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Optimal Cut-off Points of Nonfasting and Fasting Triglycerides for Prediction of Ischemic Heart Disease in Japanese General Population: The Circulatory Risk in Communities Study (CIRCS)

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Aims: We investigated the optimal cut-off points of nonfasting and fasting triglycerides in Japanese individuals with lower average triglyceride levels than westerners.

Methods: Residents aged 40–69 years without a history of ischemic heart disease or stroke were enrolled between 1980 and 1994 and followed. Serum triglyceride concentrations were measured from 10851 nonfasting (<8 h after meal) and 4057 fasting (≥ 8 h) samples. As a prerequisite, we confirmed the shape of a receiver operating characteristic (ROC) curves, the area under ROC curves (AUC), and the integrated time-dependent AUC. We identified optimal cut-off points for incident ischemic heart disease based on C-statistic, Youden index, and Harrell's concordance statistic. We used dichotomized concentrations of triglycerides via the univariate logistic regression and Cox proportional hazards regression models. We also calculated multivariable hazard ratios and population attributable fractions to evaluate the optimal cut-off points.

Results: Nonfasting and fasting optimal cut-off points were 145 mg/dL and 110 mg/dL, with C-statistic of 0.594 and 0.626, Youden index of 0.187 and 0.252, and Harrell's concordance statistic of 0.590 and 0.630, respectively. The corresponding multivariable hazard ratios of ischemic heart disease were 1.43 (95%CI 1.09–1.88) and 1.69 (1.03–2.77), and the corresponding population attributable fractions were 16.1% (95%CI 3.3–27.2%) and 24.6 (–0.3–43.3).

Conclusion: The optimal cut-off points of nonfasting and fasting triglycerides in the Japanese general population were 145 mg/dL and 110 mg/dL, respectively, lower than the current cut-off points recommended in the US and Europe.

See editorial vol. 30: 105-106

Key words: Triglycerides, Optimal cut-off point, Ischemic heart disease, General population, Cohort study

Abbreviations: AHA, American Heart Association; CIRCS, Circulatory Risk in Communities Study; CDC, Centers for Disease Control and Prevention; ROC, receiver operating characteristic; AUC, area under the ROC curve; HR, hazard ratio; CI, confidence interval; PAF, population attributable fraction.

Introduction

Lipid profiles are integral components for predicting and controlling cardiometabolic diseases. Low-density lipoprotein cholesterol is the dominant form of atherogenic cholesterol and an established lipid associated with the risk of atherosclerotic cardiovascular disease[1]. It is unlikely to fluctuate after

a meal. In contrast, serum triglyceride concentrations likely increase after a meal. In the last decade (between 2008 and 2018), serum triglyceride levels have increased, whereas serum low-density lipoprotein cholesterol levels have remained unchanged among the Japanese general population[2]. However, there have been a few cohort studies on serum triglycerides and cardiovascular diseases among the Japanese general population, focusing on nonfasting state[3, 4], in fasting state[5], and both of nonfasting and fasting state[6]. Generally, in clinical practice, blood samples are obtained after fasting for at least 8 h, which is considered a necessary measure to minimize the analytic variability of blood lipids such as triglycerides and glucose. Nonetheless, the nonfasting state predominates for most of a 24-h cycle, and the nonfasting state may better capture the total amount of atherogenic lipoproteins[7]. Therefore, the multiple population-based cohort studies on nonfasting triglycerides, including our previous study[8], were conducted between 2007 and 2014. As a result, evidence has been accumulating that nonfasting triglycerides constituted similar or superior predictors for atherosclerotic cardiovascular disease than fasting triglycerides[6, 8-13]. The Danish Society for Clinical Chemistry adopted nationwide nonfasting triglyceride measurements in 2009 [14], followed by clinical guidelines in the US[15, 16] and the UK[17].

Therefore, it is valuable to identify an optimal cut-off point for serum triglyceride concentrations for the risk of incident atherosclerotic cardiovascular disease according to the nonfasting and fasting state. For the first time in 2015, the Women's Health Study identified an optimal cut-off point of nonfasting triglycerides based on the C-statistic and Youden index, using the dichotomized level of triglycerides as a dependent variable in the univariable logistic regression model[18]. They reported 175 mg/dL as a nonfasting optimal cut-off point to predict total cardiovascular disease events. Their methods were more accurate than the 2011 scientific statements of the American Heart Association (AHA) recommending 200 mg/dL for nonfasting triglycerides[15]. Since then, several guidelines have emerged recommending nonfasting triglyceride screening[7].

Aim

Previous guidelines had no consistent optimal cut-off points for nonfasting triglycerides: 200 mg/dL (2.26 mmol/L) from the AHA[15], 175 mg/dL (1.98 mmol/L) from the European Atherosclerosis Society[19], and the task force of the American College of Cardiology/AHA[20]. Furthermore, the study, which provided the rationale for the value of 175 mg/dL[18], was conducted only among women. Cardiovascular outcomes included total stroke, and the association with triglycerides was not as strong as ischemic heart disease. As described in the 2011 scientific statement of AHA[15], the optimal cut-off point of triglycerides among the populations with a lower prevalence of dyslipidemia and lower mortality from ischemic heart disease like Japanese[21] may be lower than that recommended in the US and Europe. It is necessary to determine the appropriate optimal cut-off points for triglyceride levels at each of nonfasting and fasting state in the Japanese general population. Therefore, we investigated the optimal cut-off points for ischemic heart disease in a population-based prospective cohort study of Japanese men and women.

Methods

Study Population

The Circulatory Risk in Communities Study (CIRCS) is an ongoing dynamic population-based cohort study designed to determine cardiovascular risk factors in the Japanese general population since 1963 [22]. The survey population came from three rural Japanese communities, namely, Ikawa town, the Kyowa district of Chikusei city, and the Noichi district of Konan city, and one urban community, the Minami-Takayasu district of Yao city. The 1980–1994 baseline was used to identify optimal cut-off points for nonfasting and fasting triglycerides to discriminate incident ischemic heart disease cases and noncases in Japanese populations. A total of 15213 residents aged 40–69 years underwent blood tests during annual community health checkups. We excluded 305 participants who had a history of ischemic heart disease and/or stroke at baseline so that 14908 participants (5996 men, 8912 women). Informed consent was obtained from the community representatives because this study was based on the secondary use of existing data from cardiovascular disease prevention programs[22]. This study was approved by the ethics committees of the Osaka Center for Cancer and Cardiovascular Disease Prevention and Osaka University.

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Follow-up and Ascertainment of Cases

Follow-up of participants was done from the baseline survey to the date of the first incident of ischemic heart disease, death, move-out, or end of the follow-up in 2010 for the Noichi district, 2015 for the Kyowa district, 2018 for the Minami-Takayasu district, and 2019 for Ikawa town. The median follow-up periods were 23.1 years for nonfasting participants and 24.8 years for fasting participants. During the follow-up, 1032 (6.9%) participants moved away from their baseline community, and 5262 (35.3%) participants died.

The surveillance of the first incident ischemic heart disease was performed on multiple sources, including death certificates, national insurance claims, annual household questionnaires, annual cardiovascular risk surveys, and reports from local physicians, public health nurses, and healthcare volunteers. We telephoned, visited for all living participants suspected cases, or invited them to annual health checkups. In addition, we reviewed medical records from local clinics and hospitals. We obtained related medical records and medical histories for death cases and referred them from either family or attending physicians. Ischemic heart disease (definite and probable myocardial infarction, angina pectoris, and sudden cardiac death occurring within 1 h after onset) was diagnosed according to the modified criteria of the World Health Organization Expert Committee[23]. Definite myocardial infarction was determined by the following symptoms: typical chest pain lasting more than 30 min without a definite non-ischemic cause, the electrocardiographic appearance of persistent Q or QS waves, and consistent elevations of cardiac enzymes. Individuals with typical chest pain but non-diagnostic or unavailable electrocardiographic imaging and enzyme concentrations were classified as possible myocardial infarctions. Angina pectoris was defined by the classic presentation of effort angina; this included repeated episodes of chest discomfort related to physical activity (running, walking, etc.), which usually disappeared rapidly after rest or the use of sublingual nitroglycerin. Sudden cardiac death was defined as death occurring within 1 h after the onset of cardiac arrest or abrupt collapse. The initial case of definite or probable myocardial infarction, angina pectoris, or sudden cardiac death was defined as incident ischemic heart disease. The final diagnoses were discussed and adjudicated by a team of experienced physician-epidemiologists who were blinded to the data on cardiovascular risk factors.

Baseline Examination

Data on cardiovascular risk factors were collected during the annual community health checkups. Blood samples were drawn into plain, siliconized glass tubes, and the serum was separated immediately after centrifugation. Dietary restrictions did not request before blood tests. Serum was collected from 10851 nonfasting (<8 h after meal) and 4057 fasting (≥ 8 h after meal) participants. **Supplementary Table 1** shows the number and proportion of nonfasting and fasting statuses. The number and proportion of samples according to time intervals after the last meal were 617 (4.1%) for <1 h, 3165 (21.2%) for 1 to < 2 h, 3714 (24.9%) for 2 to <3 h, 3355 (22.5%) for 3 to <8 h, and 4057 (27.3%) for ≥ 8 h.

