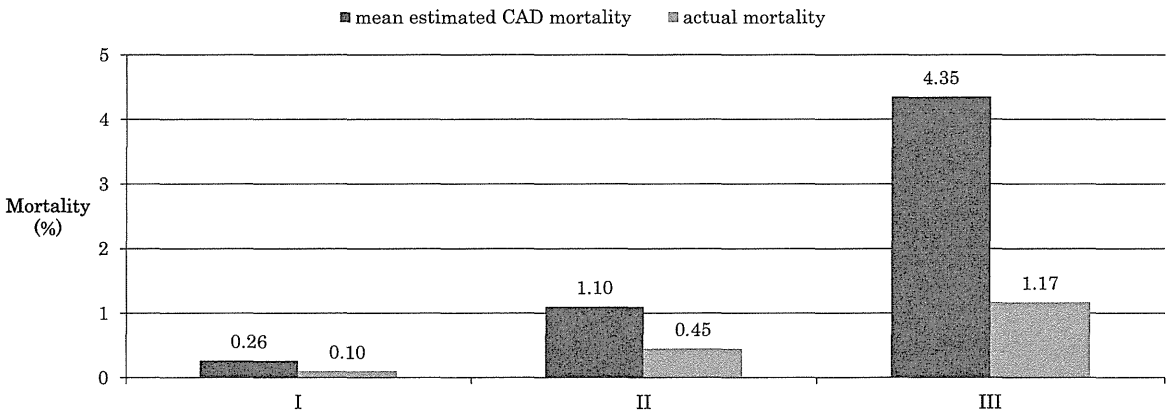


	I	II	III
Difference between two mortality [2]	0.12	0.33	0.37
Number of participant	4236	1142	13211
Number of death	1	8	31

1) Category I:<0.5%, Category II: ≥0.5% <2.0%, Category III: ≥2.0% or DM

2) Calculated the difference between the mean estimated CAD mortality and the actual cumulative mortality in each category

Fig. 3B. Mean estimated CAD mortality of women in NIPPON DATA80 and actual mortality of women in EPOCH-JAPAN according to the JAS Guidelines 2012.[1] Hosmer–Lemeshow test (χ^2 statistic=34.89, d.f.=1, $P<0.001$)

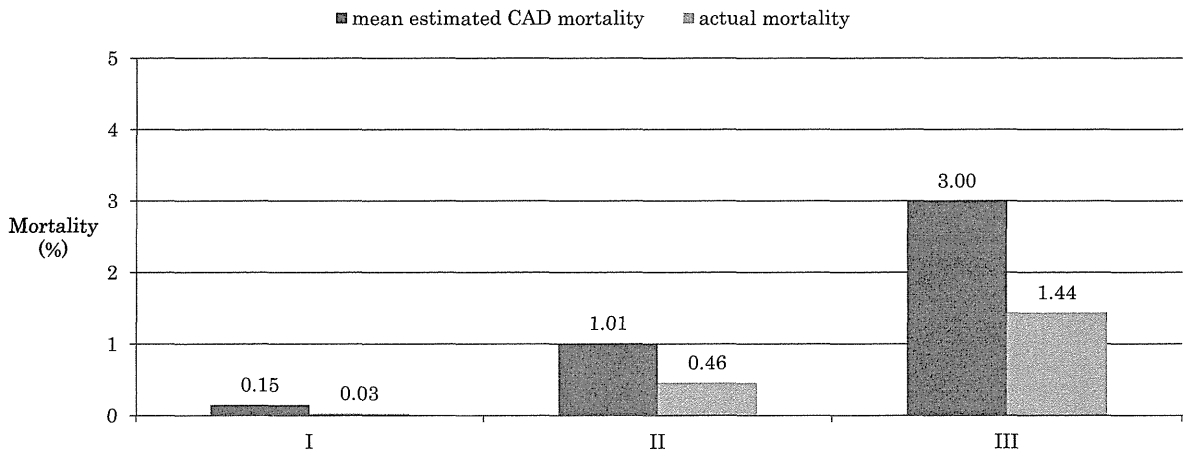


	I	II	III
Difference between two mortality [2]	0.16	0.65	3.18
Number of participants	5168	5719	4204
Number of death	5	26	49

1) Category I:<0.5%, Category II: ≥0.5% <2.0%, Category III: ≥2.0%

2) Calculated the difference between the mean estimated CAD mortality and the actual cumulative mortality in each category

Fig. 4A. Mean estimated CAD mortality of men in NIPPON DATA80 and actual mortality of men in EPOCH-JAPAN according to the JAS Guidelines 2012 excluding the inclusion criteria of DM in Category III.[1] Hosmer–Lemeshow test (χ^2 statistic=129.67, d.f.=1, $P<0.001$)



	I	II	III
Difference between two mortality [2]	0.12	0.55	1.56
Number of participants	12847	4772	970
Number of death	4	22	14

1) Category I:<0.5%, Category II: ≥0.5% <2.0%, Category III: ≥2.0%

2) Calculated the difference between the mean estimated CAD mortality and the actual cumulative mortality in each category

Fig. 4B. Mean estimated CAD mortality of women in NIPPON DATA80 and actual mortality of women in EPOCH-JAPAN according to the JAS Guidelines 2012 excluding the inclusion criteria of DM in Category III.[1] Hosmer–Lemeshow test (χ^2 statistic=34.58, d.f.=1, $P<0.001$)

lute difference between the mean estimated and actual mortality was relatively small. However, in higher CAD mortality groups, the mean estimated mortality was much higher than the actual mortality. For stroke, in both sexes, the mean estimated mortality was almost concordant with the actual mortality in low/moderate mortality groups, and the mean estimated mortality was higher than the actual mortality in higher estimated mortality groups. For three categories of JAS guidelines 2012, the mean estimated CAD mortality was higher than its actual mortality in all categories. However, the actual mortality in Category III did not increase significantly from Category II in men while that in Category III was lower than Category II in women. When we did not consider the presence of DM in risk classification, the actual mortality increased in ascending order of category in both sexes.

Comparison studies have been performed in the well-established risk charts such as the FRS and SCORE (Systematic Coronary Risk Evaluation) in the previous study[7-11, 28-30]. However, while there exist several risk assessment charts in Japan such as the NIPPON DATA80[15], Hisayama study[26], JALS-ECC[31], JMS cohort study[32, 33], and Suita study[3], few studies have evaluated the calibration with external Japanese cohort studies. Hisayama's study had attempted to develop and validate a new cardiovascular risk prediction model. Two-thirds of their participants were randomly assigned to a risk prediction model derivation cohort ($n=1,756$) and the remaining one-third of the participants were reserved as an independent validation cohort ($n=878$). Among subjects allocated to the derivation cohort, a new risk prediction model was developed using Cox's proportional hazards model, in which age, sex, SBP, diabetes, LDL cholesterol, high-density lipoprotein cholesterol, and smoking status were included as risk factors. The performance of the risk prediction model was tested among subjects allocated to the validation cohorts. However, the limitation of Hisayama's study was the lack of external validation[26], that is, the split sample as an internal validation was performed to justify the risk prediction model. To the best of our knowledge, this is the first study to review and evaluate ND80RAC with the large-scale nationwide Japanese cohort study.

The baseline period was different between NIPPON DATA80 and most cohort studies in EPOCH-JAPAN except NIPPON DATA80. The baseline survey of NIPPON DATA80 started from 1980, while the majority of the cohort studies in EPOCH-JAPAN started after 1990. In Japan, age-adjusted mortality from stroke increased after World War II until 1965 and significantly declined until 1990[13]. According to the vital statistics in Japan, the mortality from myocardial infarction in men was also decreased from 1980 to 1990[34]. The above-mentioned trend in mortality may be one reason for lower actual mortality in EPOCH-JAPAN than the mean estimated CAD/stroke mortality calculated by ND80RAC. Furthermore, mortality in the elderly is significantly decreasing during the last decade in Japan[2], which could also contribute to reduce the actual mortality in the elderly who were classified into the high-risk category.

Furthermore, due to the remarkable medical progress, the percutaneous coronary intervention had become one of the standard therapies for CAD since 1980s and the prevalence of stroke care units was associated with reduced in-hospital mortality. In addition, the advanced therapeutic agents such as statin have contributed to the cause of decreasing CAD mortality, particularly in high-risk individuals[35]. These factors could also explain the difference between the mean estimated mortality calculated by ND80RAC and the actual cumulative mortality in EPOCH-JAPAN, particularly in higher mortality groups.

The participants of most cohort studies in EPOCH-JAPAN were community dwellers or workers who participated in annual checkups performed under the health service law[36]. Accordingly, the participants of EPOCH-JAPAN could be considered to have high motivation for being healthy. In addition, participants of annual checkups usually could get health education or advice at their health checkups continuously after the baseline survey. In addition, workers have to get annual checkups under the law every year, and their health conditions are strictly managed after every checkup. Thus, the participants of EPOCH-JAPAN may be healthier than the general Japanese population. A previous study has reported that incidence and mortality due to CVD in the participants of annual checkups were much lower than those in non-participants[37]. On the other hand, the baseline survey of NIPPON DATA80 was performed in 1980, and such health checkup system by law has not been established yet. Furthermore, in NIPPON DATA80, all household members aged ≥30 years in 300 randomly selected census tracts across Japan were invited to participate with a high participation rate (76.6%). Thus, the participants of NIPPON DATA80 could have different characteristics from those of EPOCH-JAPAN.

We also calibrated the mean estimated CAD mortality and its actual cumulative mortality according to the three categories of JAS guidelines 2012. When we did not consider the presence of DM in risk

classification, the actual mortality increased in the ascending order of category in both sexes (**Fig. 4**). DM is one of the important risk factors for CAD/stroke. However, the results of the present study may indicate the need for reconsideration of the definition of diabetes when we estimate an individual's absolute risk for CAD/stroke for apparently healthy community dwellers. DM is associated with several complications[38, 39], and previous studies in Japan have already shown that DM complications were one of the major risk factors in CVD[40-42]. Furthermore, the prediction tools in the Japanese general population have demonstrated that the predicted risk for CVD due to DM, which was usually defined by glucose level or self-reported diabetes history, was nearly equivalent or even smaller than that of smoking[3, 31-33]. Therefore, when we estimate the individual's absolute risk for CVD, it may be important not only to diagnose DM by self-reported medical checkup but also to consider the disease duration of DM or the presence of DM complications such as nephropathy, neuropathy, visual acuity, and retinopathy.