Serum glycerol-blanked triglycerides were measured using the fluorometric method from 1980 to August 1986 and the enzymatic method from September 1986 to 1994 [24]. Serum total cholesterol was measured using the direct Liebermann–Burchard method from 1980 to August 1986 and the enzymatic method from September 1986 to 1994 [25]. Lipid profile measurements were performed, using the National Heart Lung and Blood Institute Lipid Standardized Program provided by the Centers for Disease Control and Prevention (CDC) (Atlanta, GA, USA), at the laboratory of the Osaka Center for Cancer and Cardiovascular Disease Prevention, an international member of the US National Cholesterol Reference Method Laboratory Network. They successfully maintained the precision and accuracy goals of serum triglyceride and total cholesterol since 1975 [24, 25]. Serum glucose was measured using the cupric-neocuproine method between 1980 and August 1986 and the hexokinase method between September 1986 and 1994. Glucose values (mmol/L) in the first method were adjusted using the following formula: 0.0474 × (glucose concentration in mg/dL) + 0.541 [26].

Height in stocking feet and weight in light clothing were measured to calculate body mass index (weight [kg] divided by the height squared [m^2]). Trained interviewers obtained information on lifestyle risk factors to ascertain the smoking and drinking status, the number of cigarettes per day, their usual weekly intake of alcohol evaluated by units of "go" (a traditional Japanese unit of volume corresponding to 23 g of ethanol), and medications used for dyslipidemia, hypertension, diabetes, and other diseases. Systolic and diastolic blood pressure in the right arm was measured by trained physicians using standard mercury sphygmomanometers and unified epidemiological methods[27]. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg, a diastolic blood pressure ≥ 90 mmHg, and/or the use of antihypertensive medication. Diabetes mellitus was defined as a fasting glucose level of ≥ 126 mg/dL (7.0

Table 1. Baseline characteristics of participants according to nonfasting and fasting status

	Nonfasting (<8 h)	Fasting (≥ 8h)
No, at risk	10 851	4057
Age, year	53 (44–61)	55 (48–61)
Men	4364 (40.2%)	1632 (40.2%)
Body mass index, kg/m^2	23.0 (21.1–25.2)	23.1 (21.2–25.2)
Systolic blood pressure, mmHg	132 (120–148)	132 (118–146)
Diastolic blood pressure, mmHg	80 (72–88)	82 (74–90)
Antihypertensive medication use	1472 (13.6%)	563 (13.9%)
Serum triglycerides, mmol/L	1.32 (0.94–1.93)	1.02 (0.76–1.45)
Serum triglycerides, mg/dL	117 (83–171)	90 (67–128)
Serum total cholesterol, mmol/L	4.94 (4.37–5.56)	5.28 (4.71–5.92)
Serum total cholesterol, mg/dL	191 (169–215)	204 (182–229)
Antihyperlipidemic medication	60 (0.6%)	75 (1.8%)
Diabetes mellitus	419 (3.9%)	394 (9.7%)
Current smokers	3135 (28.9%)	1034 (25.5%)
Current drinkers	3646 (33.6%)	1561 (38.5%)

Values were presented as median (25th–75th percentile) or number (proportion).

mmol/L), a nonfasting glucose level of ≥ 200 mg/dL (11.1 mmol/L), and/or the use of medications for diabetes mellitus.

Statistical Analysis

We calculated the median (25th–75th percentile) or the proportion of baseline characteristics in nonfasting and fasting participants. We used multiple indicators to verify the optimal cut-off points for nonfasting and fasting triglycerides. First, as a prerequisite, we confirmed the shape of a receiver operating characteristic (ROC) curves (arc-like or near-linear, and smoothness) and the area under ROC curves (AUC), known as the C-statistic, by continuous triglycerides in the univariable logistic regression model. In addition, we also confirmed the ROC curves in the survival models, namely the integrated time-dependent AUC[28] and the designated ROC curves, and AUC at 10, 15, 20, and 25 years of follow-up. Then, we identified optimal cut-off points of incident ischemic heart disease based on the C-statistic and Youden index defined as sensitivity + specificity − 1[18]. Those indicators were calculated by dichotomized concentrations of triglycerides, designated from 100 to 200 mg/dL (1.13–2.26 mmol/L) in increments of 5–25 mg/dL (0.06 or 0.28 mmol/L), using univariate logistic regression models. We also indicated Harrell's concordance statistic[29] calculated by the above-mentioned dichotomized triglyceride concentrations using univariate Cox proportional hazards regression models. The triglyceride concentration at which each of these indices showed a maximal value, identified as the optimal cut-off point.

To evaluate the performance of optimal triglyceride cut-off points in predicting ischemic heart disease, we calculated multivariable hazard ratios (HRs) with 95% confidence intervals (CIs) for ischemic heart disease according to the cut-off points of ≥ versus < triglyceride concentrations using Cox proportional hazard regression models. Further, we estimated population attributable fractions (PAFs)[30] of nonfasting and fasting triglyceride cut-off points and calculated 95% CIs[31] using the formula: PAF = Pe (RR − 1)/RR, where Pe is the exposure prevalence among cases and RR is the multivariable HR. Potential confounders were adjusted for age, sex, community, sex-specific quartiles of body mass index (kg/m^2), cigarette smoking status (never, former, and current 1–19 or ≥ 20 cigarettes per day), alcohol intake category (never, former, and current <46, 46–68, or ≥ 69 g ethanol per day), systolic blood pressure (mmHg), antihypertensive medication use (yes or no), serum total cholesterol (mg/dL), antihyperlipidemic medication use (yes or no), serum glucose category (normal, impaired glucose tolerance, and diabetes), time since last meal for nonfasting triglycerides (0–2 h, 2–3 h, and 3–8 h), and menopausal status (yes or no). We conducted Fine-Gray model analyses for competing risk of deaths and incident coronary heart disease events. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). All p-values were 2-tailed, and p-values <0.05 were considered statistically significant.

Table 2. Comparison of median (25th to 75th percentile) nonfasting and/or fasting triglycerides among previous population-based studies in the US and Europe and our study

	Country	Number of participants	Median age (25th–75th percentile), year	Nonfasting triglycerides		Fasting triglycerides	
				mg/dL	mmol/L	mg/dL	mmol/L
Copenhagen General Population Study, 2003–2009 [13]	Denmark	47351 men and women	55 (46–65)	124 (89–186)	1.4 (1.0–2.1)		
Copenhagen City Heart Study, 1991–1994/2001–2003 [13]	Denmark	10609 men and women	55 (46–65)	132 (97–195)	1.5 (1.1–2.2)		
Copenhagen Ischemic Heart Disease Study, 1991–2009 [13]	Denmark	15553 men and women	63 (56–71)	142 (97–204)	1.6 (1.1–2.3)		
Women's Health Study, 1992–1995 [9]	The US	6347 nonfasting and 19983 fasting women	53.8 (6.6) for nonfasting and 55.0 (7.2) for fasting[a]	133 (93–196)	1.5 (1.1–2.2)	115 (81–169)	1.3 (0.9–1.9)
Framingham Offspring Study, 1971–2008[b] [33]	The US	2056 men and women	54 (50–60)			94 (69–132)	1.1 (0.8–1.5)
Atherosclerosis Risk in Communities Study, 1987–2013[c] [33]	The US	6012 men and women	59 (56–62)			116 (86–160)	1.3 (1.0–1.8)
Circulatory Risk in Communities Study (our study), 1980–1994	Japan	10851 nonfasting and 4057 fasting men and women	53 (44–61) for nonfasting and 55 (48–61) for fasting	117 (83–171)	1.3 (0.9–1.9)	90 (67–128)	1.0 (0.8–1.5)

[a] Values are presented as mean (standard deviation).
[b] Mean triglycerides are presented. The first visit was conducted between 1971 and 1975, with follow-up visits every 3–4 years, and a final visit was conducted between 2005 and 2008.
[c] Mean triglycerides are presented. The first visit was conducted between 1987 and 1989, with follow-up visits every 2–3 years until 1998, and a final visit was conducted between 2011 and 2013.

Results

The baseline characteristics of the participants according to the nonfasting and fasting triglyceride levels are listed in **Table 1**. The nonfasting group had similar mean age, the proportion of men, mean values of body mass index, blood pressure levels, and proportion of antihypertensive medication use to the fasting group. However, the nonfasting group had lower proportions of antihyperlipidemic medication use, diabetes mellitus, and current drinkers, and a higher proportion of current smokers than the fasting group. The mean serum triglyceride levels were 27 mg/dL (0.30 mmol/L) higher and the mean serum cholesterol was 13 mg/dL (0.34 mmol/L) lower in the nonfasting group than in the fasting group.

Table 2 shows the comparison of triglyceride levels between previous population-based studies in the US and Europe and our study. The median value of nonfasting triglycerides ranged from 124 mg/dL (1.4 mmol/L) to 142 mg/dL (1.6 mmol/L) in previous studies, which was higher than the median of 117 mg/dL (1.3 mmol/L) noted our study. Additionally, the median value of fasting triglycerides ranged from 94 mg/dL (1.1 mmol/L) to 116 mg/dL (1.3 mmol/L) in previous studies, while this value was 90 mg/dL (1.0 mmol/L) in our study.

During median follow-ups of 23.1 years totaling 242916 person-years for nonfasting participants and 24.8 years totaling 88350 person-years for fasting participants, 256 and 83 incident cases of ischemic heart disease, respectively, were documented.

Fig. 1 shows the ROC curve for predicting ischemic heart disease by continuous nonfasting triglycerides in the univariable logistic regression model with an AUC of 0.621. **Fig. 2** shows corresponding ROC curves for survival models. The integrated time-dependent AUC was 0.622, and each time-dependent AUC was 0.578 for 10 years of follow-up, 0.569 for 15 years, 0.576 for 20 years, and 0.604 for 25 years.

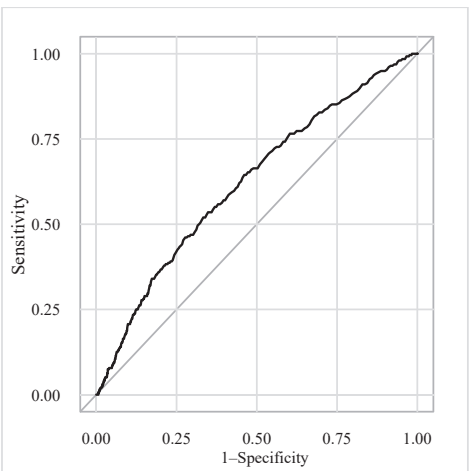

Fig. 1. ROC curve for predicting ischemic heart disease by nonfasting triglycerides in the univariable logistic regression model

The area under the ROC curve was 0.621.

The ROC of fasting triglycerides in the univariate logistic regression model is illustrated in **Fig. 3**, with an AUC of 0.649. **Fig. 4** shows the ROC curves for survival models. The integrated time-dependent AUC was 0.659, and each time-dependent AUC was 0.635 for 10 years, 0.662 for 15 years,

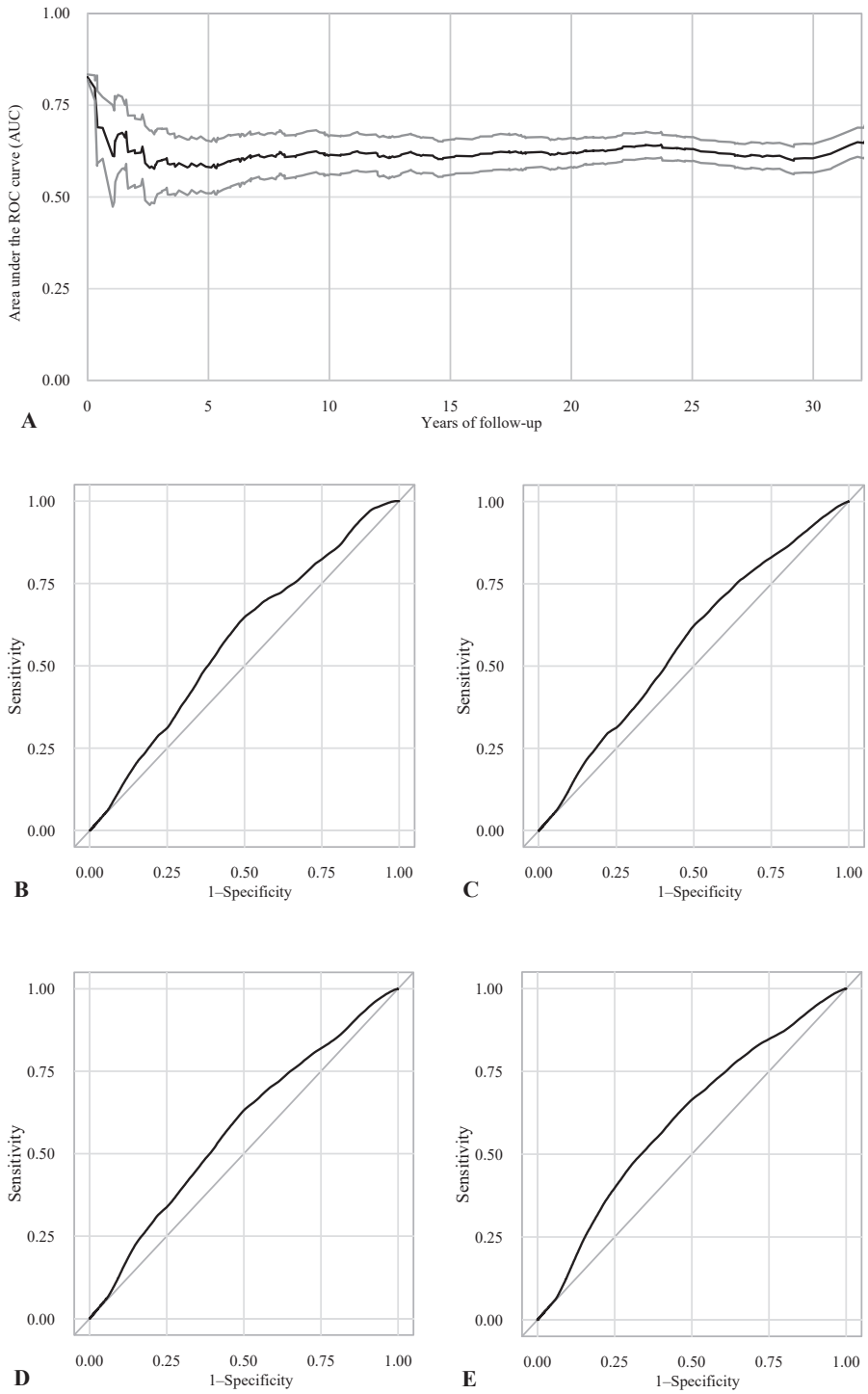

Fig. 2. ROC curves for predicting ischemic heart disease by nonfasting triglycerides in the survival model

(A) The time-dependent area under the ROC curve with 95% CIs according to years of follow-up; the integrated time-dependent area under the ROC curve was 0.622.
(B), (C), (D), and (E) The designated ROC curves at 10, 15, 20, and 25 years of follow-up, respectively; the areas under the ROC curves were 0.578, 0.569, 0.576, and 0.604, respectively.

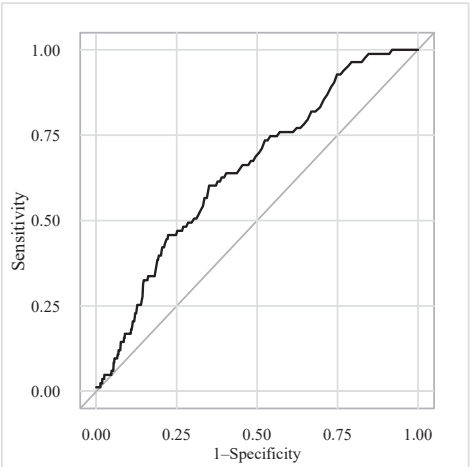

Fig. 3. ROC curve for predicting ischemic heart disease by fasting triglycerides in the univariable logistic regression model

The area under the ROC curve was 0.649.

0.646 for 20 years, and 0.633 for 25 years of follow-up.

Table 3 lists the sensitivity, specificity, C-statistic, and Youden index according to the different dichotomized concentrations of nonfasting triglycerides. The level of 145 mg/dL (1.64 mmol/L) was the optimal nonfasting cut-off point; 35.3% of the participants had triglyceride levels ≥ 145 mg/dL. The Youden index of 145 mg/dL was 0.187, and the AUC in the logistic model and Harrell's concordance statistic were almost the same (0.594 and 0.590, respectively). Similar results were observed at a cut-off point of 150 mg/dL.

Table 4 lists the related parameters according to different dichotomized concentrations of fasting triglycerides. The optimal fasting cut-off point was 110 mg/dL (1.24 mmol/L); 35.6 % of the participants had triglyceride levels ≥ 110 mg/dL. The Youden index of 110 mg/dL was 0.252, and AUC in the logistic model and Harrell's concordance statistic were 0.626 and 0.630, respectively.

The HRs with 95% CIs and PAFs for ischemic heart disease according to different nonfasting and fasting triglyceride cut-off points are shown in **Table 5**. For nonfasting triglycerides, after controlling for cardiovascular risk factors, the multivariable HR (95% CI) of ischemic heart disease was 1.43 (1.09–1.88) for the cut-off point of 145 mg/dL, which was higher than those of the other cut-off points except for 180 mg/dL, 190 mg/dL, and 200 mg/dL. The PAF was 16.1% (95% CI, 3.3%–27.2%), higher than those of the other cut-off points except for 110 mg/dL and 120 mg/dL. Similar results were observed for a cut-off point of 150 mg/dL. For fasting triglycerides, the corresponding multivariable HR (95% CI) was 1.69 (1.03–2.77) and the multivariable PAF (95% CI) was 24.6% (–0.3%–43.3%) for the cut-off point of 110 mg/dL, which were the highest HR and PAF among other cut-off points.

After considering the competing risk of death and incident ischemic heart disease, the nonfasting and fasting multivariable HRs and PAFs showed the peaks at 145 mg/dL and 110 mg/dL, respectively. However, the fasting HR and PAF were borderline significant **(Supplementary Table 2)**.

We show sex-specific optimal cut-off points of triglyceride concentrations at a nonfasting state **(Supplementary Tables 3–5 and Supplementary Figs. 1–4)**. The results at a fasting state are not shown because the number at risk and cases was too small for acquiring valid results. For men, triglyceride concentration of 140 mg/dL showed maximal AUC (0.581), Youden index (0.162), and Harrell's concordance statistic (0.575). Furthermore, 145 mg/dL showed nearly equal, namely 0.580, 0.160, and 0.573, respectively **(Supplementary Table 3)**. On the other hand, for women, the corresponding one of 120 mg/dL showed maximal AUC (0.598), Youden index (0.195), and Harrell's concordance statistic (0.600) **(Supplementary Table 4)**.