The number of participants in the present study decreased from 101,977 in 12 cohorts due to death to 33,680. As we showed the characteristics of EPOCH-JAPAN including 12 cohorts with information about the cause of death in **Supplemental Table 1** and those of the participants of the present study in **Supplemental Table 2**, the percentage of participants in men and current smokers and total cholesterol were higher, and the glucose level was lower in the participants of the present study than those in EPOCH-JAPAN including 12 cohorts. Thus, these changes of the baseline characteristics may affect the results of the present study. However, because the values of all risk factors used in ND80RAC were required to estimate the probability of CAD/stroke mortality in the present study, we excluded 38,079 missing values/outliers of risk factors, most of which were blood glucose from Oyabe study and JACC. In addition, we excluded 7,029 participants with a history of cardiovascular disease and 13,747 participants who were <40 years or >75 years. These exclusion criteria may also affect the results of the present study. However, we believe that EPOCH-JAPAN in the present study was the best available candidate for an external cohort study to calibrate ND80RAC in the present situation.

The present study has several limitations. At first, the mortality from CAD was small, particularly in women. Another large-scale cohort study may be necessary to certify the risk chart for CAD in women. Second, the dataset did not include the information of the cholesterol-lowering therapy such as statins. While the baseline surveys in 6 cohorts in EPOCH-JAPAN were conducted before the first statin usage was started in 1989[34], other 3 cohorts were conducted around 1990. Therefore, the effect of statins had little impact on most of the participants at baseline. Finally, we could not consider the risk factors suggested by JAS guidelines 2012 such as HDL-C, family history of premature CAD, past history of peripheral artery disease, chronic kidney disease, and impaired glucose tolerance in these categorization.

In conclusion, the estimated CAD mortality by ND80RAC tended to be higher than the actual mortality in the population of which baseline survey was more recently performed. ND80RAC was established in approximately 10,000 nationwide general populations for the first time as a health-education tool in Japan for primary prevention to estimate the risk of CVD mortality. The tool was expected to assess the compatibility to other nationwide Japanese populations, and we could finally perform the calibration study after integrating the dataset of EPOCH-JAPAN, which includes $>30,000$ nationwide individuals. In the present study, we showed the need for calibration of the health-education tools by constructing a nationwide larger-scaled cohort study. We also showed the need for revision or re-establishment of the tools due to the change in backgrounds of Japanese population, including the remarkable development of medicine and medical technology, or for a better definition of risk factors and other endpoints.

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Appendix

The Evidence for Cardiovascular Prevention from Observational Cohorts in Japan (EPOCH-JAPAN) Research Group consists of the following investigators. Chairperson: Hirotsugu Ueshima (Shiga University of Medical Science); Co-Chairperson: Tomonori Okamura (Keio University School of Medicine);

Executive committee: Hirotsugu Ueshima (Shiga University of Medical Science), Yutaka Imai (Tohoku University Graduate School of Pharmaceutical Sciences), Takayoshi Ohkubo (Teikyo University School of Medicine), Fujiko Irie (Ibaraki Prefecture), Hiroyasu Iso, Akihiko Kitamura (Osaka University Graduate School of Medicine), Yutaka Kiyohara (Kyushu

University Graduate School of Medicine), Katsuyuki Miura (Shiga University of Medical Science), Yoshitaka Murakami (Toho University), Hideaki Nakagawa (Kanazawa Medical University), Takeo Nakayama (Kyoto University School of Public Health), Akira Okayama (Research Institute of Strategy for Prevention), Toshimi Sairenchi (Dokkyo Medical University), Shigeyuki Saitoh (Sapporo Medical University), Kiyomi Sakata (Iwate Medical University), Akiko Tamakoshi (Hokkaido University Graduate School of Medicine), Ichiro Tsuji (Tohoku University Graduate School of Medicine), Michiko Yamada (Radiation Effects Research Foundation), Masahiko Kiyama (Osaka Center for Cancer and Cardiovascular Disease Prevention), Yoshihiro Miyamoto (National Cerebral and Cardiovascular Center), Shizukiyo Ishikawa (Jichi Medical University), Hiroshi Yatsuya (Fujita Health University) and Tomonori Okamura (Keio University School of Medicine)

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Conflict of Interest Disclosures

None.

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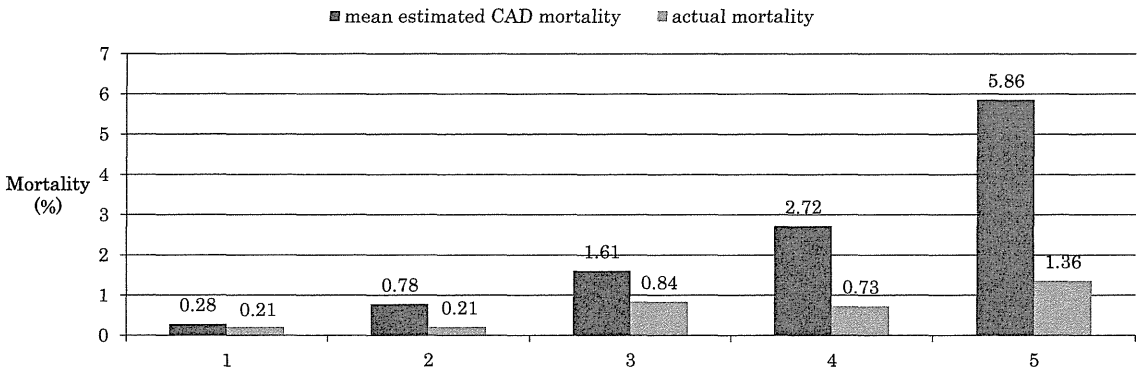