The HRs and PAFs for ischemic heart disease according to sex-specific different nonfasting triglyceride cut-off points are shown in **Supplementary Table 5**. Among men, the multivariable HR (95% CI) of ischemic heart disease was 1.36 (0.94–1.96), and the PAF (95% CI) was 15.5% (–4.2%–31.4%) for the cut-off point of 140 mg/dL. Similar results were observed for a cut-off point of 145 mg/dL. Among women, corresponding HR (95%CI) was 1.43 (0.92–2.23) and the PAF (95%CI) was 19.4% (–6.6%–39.0%) for the cut-off point of 120 mg/dL.

Discussion

Our long-term population-based study showed that the optimal triglyceride cut-off points for the evaluation of hypertriglyceridemia among the Japanese general population were 145 mg/dL for nonfasting and 110 mg/dL for fasting status, which were lower than those reported by current western guidelines. To the best of our knowledge, this is the first study to identify the optimal cut-off points of nonfasting and fasting triglycerides in Asian populations, which typically have lower triglyceride levels than western populations. Moreover, we first reported total and sex-specific optimal cut-off points of nonfasting and fasting triglycerides with the risk of incident ischemic

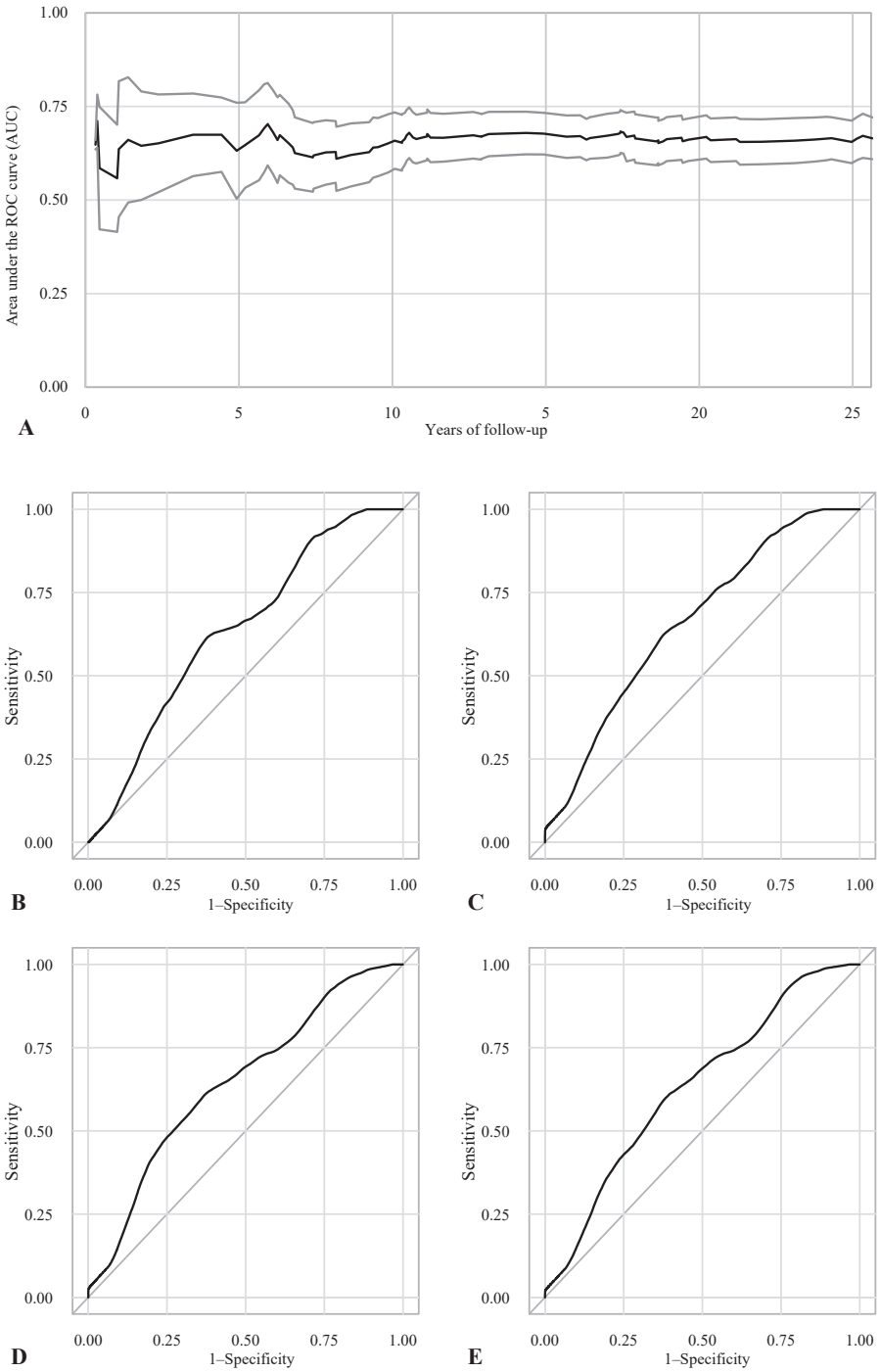

Fig. 4. ROC curves for predicting ischemic heart disease by fasting triglycerides in the survival model

(A) The time-dependent area under the ROC curve with 95% CIs according to years of follow-up; the integrated time-dependent area under the ROC curve was 0.659.
(B), (C), (D) and (E) The designated ROC curves at 10, 15, 20, and 25 years of follow-up, respectively; the areas under the ROC curves are 0.635, 0.662, 0.646, and 0.633, respectively.

Table 3. Identification of an optimal nonfasting triglyceride cut-off point for predicting ischemic heart disease (n=256) in 10,851 men and women

Nonfasting triglycerides, mg/dL	Population percentile, %[a]	Sensitivity, %[b]	Specificity, %[b]	C statistic (AUC)[b, c]	Youden index[d]	Harrell's concordance statistic[e]
100	62.00	76.6	38.4	0.575	0.149	0.574
110	55.20	71.5	45.2	0.584	0.167	0.585
120	48.70	66.0	51.7	0.589	0.178	0.590
130	43.30	59.8	57.1	0.584	0.168	0.584
135	40.50	57.0	59.9	0.585	0.169	0.583
140	37.80	55.1	62.6	0.589	0.177	0.586
145	**35.30**	**53.5**	**65.2**	**0.594**	**0.187**	**0.590**
150	32.80	50.4	67.6	0.590	0.180	0.585
155	30.50	46.9	69.9	0.584	0.167	0.577
160	28.60	46.1	71.9	0.590	0.180	0.584
165	26.80	43.8	73.6	0.587	0.174	0.581
170	25.30	41.8	75.1	0.585	0.169	0.580
175	23.80	39.1	76.5	0.578	0.156	0.574
180	22.30	38.3	78.1	0.582	0.164	0.579
190	19.80	35.9	80.6	0.583	0.166	0.582
200	17.40	33.2	82.9	0.581	0.161	0.580

[a] The proportion of participants with nonfasting triglyceride levels ≥ the cut-off point.
[b] Sensitivity, specificity, and AUC were calculated using the logistic model.
[c] AUC: area under the ROC curve.
[d] Youden index = sensitivity + specificity – 1.
[e] Harrell's concordance statistic provides overall concordance and was calculated using the survival model, which could take censored data into account.

Table 4. Identification of an optimal fasting triglyceride cut-off point for predicting ischemic heart disease (n=83) in 4057 men and women

Fasting triglycerides, mg/dL	Population percentile, %[a]	Sensitivity, %[b]	Specificity, %[b]	C statistic (AUC)[b, c]	Youden index[d]	Harrell's concordance statistic[e]
100	42.40	63.9	58.0	0.609	0.219	0.612
110	**35.60**	**60.2**	**64.9**	**0.626**	**0.252**	**0.630**
120	29.00	49.4	71.5	0.604	0.209	0.608
130	24.10	45.8	76.4	0.611	0.222	0.613
135	22.30	44.6	78.2	0.614	0.227	0.615
140	20.50	39.8	79.9	0.598	0.197	0.599
145	19.10	37.3	81.2	0.593	0.186	0.591
150	17.50	33.7	82.8	0.583	0.165	0.584
155	16.50	33.7	83.9	0.588	0.176	0.589
160	15.10	32.5	85.2	0.589	0.178	0.590
165	13.80	25.3	86.4	0.559	0.117	0.559
170	12.80	24.1	87.4	0.558	0.115	0.557
175	12.00	20.5	88.2	0.543	0.087	0.546
180	11.10	18.1	89.1	0.536	0.071	0.536
190	9.60	16.9	90.5	0.537	0.074	0.539
200	8.50	14.5	91.6	0.530	0.061	0.532

[a] The proportion of participants with fasting triglyceride levels ≥ the cut-off point.
[b] Sensitivity, specificity, and AUC were calculated using the logistic model.
[c] AUC: area under the ROC curve.
[d] Youden index = sensitivity + specificity – 1.
[e] Harrell's concordance statistic provides overall concordance and was calculated using the survival model, which could take censored data into account.

Table 5. Hazard ratios (HRs) and 95% confidence intervals (CIs) for ischemic heart disease according to different nonfasting and fasting triglyceride cut-off points in men and women

Triglycerides, mg/dL	No. at risks	Person-years	No. of events	Age, sex, and community adjusted HR (95% CI)	Multivariable HR (95% CI)	Population attributable fraction, %
Nonfasting triglycerides						
100	6725	150049	196	1.78 (1.33–2.39)	1.24 (0.91–1.70)	14.8 (-8.0–32.8)
110	5988	133624	183	1.82 (1.38–2.39)	1.32 (0.98–1.78)	17.3 (-2.0–33.0)
120	5282	117572	169	1.84 (1.42–2.39)	1.34 (1.00–1.78)	16.8 (-0.3–30.9)
130	4700	104517	153	1.76 (1.36–2.26)	1.27 (0.96–1.67)	12.7 (-2.7–25.8)
135	4398	97603	146	1.78 (1.38–2.28)	1.29 (0.98–1.69)	12.8 (-1.5–25.2)
140	4099	90605	141	1.86 (1.45–2.38)	1.35 (1.03–1.78)	14.3 (0.7–26.0)
145	**3826**	**84596**	**137**	**1.95 (1.52–2.49)**	**1.43 (1.09–1.88)**	**16.1 (3.3–27.2)**
150	3562	78668	129	1.91 (1.49–2.45)	1.40 (1.06–1.84)	14.4 (2.1–25.2)
155	3314	73060	120	1.84 (1.44–2.36)	1.32 (1.01–1.74)	11.4 (-0.4–21.7)
160	3099	68397	118	1.95 (1.52–2.50)	1.42 (1.08–1.87)	13.6 (2.4–23.6)
165	2909	64089	112	1.95 (1.52–2.50)	1.43 (1.09–1.88)	13.2 (2.5–22.6)
170	2742	60432	107	1.95 (1.51–2.50)	1.43 (1.08–1.88)	12.6 (2.2–21.8)
175	2588	57148	100	1.87 (1.45–2.41)	1.36 (1.03–1.79)	10.3 (0.4–19.3)
180	2419	53143	98	1.98 (1.53–2.55)	1.44 (1.09–1.91)	11.7 (2.1–20.4)
190	2144	47067	92	2.08 (1.60–2.69)	1.52 (1.14–2.01)	12.3 (3.3–20.4)
200	1892	41616	85	2.14 (1.64–2.78)	1.55 (1.16–2.07)	11.8 (3.3–19.5)
Fasting triglycerides						
100	1721	36915	53	1.92 (1.21–3.04)	1.36 (0.82–2.24)	16.9 (-13.7–39.3)
110	**1444**	**30627**	**50**	**2.20 (1.40–3.47)**	**1.69 (1.03–2.77)**	**24.6 (-0.3–43.3)**
120	1175	24968	41	1.87 (1.20–2.91)	1.42 (0.88–2.30)	14.6 (-7.4–32.1)
130	977	20839	38	2.09 (1.33–3.27)	1.56 (0.97–2.53)	16.4 (-3.2–32.3)
135	905	19240	37	2.22 (1.42–3.48)	1.65 (1.01–2.68)	17.6 (-1.4–32.9)
140	831	17767	33	1.96 (1.24–3.09)	1.46 (0.89–2.40)	12.5 (-5.7–27.6)
145	777	16595	31	1.92 (1.21–3.04)	1.46 (0.89–2.40)	11.8 (-5.4–26.1)
150	711	15181	28	1.80 (1.12–2.89)	1.34 (0.80–2.23)	8.6 (-8.0–22.6)
155	669	14284	28	1.94 (1.21–3.12)	1.46 (0.87–2.43)	10.6 (-5.4–24.3)
160	614	13094	27	2.03 (1.26–3.28)	1.49 (0.89–2.50)	10.7 (-4.8–23.9)
165	560	11972	21	1.54 (0.92–2.58)	1.13 (0.65–1.96)	2.9 (-11.4–15.4)
170	519	11055	20	1.56 (0.92–2.63)	1.12 (0.65–1.96)	2.6 (-11.1–14.6)
175	486	10422	17	1.32 (0.76–2.29)	0.95 (0.53–1.70)	-1.1 (-14.0–10.4)
180	450	9710	15	1.23 (0.69–2.19)	0.91 (0.50–1.67)	-1.8 (-13.6–8.8)
190	391	8365	14	1.29 (0.71–2.33)	0.97 (0.52–1.81)	-0.5 (-11.7–9.6)
200	346	7300	12	1.25 (0.67–2.34)	0.93 (0.48–1.80)	-1.1 (-11.3–8.2)

There were 10 851 nonfasting (< 8 h after meal) and 4057 fasting (≥ 8 h) participants.
Multivariable hazard ratio adjusted for age, sex, community, sex-specific quartiles of body mass index, systolic blood pressure, use of antihypertensive medication, serum total cholesterol, use of antihyperlipidemic medication, cigarette smoking status, alcohol intake status, serum glucose category, for women, menopause, and for nonfasting triglycerides, time since last meal.

heart disease, not including stroke. In our study, women's optimal cut-off point of nonfasting triglyceride concentrations (120 mg/dL) was lower than men's (140 mg/dL), although the HRs and PAFs did not reach statistical significance. It could be due to lower triglyceride levels and a lower incidence of ischemic heart disease in women than in men. Women's age- and community-adjusted mean of nonfasting triglyceride concentrations (returned after logarithmically being transformed and adjusted) was 115 mg/dL, and men's one was 131 mg/dL (p for difference <0.001). Women's age-adjusted incidence per 1,000 person-years of ischemic heart disease was 0.68 and men's one was 1.66 (p for difference <0.001).

The widely-used clinical guidelines indicate that fasting triglyceride concentrations above 150 mg/dL (1.69 mmol/L) were associated with an increased risk

of cardiovascular disease[32]. That cut-off points based on previous western studies have widely applied to other populations, some of which have a lower prevalence of dyslipidemia and lower mortality from ischemic heart disease, such as the Japanese population[32].

The data from a pooled analysis of the Framingham Offspring and Atherosclerosis Risk in Communities studies showed that widely accepted "normal" triglyceride ranges may not have been biologically optimal. The positive association between fasting triglyceride levels and cardiovascular disease risk was observed below the triglyceride level of 150 mg/dL[33]. Furthermore, the 2011 scientific statement from the AHA on triglycerides and cardiovascular disease focused on low fasting triglyceride levels that are commonly found in countries with low cardiovascular risk (Japan, Greece, etc.) or developing countries. They stated that according to data from observational studies and clinical trials, an optimal fasting triglyceride level might be <100 mg/dL, and an optimal nonfasting triglyceride level may be <150 mg/dL[15]. However, none of the studies for low-triglyceride populations has investigated the optimal cut-off point. Our study is the first to provide scientific evidence for the optimal cut-off point of triglyceride levels in Japanese populations with lower triglyceride levels and a lower risk of ischemic heart disease than western populations[21].

A hypothesis raised the possibility that atherogenesis may be a postprandial phenomenon of triglycerides metabolism in individuals without familial hyperlipoproteinemia[34]. This hypothesis has been supported by findings from population-based cohort studies that reported better predictive capabilities of nonfasting triglycerides on the risk of cardiovascular disease[6, 8-13]. Postprandial triglyceride-rich lipoprotein residues, composed of intermediate-density lipoproteins, very low-density lipoproteins, and chylomicron remnants, can penetrate the intima and occupy the subendothelial layer, contributing to the formation of atherosclerosis[34, 35]. In the nonfasting state, remnant lipoproteins in the blood originate from the liver and small intestine. The large-scale, population-based western studies indicated that the maximal mean increment between nonfasting triglycerides within 6 hours after habitual meals and fasting triglycerides was 26 mg/dL (0.29 mmol/L) in adults[8, 9, 36, 37]. A similar result was found between diabetic and non-diabetic individuals[36].

The present study provides comprehensive evidence and clinical insights into the optimal cut-off points to diagnose hypertriglyceridemia in nonfasting and fasting status in the Japanese general population. The optimal cut-off points were lower than those reported by clinical guidelines in the US and Europe. Nonfasting triglyceride measurements have several advantages. First, this approach allows the drawing of blood samples at any time of day, therefore, more convenient and acceptable for examinees. Second, it could reduce the burden on clinicians and laboratories by avoiding a large workload of blood tests in the morning. Third, nonfasting sampling could decrease the risk of hypoglycemia in patients with diabetes. Finally, the postprandial state predominates over a day, except for a short period in the early morning; hence, nonfasting triglycerides could better represent daily average concentrations and predict cardiometabolic risk.

As global standardization, triglyceride concentrations were measured after the elimination of free glycerol performed by the CDC; these are referred to as glycerol-blanked triglycerides. Glycerol-blanked triglycerides have also been used in Japan[38]. However, many western countries and most regions of China currently employ total glyceride measurement[39], and nonfasting triglyceride (including free glycerol) concentrations may be underestimated for individuals with high free glycerol concentrations during fasting[40]. Therefore, it is necessary to carefully interpret triglyceride concentrations based on whether the samples are glycerol-blanked triglycerides or total glycerides.

Our study had several strengths. First, this study includes the large sample sizes in participants and the prospective design with a follow-up of more than a median of 23 years among the Japanese general population. The sample sizes were larger, and the follow-up period was longer than those of the Women's Health Study (6391 participants; the number of developed incident cardiovascular diseases were 136 in 8 years and 353 in 17 years)[18]. Second, we identified the optimal cut-off point of triglyceride levels for ischemic heart disease both at nonfasting and fasting status while only nonfasting identified optimal cut-off point in the Women's Health Study[18]. Third, we showed sex-specific optimal cut-off points, meanwhile only women in the previous study above[18]. Fourth, in addition to the ROC curves plotted using logistic regression models, we analyzed the ROC curves using the survival models, such as the integrated time-dependent AUC, the ROC curves, and AUC at 10, 15, 20, and 25 years of follow-up, and Harrell's concordance statistic. Fifth, we estimated not only the HRs but also the PAFs at each cut-off point considering the competing risk of deaths and incident ischemic heart disease. Finally, the outcome in our study was incident ischemic heart disease

events, but not incident stroke or incident atherosclerotic cardiovascular disease (stroke and ischemic heart disease). Since the ROC curves were almost linear in stroke or atherosclerotic cardiovascular diseases, it was not appropriate to identify its optimal cut-off point.