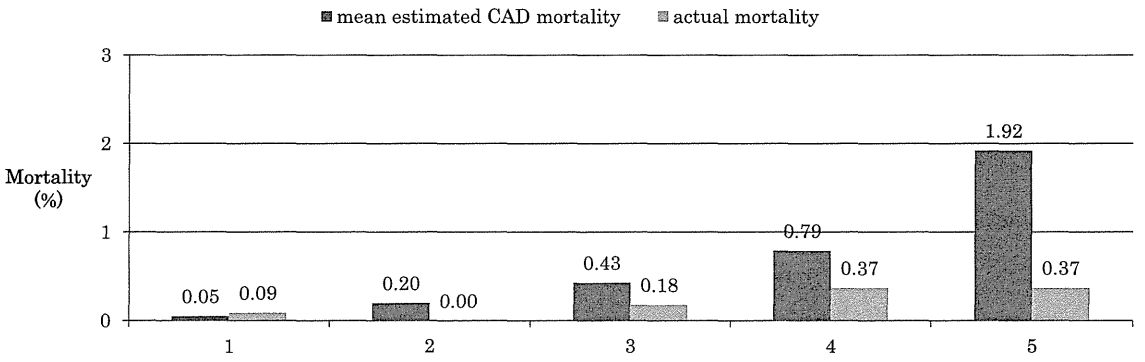
Difference between two mortality [2]	0.07	0.57	0.77	1.99	4.50
Number of participants	954	955	954	955	955
Number of deaths	2	2	8	7	13

1) Estimated from NIPPON DATA80 risk chart

2) Calculated the difference between the mean estimated CAD mortality and the actual cumulative mortality in each quintile

Supplemental Fig. 1A

Analysis between quintile of mean estimated CAD mortality of men in NIPPON DATA80 and actual mortality of men in Osaki Cohort.[1] Hosmer–Lemeshow test (χ^2 statistic=57.06, d.f.=3, $P<0.001$)



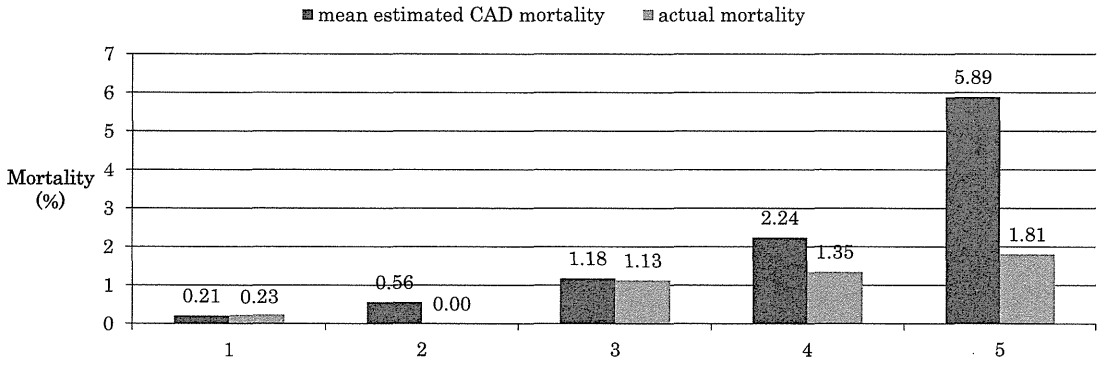
Difference between two mortality [2]	0.04	0.20	0.25	0.42	1.55
Number of participants	1081	1081	1083	1082	1082
Number of deaths	1	0	2	4	4

1) Estimated from NIPPON DATA80 risk chart

2) Calculated the difference between the mean estimated CAD mortality and the actual cumulative mortality in each quintile

Supplemental Fig. 1B

Analysis between quintile of mean estimated CAD mortality of women in NIPPON DATA80 and actual mortality of women in Osaki Cohort.[1] Hosmer–Lemeshow test (χ^2 statistic=20.33, d.f.=3, $P<0.001$)



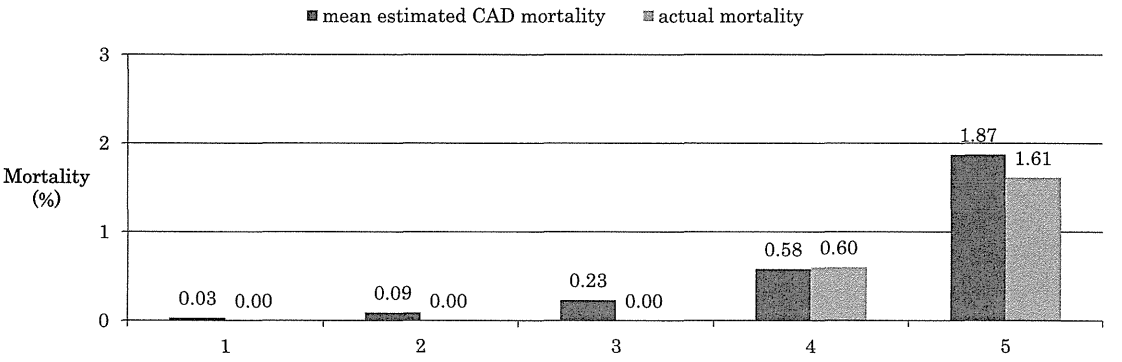
Difference between two mortality [2]	0.02	0.56	0.05	0.89	4.08
Number of participants	442	443	443	443	443
Number of deaths	1	0	5	6	8

1) Estimated from NIPPON DATA80 risk chart

2) Calculated the difference between the mean estimated CAD mortality and the actual cumulative mortality in each quintile

Supplemental Fig. 2A

Analysis between quintile of mean estimated CAD mortality of men in NIPPON DATA80 and actual mortality of men in Suita Cohort.[1] Hosmer–Lemeshow test (χ^2 statistic=17.43, d.f.=3, $P<0.001$)



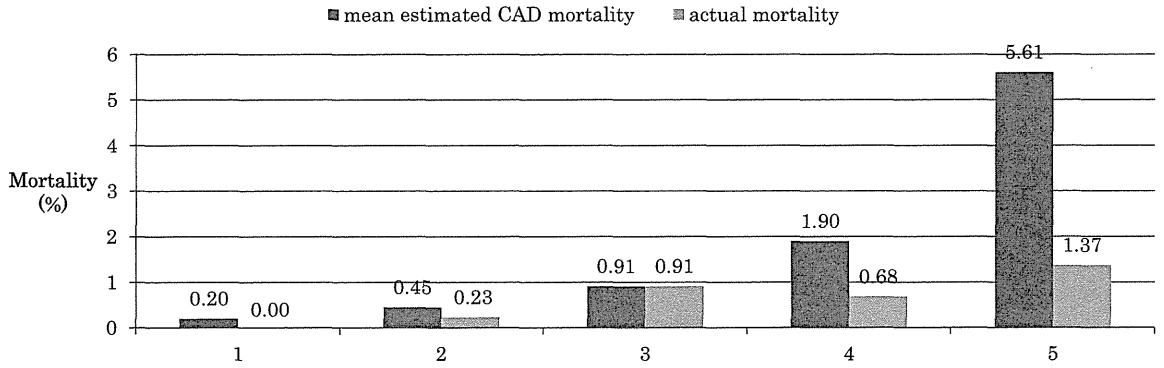
Difference between two mortality [2]	0.03	0.09	0.23	0.02	0.26
Number of participants	495	495	497	496	496
Number of deaths	0	0	0	3	8

1) Estimated from NIPPON DATA80 risk chart

2) Calculated the difference between the mean estimated CAD mortality and the actual cumulative mortality in each quintile

Supplemental Fig. 2B

Analysis between quintile of mean estimated CAD mortality of women in NIPPON DATA80 and actual mortality of women in Suita Cohort.[1] Hosmer–Lemeshow test (χ^2 statistic=1.92, d.f.=3, $P=0.59$)

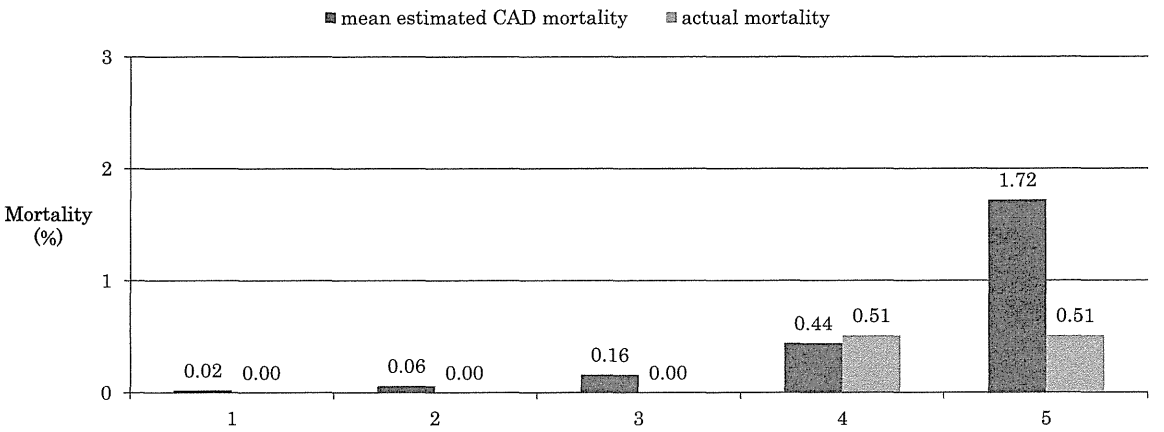


Difference between two mortality [2]	0.20	0.22	0.00	1.22	4.24
Number of participants	437	438	438	438	438
Number of deaths	0	1	4	3	6

1) Estimated from NIPPON DATA80 risk chart

2) Calculated the difference between the mean estimated CAD mortality and the actual cumulative mortality in each quintile

Supplemental Fig. 3A
Analysis between quintile of mean estimated CAD mortality of men in NIPPON DATA80 and actual mortality of men in NIPPON DATA90.[1] Hosmer–Lemeshow test (χ^2 statistic=19.7, d.f.=3, $P<0.001$)

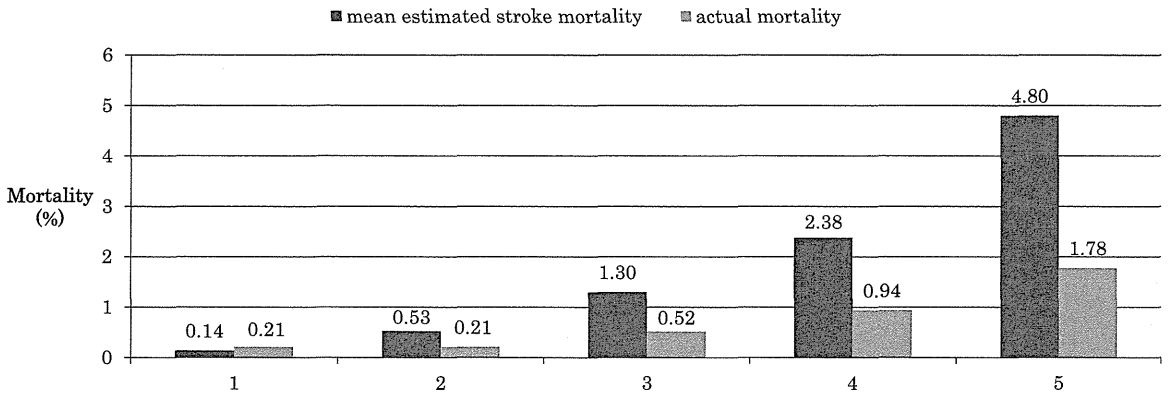


Difference between two mortality [2]	0.02	0.06	0.16	0.07	1.21
Number of participants	587	588	588	588	588
Number of deaths	0	0	0	3	3