Our study had several limitations. First, the single measurement of triglyceride concentrations could lead to a regression dilution bias due to its variability. Average triglycerides over time had greater discrimination for cardiovascular risk compared to a single triglyceride measurement (C-statistic, 0.60 vs. 0.57)[33]. Second, we did not consider long-term changes in the cardiovascular risk factors. Third, our study could not rule out residual confounding or confounding by unmeasured variables. Fourth, it should be cautious about confirming sex-specific optimal cut-off points because the HRs and PAFs of optimal cut-off points did not reach statistical significance. Therefore, a larger sample-sized study would be needed. Fifth, optimal cut-off points might differ among communities depending on serum triglyceride levels and the incidence of ischemic heart disease. Still, we could not estimate community-specific optimal cut-off points due to insufficient numbers at risk and cases. However, the difference in triglyceride levels between the rural and urban areas was not very large, e.g., age- and sex-adjusted means of nonfasting triglyceride concentrations were 120 mg/dL in the rural areas and 126 mg/dL in the urban area, and the corresponding fasting triglyceride concentrations were 97 mg/dL and 94 mg/dL (p=0.087), respectively. Moreover, age-adjusted incidences per 1,000 person-years of ischemic heart disease were not significantly different between the rural and urban areas: 1.78 vs. 1.31 in men (p=0.103) and 0.65 vs. 0.47 in women (p=0.144). Further, the HRs and PAFs adjusted by covariates, including communities, provided the validity of the optimal cut-off points. Therefore, the optimal cut-off points identified in this study can be generalizable to the other populations with lower triglyceride levels and lower incidence of ischemic heart disease than western populations. Sixth, the multiple HRs for evaluating the identified optimal cut-off points were not adjusted for high-density lipoprotein and low-density lipoprotein because they were available only 37% and none of the participants, respectively, at the time of baseline. However, we adjusted for serum total cholesterol and antihyperlipidemic medication use. Finally, we built the baseline period as 15 years long because a sufficient number at risk and cases were needed to verify optimal cut-off points in the nonfasting and fasting status. However, the nonfasting optimal cut-off point of 145 mg/dL did not change by using the baseline values for ten years between 1980 and 1989 (data not shown), while the fasting one was not enough for the analysis (data not shown).

Conclusion

In conclusion, the present study showed optimal cut-off points of nonfasting and fasting triglycerides in the Japanese general population were 145 mg/dL and 110 mg/dL, respectively. Given the growing evidence from population-based studies confirming that nonfasting triglycerides have adequate diagnostic potential to replace fasting triglyceride measurements, our study provided evidence that a cut-off point of nonfasting triglycerides around 145 mg/dL is useful for preventing and controlling ischemic heart disease in the Japanese general population. Moreover, our estimates were lower than the current cut-off points recommended in the US and Europe.

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Conflict of Interest

None.

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Supplementary Table 1. The community-specific number and the proportion according to the nonfasting and fasting status

	Nonfasting	Fasting
	n	*n*
Ikawa	1486 (53.0%)	1316 (47.0%)
Noichi	3082 (89.8%)	351 (10.2%)
Kyowa	4544 (88.8%)	573 (11.2%)
Minami-Takayasu	1739 (48.9%)	1817 (51.1%)
Total	10851 (72.8%)	4057 (27.2%)

The percentages in parenthesis show the proportion in each nonfasting and fasting.

Supplementary Table 2. Hazard ratios (HRs) and 95% confidence intervals (CIs) for ischemic heart disease according to different nonfasting and fasting triglyceride cut-off points in men and women by the analyses for competing risk of death and incident coronary heart disease events

Triglycerides, mg/dL	No. at risks	Person-years	No. of events	Age, sex, and community adjusted HR (95%CI)	Multivariable HR (95%CI)	Population attributable fraction, %
Nonfasting triglycerides, mg/dL						
100	6725	150 049	196	1.83 (1.36–2.45)	1.25 (0.92–1.71)	15.3 (-7.2–33.1)
110	5988	133 624	183	1.86 (1.42–2.45)	1.33 (0.98–1.79)	17.7 (-1.7–33.4)
120	5282	117 572	169	1.88 (1.44–2.44)	1.33 (0.99–1.79)	16.4 (-1.2–30.9)
130	4700	104 517	153	1.78 (1.38–2.30)	1.26 (0.95–1.67)	12.3 (-3.4–25.7)
135	4398	97 603	146	1.79 (1.39–2.30)	1.27(0.95–1.68)	12.1 (-3.0–25.0)
140	4099	90 605	141	1.86 (1.45–2.39)	1.33 (1.00–1.76)	13.7 (-0.4–25.8)
145	**3826**	**84 596**	**137**	**1.95 (1.52–2.51)**	**1.41 (1.06–1.86)**	**15.6 (2.4–27.0)**
150	3562	78 668	129	1.92 (1.49–2.46)	1.37 (1.04–1.82)	13.6 (1.0–24.6)
155	3314	73 060	120	1.84 (1.44–2.36)	1.30 (0.98–1.72)	10.8 (-1.3–21.5)
160	3099	68 397	118	1.96 (1.53–2.51)	1.40 (1.05–1.86)	13.2 (1.5–23.5)
165	2909	64 089	112	1.95 (1.52–2.51)	1.40 (1.06–1.86)	12.5 (1.5–22.3)
170	2742	60 432	107	1.96 (1.52–2.52)	1.40(1.06–1.85)	11.9 (1.5–21.3)
175	2588	57 148	100	1.88 (1.45–2.42)	1.33 (1.01–1.75)	29.9 (-5.5–53.4)
180	2419	53 143	98	1.98 (1.53–2.55)	1.41 (1.07–1.86)	11.1 (1.5–19.8)
190	2144	47 067	92	2.08 (1.60–2.69)	1.49 (1.13–1.96)	11.8 (2.9–19.9)
200	1892	41 616	85	2.15 (1.65–2.80)	1.53 (1.16–2.04)	11.5 (3.1–19.2)
Fasting triglycerides, mg/dL						
100	1721	36 915	53	1.93 (1.21–3.06)	1.32 (0.80–2.20)	15.5 (-15.9–38.4)
110	**1444**	**30 627**	**50**	**2.20 (1.39–3.48)**	**1.62 (0.99–2.68)**	**23.1 (-2.6–42.3)**
120	1175	24 968	41	1.87 (1.20–2.93)	1.39 (0.87–2.21)	13.9 (-7.9–31.2)
130	977	20 839	38	2.10 (1.33–3.31)	1.54 (0.95–2.49)	16.1 (-3.7–32.1)
135	905	19 240	37	2.21 (1.40–3.49)	1.60 (0.98–2.60)	16.7 (-2.4–32.3)
140	831	17 767	33	1.97 (1.24–3.15)	1.45 (0.88–2.38)	12.3 (-5.9–27.5)
145	777	16 595	31	1.92 (1.20–3.08)	1.43 (0.86–2.37)	11.2 (-6.4–25.9)
150	711	15 181	28	1.81 (1.12–2.93)	1.33 (0.79–2.24)	8.4(-8.5–22.6)
155	669	14 284	28	1.95 (1.21–3.16)	1.47 (0.87–2.47)	10.8 (-5.4–24.5)
160	614	13 094	27	2.04(1.26–3.32)	1.50 (0.89–2.54)	10.8 (-4.8–24.1)
165	560	11 972	21	1.55 (0.92–2.61)	1.13 (0.64–2.00)	2.9(-11.8–15.7)
170	519	11 055	20	1.57 (0.93–2.64)	1.14 (0.64–2.02)	3.0(-11.1–15.3)
175	486	10 422	17	1.35 (0.77–2.36)	0.99 (0.54–1.83)	-0.2 (-13.6–11.6)
180	450	9710	15	1.27 (0.71–2.27)	0.94 (0.50–1.76)	-1.2 (-13.5–9.8)
190	391	8365	14	1.32 (0.73–2.40)	1.00 (0.52–1.90)	0.0(-11.5–10.4)
200	346	7300	12	1.25 (0.67–2.35)	0.93 (0.47–1.88)	-1.1 (-11.9–8.7)

There were 10 851 nonfasting (<8 h after meal) and 4057 fasting (≥ 8 h) participants.
Multivariable hazard ratio adjusted for age, sex, community, sex-specific quartiles of body mass index, systolic blood pressure, use of antihypertensive medication, serum total cholesterol, use of antihyperlipidemic medication, cigarette smoking status, alcohol intake status, serum glucose category, for women, menopause, and for nonfasting triglycerides, time since last meal.