1) Estimated from NIPPON DATA80 risk chart

2) Calculated the difference between the mean estimated CAD mortality and the actual cumulative mortality in each quintile

Supplemental Fig. 3B
Analysis between quintile of mean estimated CAD mortality of women in NIPPON DATA80 and actual mortality of women in NIPPON DATA90.[1] Hosmer–Lemeshow test (χ^2 statistic=6.57, d.f.=3, $P=0.09$)

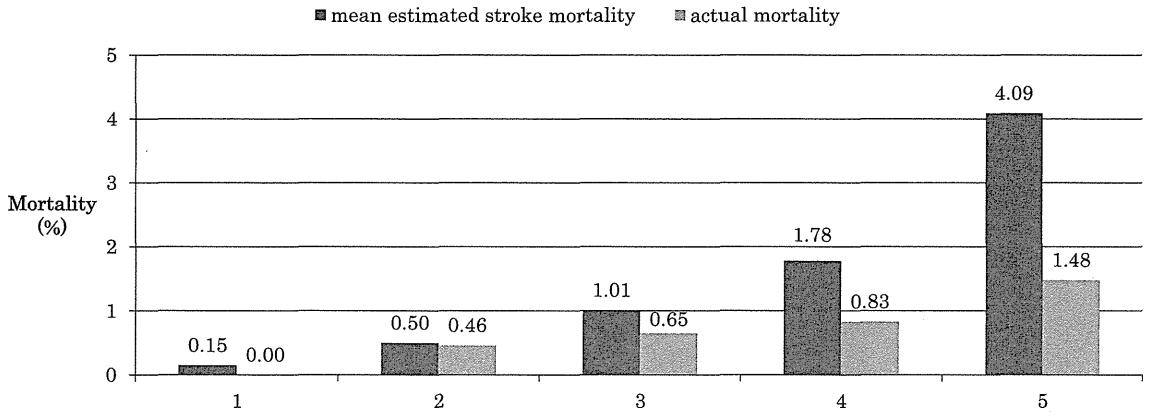


Difference between two mortality [2)]	0.07	0.32	0.78	1.44	3.02
Number of participants	954	955	954	955	955
Number of deaths	2	2	5	9	17

1) Estimated from NIPPON DATA80 risk chart

2) Calculated the difference between the mean estimated stroke mortality and the actual cumulative mortality in each quintile

Supplemental Fig. 4A
Analysis between quintile of mean estimated stroke mortality of men in NIPPON DATA80 and actual mortality of men in Osaki Cohort.[1)] Hosmer–Lemeshow test (χ^2 statistic=34.2, d.f.=3, $P<0.001$)

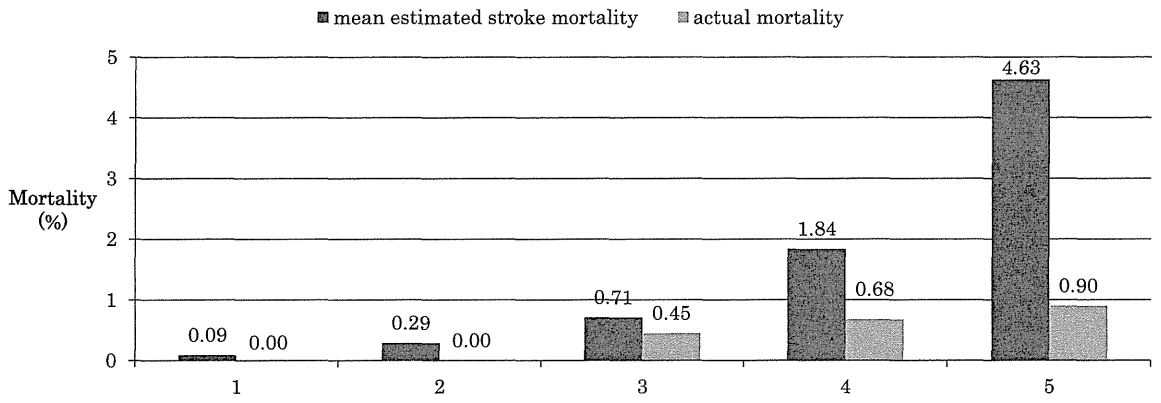


Difference between two mortality [2)]	0.15	0.04	0.36	0.95	2.61
Number of participants	1081	1082	1082	1082	1082
Number of deaths	0	5	7	9	16

1) Estimated from NIPPON DATA80 risk chart

2) Calculated the difference between the mean estimated stroke mortality and the actual cumulative mortality in each quintile

Supplemental Fig. 4B
Analysis between quintile of mean estimated stroke mortality of women in NIPPON DATA80 and actual mortality of women in Osaki Cohort.[1)] Hosmer–Lemeshow test (χ^2 statistic=27.5, d.f.=3, $P<0.001$)

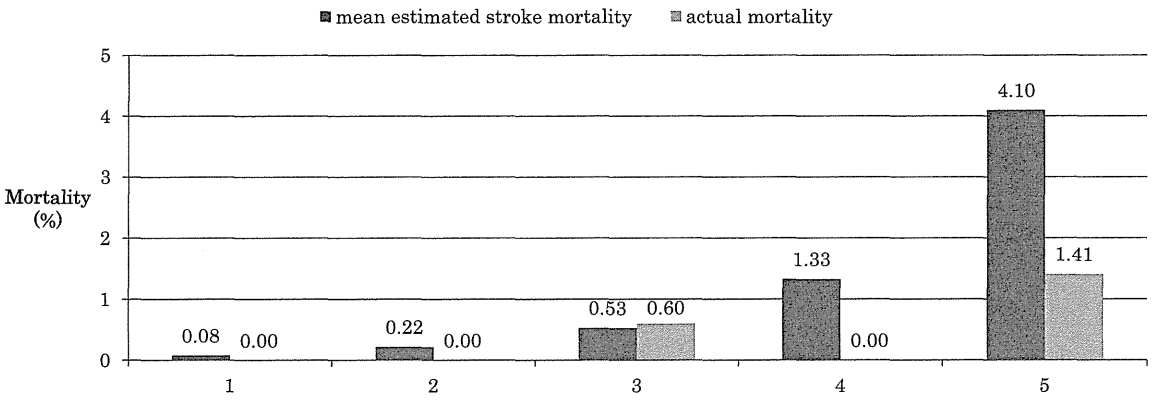


Difference between two mortality [2)]	0.09	0.29	0.26	1.16	3.73
Number of participants	442	443	443	443	443
Number of deaths	0	0	2	3	4

1) Estimated from NIPPON DATA80 risk chart

2) Calculated the difference between the mean estimated stroke mortality and the actual cumulative mortality in each quintile

Supplemental Fig. 5A
Analysis between quintile of mean estimated stroke mortality of men in NIPPON DATA80 and actual mortality of men in Suita Cohort.[1)] Hosmer–Lemeshow test (χ^2 statistic=19.4, d.f.=3, $P<0.001$)

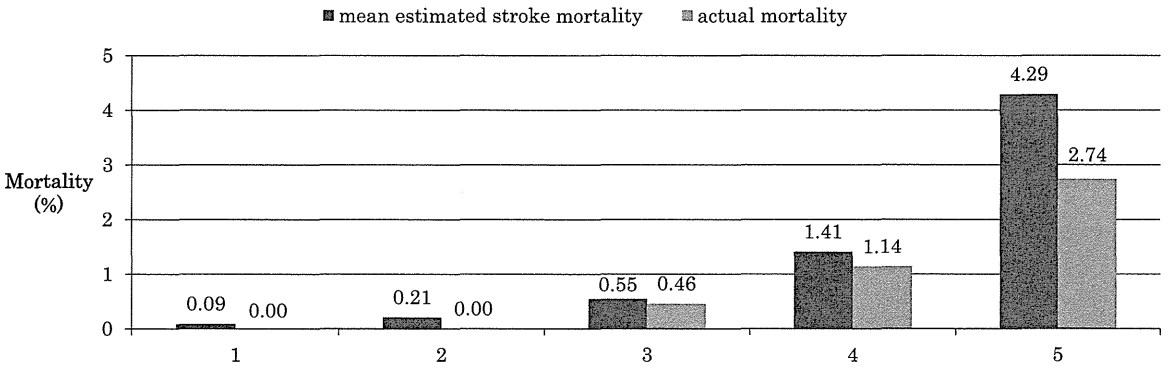


Difference between two mortality [2)]	0.08	0.22	0.07	1.33	2.69
Number of participants	495	496	496	496	496
Number of deaths	0	0	3	0	7

1) Estimated from NIPPON DATA80 risk chart

2) Calculated the difference between the mean estimated stroke mortality and the actual cumulative mortality in each quintile

Supplemental Fig. 5B
Analysis between quintile of mean estimated mortality of women in NIPPON DATA80 and actual mortality of women in Suita Cohort.[1)] Hosmer–Lemeshow test (χ^2 statistic=17.4 d.f.=3, $P<0.001$)

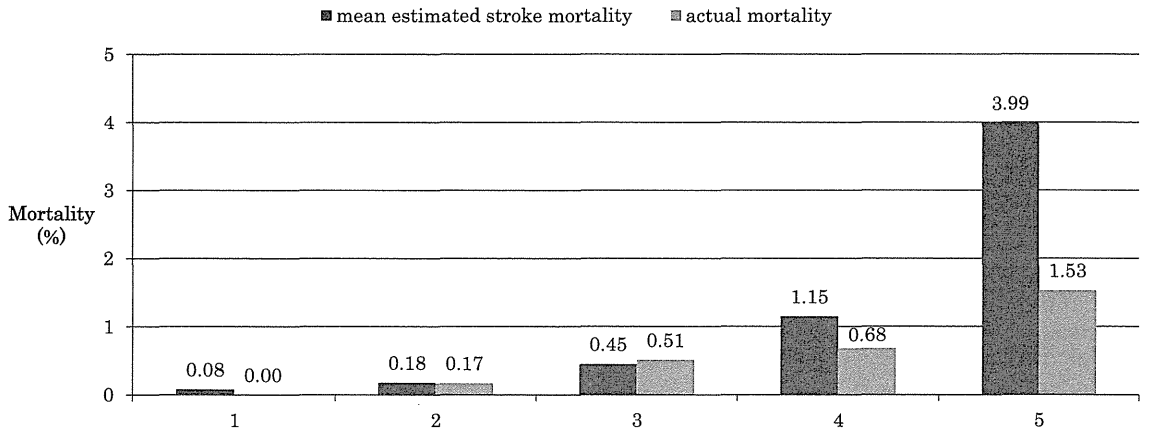


Difference between two mortality [2]	0.09	0.21	0.09	0.27	1.55
Number of participants	437	438	438	438	438
Number of deaths	0	0	2	5	12