Supplementary Table 3. Identification of an optimal nonfasting triglyceride cut-off points for predicting ischemicheart disease (n=152) in 4364 men

Nonfasting triglycerides, mg/dL	Population percentile[a]	Sensitivity, %[b]	Specificity, %[b]	C statistic (AUC)[b, c]	Youden index[d]	Harrell's concordance statistic[e]
100	33.6%	78.3	34.1	0.562	0.124	0.551
110	40.0%	72.4	40.4	0.564	0.128	0.559
120	46.2%	67.1	46.7	0.569	0.138	0.566
130	51.4%	61.8	51.9	0.569	0.137	0.567
135	54.4%	59.9	54.9	0.574	0.148	0.571
140	**57.1%**	**58.6**	**57.6**	**0.581**	**0.162**	**0.575**
145	59.5%	55.9	60.0	0.580	0.160	0.573
150	61.8%	52.6	62.3	0.575	0.150	0.569
155	64.0%	50.7	64.6	0.576	0.152	0.567
160	66.1%	49.3	66.6	0.58	0.160	0.572
165	68.2%	46.1	68.7	0.574	0.147	0.568
170	69.9%	44.1	70.4	0.572	0.145	0.568
175	71.2%	40.8	71.7	0.562	0.125	0.559
180	72.6%	39.5	73.1	0.563	0.126	0.560
190	75.3%	38.8	75.8	0.573	0.146	0.571
200	77.9%	34.9	78.3	0.566	0.132	0.567

[a]The proportion of participants with nonfasting triglyceride levels ≥ the cut-off point.
[b]Sensitivity, specificity, and AUC were calculated using logistic models.
[c]AUC: area under the ROC curve.
[d]Youden index=sensitivity+specificity–1.
[e]Harrell's concordance statistic provides overall concordance and was calculated using the survival model, which can take censored data into account.

Supplementary Table 4. Identification of an optimal nonfasting triglyceride cut-off points for predicting ischemic heart disease (n=104) in 6487 women

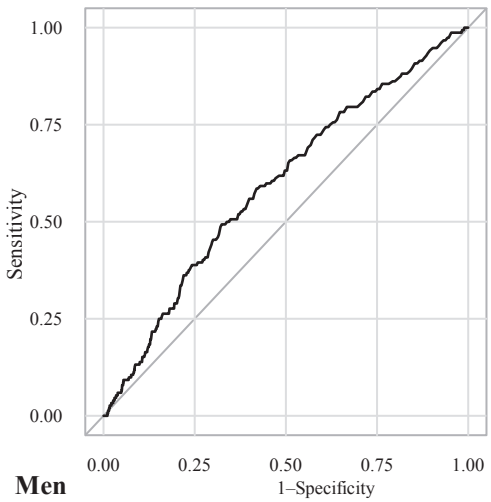
Nonfasting triglycerides, mg/dL	Population percentile[a]	Sensitivity, %[b]	Specificity, %[b]	Cstatistic (AUC)[b, c]	Youden index[d]	Harrell's concordance statistic[e]
100	41.0%	74.0	41.2	0.576	0.153	0.584
110	48.1%	70.2	48.4	0.593	0.186	0.599
120	**54.8%**	**64.4**	**55.1**	**0.598**	**0.195**	**0.600**
130	60.2%	56.7	60.5	0.586	0.172	0.585
135	62.9%	52.9	63.2	0.58	0.160	0.577
140	65.7%	50.0	65.9	0.58	0.159	0.577
145	68.3%	50.0	68.6	0.593	0.186	0.589
150	70.8%	47.1	71.1	0.591	0.182	0.585
155	73.1%	41.3	73.4	0.573	0.147	0.567
160	75.1%	41.3	75.3	0.583	0.167	0.576
165	76.6%	40.4	76.8	0.586	0.172	0.578
170	78.0%	38.5	78.3	0.584	0.167	0.577
175	79.5%	36.5	79.7	0.581	0.163	0.575
180	81.1%	36.5	81.4	0.59	0.179	0.583
190	83.6%	31.7	83.8	0.578	0.156	0.574
200	85.7%	30.8	86.0	0.584	0.168	0.579

[a]The proportion of participants with nonfasting triglyceride levels ≥ the cut-off point.
[b]Sensitivity, specificity, and AUC were calculated using logistic models.
[c]AUC: area under the ROC curve.
[d]Youden index=sensitivity+specificity–1.
[e]Harrell's concordance statistic provides overall concordance and was calculated using the survival model, which can take censored data into account.

Supplementary Table 5. Sex-specific hazard ratios (HRs) and 95% confidence intervals (CIs) for ischemic heart disease according to different nonfasting triglyceride cut-off points

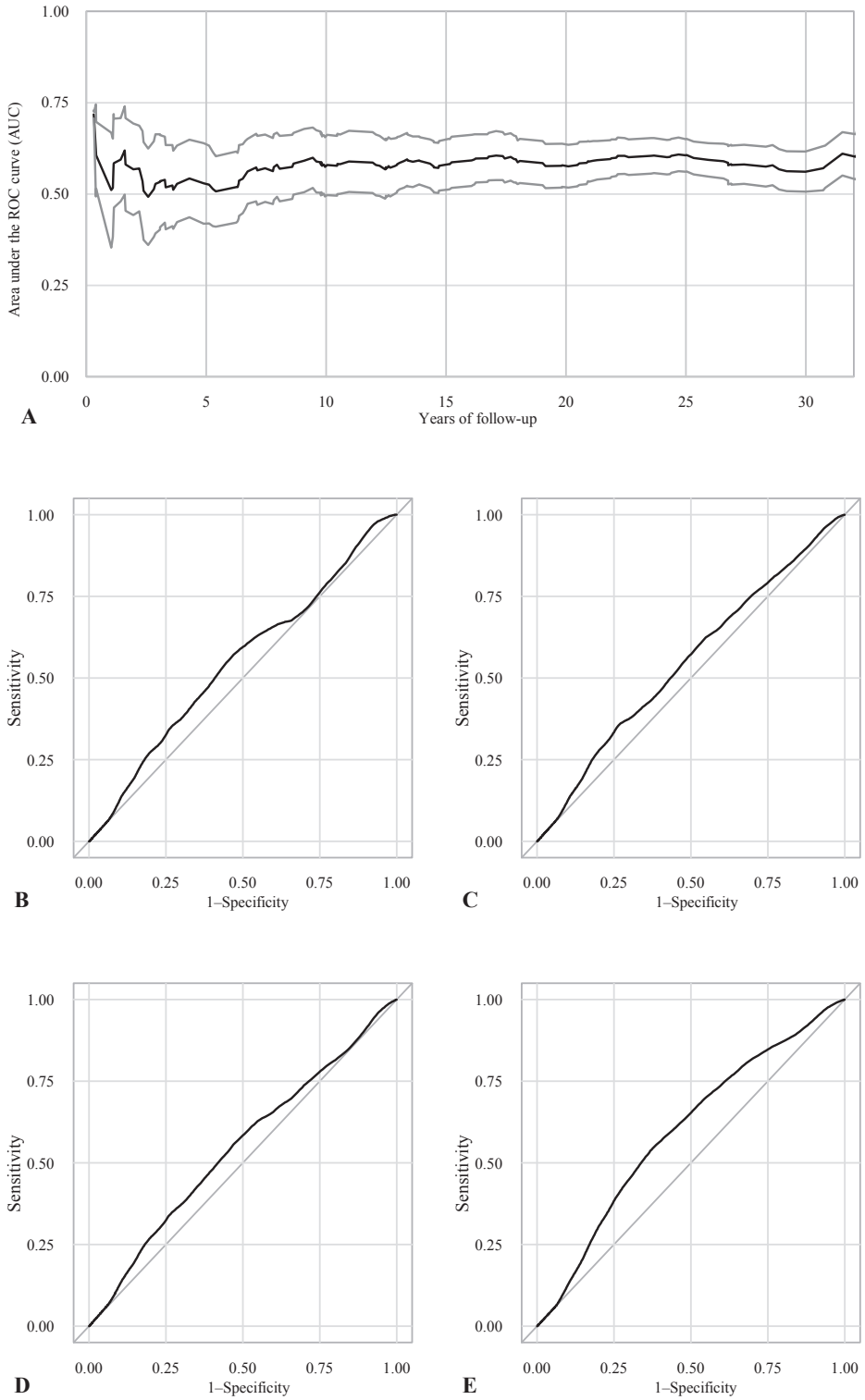
Nonfasting triglycerides, mg/dL	No. at risks	Person-years	No. of events	Age and community adjusted HR (95% CI)	Multivariable HR (95% CI)	Population attributable fraction, %
Men						
100	2896	61583	119	1.88 (1.27–2.78)	1.23 (0.80–1.87)	14.6 (-18.7–38.6)
110	2619	55776	110	1.81 (1.26–2.60)	1.20 (0.80–1.78)	12.1 (-17.1–34.0)
120	2349	49944	102	1.83 (1.30–2.59)	1.21(0.83–1.77)	11.6 (-13.5–31.3)
130	2120	45156	94	1.80 (1.29–2.51)	1.20 (0.83–1.73)	10.3 (-12.2–28.3)
135	1991	42307	91	1.89 (1.36–2.63)	1.26 (0.87–1.82)	12.4 (-8.8–29.4)
140	**1873**	**39723**	**89**	**2.01 (1.45–2.79)**	**1.36 (0.94–1.96)**	**15.5 (-4.2–31.4)**
145	1768	37498	85	2.01 (1.45–2.78)	1.36 (0.95–1.96)	14.8 (-3.7–30.0)
150	1666	35323	80	1.94 (1.40–2.68)	1.30 (0.91–1.87)	12.1 (-5.7–27.0)
155	1570	33267	77	1.96 (1.42–2.72)	1.30 (0.91–1.87)	11.7 (-5.5–26.1)
160	1481	31432	75	2.03 (1.46–2.80)	1.36 (0.95–1.95)	13.1 (-3.2–26.8)
165	1389	29512	70	1.95 (1.41–2.70)	1.31 (0.91–1.88)	10.9 (-4.8–24.2)
170	1314	27935	67	1.94 (1.40–2.69)	1.31 (0.91–1.87)	10.4 (-4.5–23.2)
175	1255	26732	62	1.82 (1.31–2.52)	1.20 (0.83–1.73)	6.8 (-7.9–19.5)
180	1194	25384	60	1.86 (1.34–2.59)	1.23 (0.85–1.77)	7.4 (-6.7–19.6)
190	1080	22974	59	2.08 (1.49–2.90)	1.42 (0.98–2.04)	11.5 (-1.5–22.8)
200	966	20629	53	2.02 (1.44–2.83)	1.35 (0.93–1.96)	9.0 (-3.1–19.8)
Women						
100	3829	88466	77	1.47 (0.94–2.29)	1.20 (0.75–1.93)	12.3 (-24.1–38.1)
110	3369	77848	73	1.62 (1.05–2.49)	1.40 (0.89–2.22)	20.1 (-9.6–41.7)
120	**2933**	**67628**	**67**	**1.65 (1.09–2.49)**	**1.43 (0.92–2.23)**	**19.4 (-6.6–39.0)**
130	2580	59361	59	1.50 (1.01–2.23)	1.27 (0.83–1.96)	12.1 (-11.7–30.8)
135	2407	55296	55	1.44 (0.97–2.14)	1.21(0.79–1.86)	9.2 (-13.5–27.3)
140	2226	50882	52	1.47 (0.99–2.18)	1.25 (0.82–1.91)	10.0 (-10.8–26.9)
145	2058	47098	52	1.66 (1.12–2.47)	1.43 (0.93–2.18)	15.0 (-4.5–30.9)
150	1896	43345	49	1.68 (1.13–2.48)	1.45 (0.95–2.21)	14.6 (-3.6–29.6)
155	1744	39793	43	1.50 (1.01–2.23)	1.26 (0.82–1.94)	8.5 (-8.9–23.1)
160	1618	36965	43	1.66 (1.11–2.47)	1.40 (0.91–2.15)	11.8 (-4.8–25.8)
165	1520	34576	42	1.75 (1.17–2.60)	1.46 (0.95–2.25)	12.7 (-3.3–26.2)
170	1428	32497	40	1.75 (1.17–2.61)	1.46 (0.95–2.26)	12.1 (-3.2–25.2)
175	1333	30416	38	1.74 (1.16–2.62)	1.47 (0.95–2.28)	11.7 (-3.1–24.3)
180	1225	27759	38	1.94 (1.29–2.92)	1.64 (1.06–2.55)	14.3 (0.0–26.4)
190	1064	24093	33	1.86 (1.22–2.83)	1.51 (0.96–2.39)	10.7 (-2.6–22.3)
200	926	20986	32	2.10 (1.37–3.21)	1.76 (1.11–2.79)	13.3 (0.8–24.2)

There were 4364 male and 6487 female nonfasting participants.
Multivariable hazard ratio adjusted for age, community, quartiles of body mass index, systolic blood pressure, use of antihypertensive medication, serum total cholesterol, use of antihyperlipidemic medication, cigarette smoking status, alcohol intake status, serum glucose category, time since last meal, and for women, menopause.



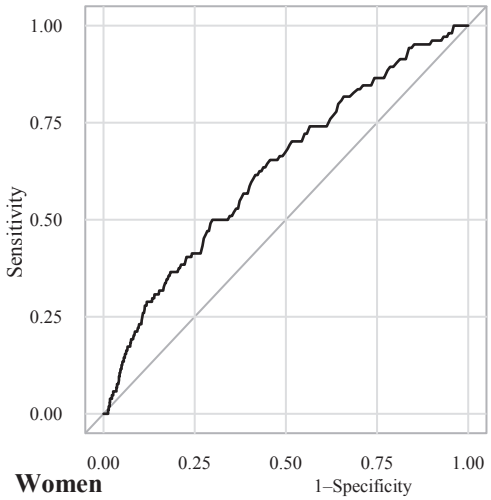
Supplementary Fig. 1. Receiver Operating Characteristic (ROC) curve for predicting ischemic heart disease by nonfasting triglycerides in the univariable logistic regression model in men

The area under the ROC curve was 0.595.



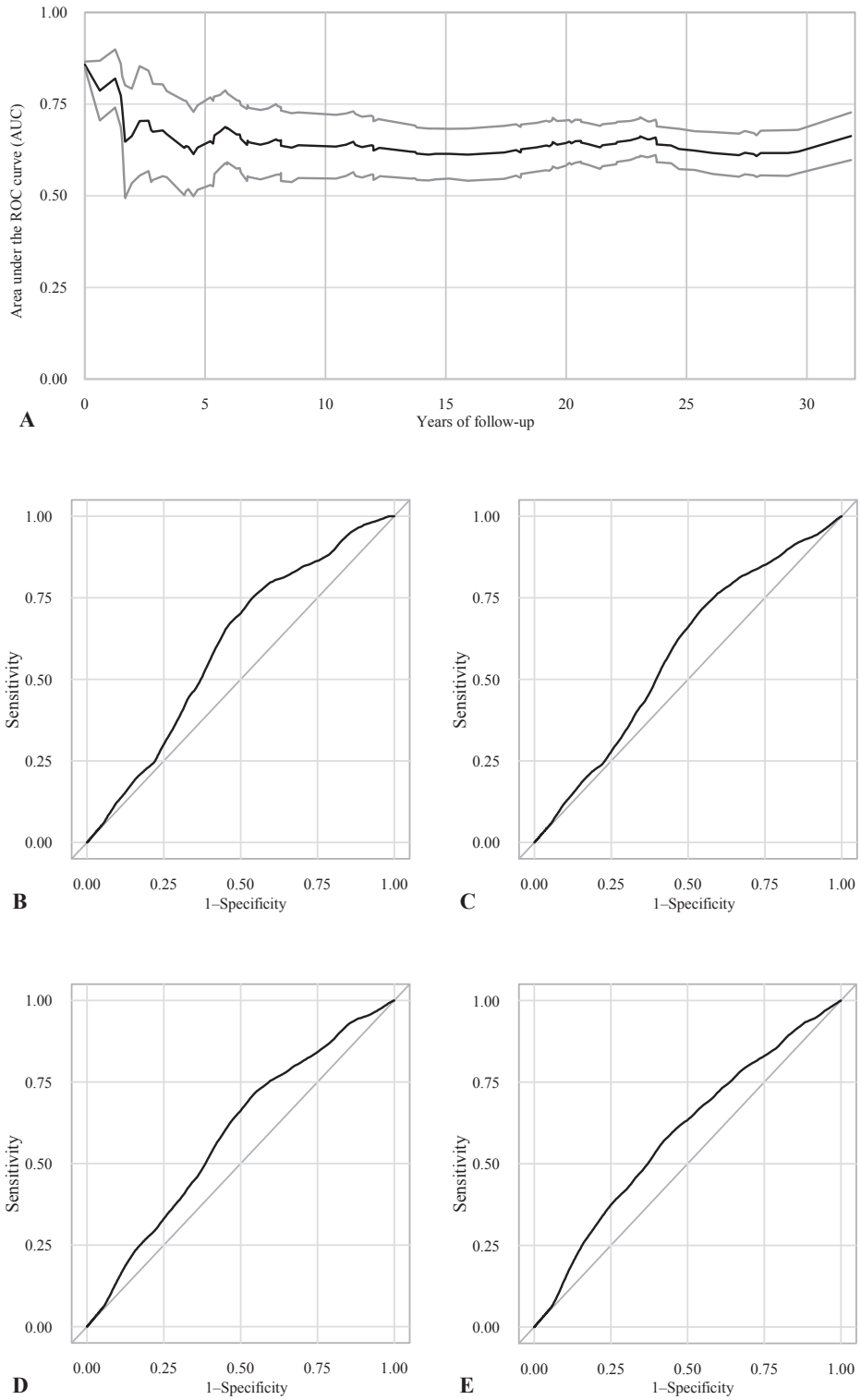
Supplementary Fig. 2. Receiver operating characteristics (ROC) curves for predicting ischemic heart disease by nonfasting triglycerides in the survival model among men

(A) The time-dependent area under the ROC curve with 95% confidence intervals according to years of follow-up; the integrated time-dependent area under the ROC curve was 0.583.
(B), (C), (D), and (E) The designated ROC curves at 10, 15, 20, and 25 years of follow-up, respectively; the areas under the ROC curves were 0.549, 0.549, 0.546, and 0.597, respectively.



Supplementary Fig. 3. Receiver Operating Characteristic (ROC) curve for predicting ischemic heart disease by nonfasting triglycerides in the univariable logistic regression model in women

The area under the ROC curve was 0.630.



Supplementary Fig. 4. Receiver operating characteristics (ROC) curves for predicting ischemic heart disease by nonfasting triglycerides in the survival model among women

(A) The time-dependent area under the ROC curve with 95% confidence intervals according to years of follow-up; the integrated time-dependent area under the ROC curve was 0.646.
(B), (C), (D), and (E) The designated ROC curves at 10, 15, 20, and 25 years of follow-up, respectively; the areas under the ROC curves were 0.603, 0.578, 0.590, and 0.589, respectively.