1) Estimated from NIPPON DATA80 risk chart

2) Calculated the difference between the mean estimated stroke mortality and the actual cumulative mortality in each quintile

Supplemental Fig. 6A
Analysis between quintile of estimated mean stroke mortality of men in NIPPON DATA80 and actual mortality of men in NIPPON DATA90.[1] Hosmer–Lemeshow test (χ^2 statistic=4.18, d.f.=3, P=0.24)



Difference between two mortality [2]	0.08	0.01	0.06	0.47	2.46
Number of participants	587	588	588	588	588
Number of deaths	0	1	3	4	9

1) Estimated from NIPPON DATA80 risk chart

2) Calculated the difference between the mean estimated stroke mortality and the actual cumulative mortality in each quintile

Supplemental Fig. 6B
Analysis between quintile of mean estimated stroke mortality of women in NIPPON DATA80 and actual mortality of women in NIPPON DATA90.[1] Hosmer–Lemeshow test (χ^2 statistic=11.0, d.f.=3, P=0.01)

Supplemental Table 1. Baseline characteristics of EPOCH-JAPAN by cohorts including the 12 cohorts with the cause of death

Cohort Name	N	Men, N (%)	Age, years (SD)	Systolic blood pressure, mmHg (SD)	Total cholesterol, mg/dL (SD)	Blood glucose, mg/dL (SD)	Current Smoker (%)
Tanno-Sobetsu	2489	1097 (44.1)	47 (11)	132 (20)	189 (37)	93 (17)	36.3
Ohsaki	16238	6907 (42.5)	62 (9)	131 (18)	204 (35)	107 (30)	25.7
Ohasama	3174	1269 (40.0)	58 (13)	131 (17)	196 (37)	117 (46)	21.0
Oyabe	5197	1624 (31.3)	57 (11)	127 (20)	194 (36)	.	19.3
YKK workers[1]	7039	4380 (62.2)	38 (10)	119 (15)	190 (35)	93 (13)	38.9
Suita	6448	3092 (48.0)	55 (13)	128 (22)	207 (37)	99 (19)	31.2
RERF cohort[2]	4670	1521 (32.6)	62 (12)	135 (23)	210 (40)	105 (33)	23.5
Hisayama	2736	1162 (42.5)	60 (12)	134 (22)	206 (42)	106 (24)	25.0
JACC[3]	30265	11044 (36.5)	57 (10)	133 (19)	198 (37)	.	21.9
NIPPON DATA80[4]	9442	4157 (44.0)	51 (13)	136 (21)	189 (34)	130 (36)	32.6
NIPPON DATA90	8099	3405 (42.0)	53 (14)	135 (21)	203 (38)	103 (32)	28.5
Osaka	6180	2228 (36.1)	55 (13)	134 (21)	210 (37)	100 (27)	24.2
Total	101977	41886 (41.1)	56 (13)	132 (20)	200 (37)	107 (31)	26.3

1) YKK: Yoshida Kogyo Kabushikigaisya
2) RERF: Radiation Effects Research Foundation
3) JACC: Japan Collaborative Cohort
4) NIPPON DATA: National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged

Supplemental Table 2. Baseline characteristics of EPOCH-JAPAN by cohorts in the present study

Cohort Name	N	Men, N (%)	Age, years (SD)	Systolic blood pressure, mmHg (SD)	Total cholesterol, mg/dL (SD)	Blood glucose, mg/dL (SD)	Current Smoker (%)
Tanno-Sobetsu	1606	743 (46.3)	50 (7)	132 (20)	190 (38)	93 (18)	36.2
Ohsaki	10182	4773 (46.9)	60 (9)	131 (17)	204 (35)	106 (29)	26.1
Ohasama	729	245 (33.6)	58 (8)	132 (16)	202 (36)	117 (40)	16.7
YKK workers[1]	2798	1884 (67.3)	47 (5)	119 (16)	203 (35)	94 (14)	39.2
Suita	4693	2214 (47.2)	57 (10)	129 (22)	211 (37)	100 (20)	29.9
RERF cohort[2]	3402	1082 (31.8)	58 (9)	132 (21)	212 (39)	101 (27)	25.3
Hisayama	2305	990 (43.0)	56 (9)	131 (20)	207 (42)	105 (24)	25.5
NIPPON DATA90[3]	5128	2189 (42.7)	55 (10)	138 (20)	207 (38)	104 (34)	28.3
Osaka	2837	971 (34.2)	55 (8.9)	127 (16)	212 (37)	99 (26)	25.0
Total	33680	15091 (44.8)	56 (10)	131 (19)	206 (37)	102 (27)	28.1

1) YKK: Yoshida Kogyo Kabushikigaisya
2) RERF: Radiation Effects Research Foundation
3) NIPPON DATA: National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged