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Original Article

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Serum High-Sensitivity Cardiac Troponin T as an Independent Predictor for Incident Coronary Heart Disease in the Japanese General Population: The Circulatory Risk in Communities Study (CIRCS)

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Aims: Epidemiological evidence is extremely limited about high-sensitivity cardiac troponin T (hs-cTnT) and future coronary heart disease (CHD) events for the general population in countries with low mortality from CHD. Therefore, we investigated the association between hs-cTnT levels and the risk of incident CHD using a nested case–control study in a large Japanese cohort study.

Methods: The participants were residents of four Japanese communities in the Circulatory Risk in Communities Study (CIRCS). We obtained 120 cases (81 men and 39 women, aged 38–86 years at baseline) of first incident CHD and 240 controls matched by age, sex, communities, and blood sampling term. Serum hs-cTnT levels were measured using an electrochemiluminescence immunoassay with stored sera collected between 2001 and 2011. The median period between sampling at survey and CHD incidence was 2.0 (interquartile range, 0.9–3.7) years. After adjusting for conventional risk factors, the multivariable odds ratios (ORs) of CHD were calculated using conditional logistic regression analyses.

Results: hs-cTnT ranged from ≤ 3 (assay detection limit) to 155 ng/L. Compared with the lowest quartile of hs-cTnT, multivariable ORs (95% confidence intervals) of CHD for the second, third, and highest quartiles were 1.30 (0.57–2.95), 2.48 (1.09–5.64), and 3.01 (1.27–7.12), respectively. Similar associations were observed after adjusting for estimated glomerular filtration, or after excluding matched groups, including people with chronic kidney disease.

Conclusion: Serum hs-cTnT could predict CHD in the Japanese general population. These findings implicate a benefit from monitoring hs-cTnT to predict CHD even among populations in countries with low mortality from CHD.

Key words: High-sensitivity cardiac troponin T, Coronary heart disease, Incidence, Nested case-control study, General population

Abbreviations: hs-cTnT, high-sensitivity cardiac troponin T; hs-cTn, high-sensitivity cardiac troponin; CHD, coronary heart disease; CIRCS, Circulatory Risk in Communities Study; OR, odds ratio; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; BMI, body mass index; CI, confidence interval; CT, computed tomography; hs-cTnI, high-sensitivity cardiac troponin I

Introduction

The mortality from heart disease is growing and remains the leading cause of death worldwide for the last 20 years. Notably, 16% of the world's total deaths in 2019 were reportedly caused by ischemic heart disease[1]. In contrast, some countries report lower mortality from coronary heart disease (CHD), including Japan, Greece, and China[2]. However, in Japan, the population levels of conventional risk factors such as hypercholesterolemia and diabetes mellitus have increased[3]. We have previously reported increased incidence of CHD in a suburban area of Japan, which was the first among Asian communities[4]. In addition to controlling conventional risk factors to prevent CHD, biomarkers that can predict coronary events remain crucial.

One potential predictor is high-sensitivity cardiac troponin (hs-cTn), which has high myocardial tissue specificity and high clinical sensitivity beyond the creatine kinase myocardial band and is recommended as the first requirement for the diagnosis of any type of myocardial infarction[5]. Additionally, recently accumulated epidemiological data[6-8] suggest the possibility of using hs-cTn as a predictor of cardiovascular events.

Aims

Most of these studies are based on data from Western populations, and evidence for countries with low mortality from CHD, such as Japan and China, remains extremely limited[8]. Therefore, we investigated the association between serum high-sensitivity cardiac troponin T (hs-cTnT) and the risk of incident CHD in a nested case-control study based on a large Japanese cohort.

Methods

Study Population

The study population comprised a total of 69,758 (26,250 men and 43,508 women), aged 38–86 years at the 2001–2011 baseline surveys of the Circulatory Risk in Communities Study (CIRCS)[9], an ongoing dynamic community cohort study since 1963. We used a nested case-control study design. The participants were from four communities: Ikawa town (a rural community in the Akita Prefecture of northwestern Japan), Minami-Takayasu district in Yao City (a southwestern suburb community in the Osaka Prefecture of mid-west Japan), Noichi district in Konan City (a rural community in the Kochi Prefecture of southwestern Japan), and Kyowa district in Chikusei City (a rural community in Ibaraki Prefecture in central Japan). Informed consent was implied by participation in cardiovascular risk factor surveys. According to the Council for International Organizations of Medical Science guidelines[10], it was obtained from representatives in communities, which was a common practice at that time in Japan. This study was approved by the ethics committees of Osaka Medical Center for Health Science and Promotion and Osaka University.

Follow-Up and Ascertainment of Cases

The first-ever incidences of CHD between April 2002 and February 2014 were ascertained by systematic active surveillance. As the details of endpoint determination have been described in a previous CIRCS report[3, 11], the ascertainment system for cardiovascular diseases in CIRCS has used the same epidemiological diagnostic criteria throughout all study periods. CHD endpoints were first screened from death certificates, national insurance claims, annual questionnaires, annual cardiovascular risk surveys, and reports by local physicians, public health nurses, or health volunteers. All living patients were telephoned, visited, or invited to participate in risk factor surveys; alternatively, a medical history at onset was obtained from their families to confirm the diagnosis. Furthermore, medical records from local clinics and hospitals were reviewed. In cases of death, histories at onset were obtained from families or attending physicians, and medical records were reviewed. The criteria for CHD were modified from those established by the World Health Organization Expert Committee[12]. CHD was defined as definite or probable cases of myocardial infarction, definite cases of angina pectoris, and sudden death, including sudden cardiac death. Definite myocardial infarction was diagnosed as typical severe chest pain (lasting at least 30 min) accompanied by the appearance of new abnormal and persistent Q or QS waves, consistent changes in cardiac enzyme levels, or both. Probable myocardial infarction was indicated by typical chest pain, but electrocardiographic findings or findings related to enzyme activity were unavailable. Angina

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pectoris was defined as repeated episodes of chest pain during activity, especially when walking, usually disappearing rapidly after the cessation of activity or after taking sublingual nitroglycerin. Death within 24 h of onset was defined as sudden death, and sudden cardiac death was defined as death within 1 h of onset, witnessed cardiac arrest, or abrupt collapse not preceded by more than 1 h of symptoms.

The first-ever incidence of CHD in our survey was 216. These cases were randomly matched with two controls using the combination of the SAS System for Windows (version 9.4; SAS Institute Inc., Cary, NC, USA) and the many-to-many function by Microsoft Office Access (Microsoft Corporation, Redmond, WA, USA) matching by age (±0 year old), sex, communities, and sampling term (day's difference; median 4 days, range 0–19 days). Overall, a total of 120 cases (81 men and 39 women) fully matched with two controls were extracted. Some cases had a history of other cardiovascular diseases (six of prior stroke and seven of atrial fibrillation). The median period between sampling at survey and CHD incidence was 2.0 (interquartile range 0.9–3.7) years.

Baseline Examination

Serum samples were collected at annual examinations and stored at −80℃ in an ultracold freezer until analysis. Blood was collected into plastic serum separator gel tubes, and the serum was separated by centrifugation within 30 min. Samples for measuring hs-cTnT were selected from sera collected before CHD onset and stored from 2001 to 2011. Serum hs-cTnT levels were determined using an ECLusys Troponin T highly sensitive assay (Roche Diagnostics KK, Tokyo, Japan) via an electrochemiluminescence immunoassay method. The assay was performed on a chemical analyzer (Hitachi/Roche Modular Analytics) at Kotobiken Medical Laboratories (Tsukuba, Japan).

Serum glucose, total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, and creatinine were measured using an Autoanalyzer AU2700 (Olympus Corp., Tokyo, Japan) at the annual examination, measured at the laboratory of the Osaka Medical Center for Health Science and Promotion, an international member of the US National Cholesterol Reference Method Laboratory Network. Laboratory tests have been standardized since 1975 by the National Heart Lung and Blood Institute Lipid Standardized Program provided by the Centers for Disease Control and Prevention (Atlanta, GA, USA) and successfully met the criteria for both precision and accuracy of cholesterol measurements[13-15]. Serum glucose was determined using the hexokinase method. Diabetes mellitus was defined as fasting (≥ 8 h after meal) glucose level of ≥ 7.0 mmol/L (126 mg/dL) or a nonfasting (<8 h) glucose level of ≥ 11.1 mmol/L (200 mg/dL) or the use of medication for diabetes mellitus. Hyperglycemia was defined as diabetes mellitus or a fasting glucose level of 6.1–6.9 mmol/L (110–125 mg/dL) or a nonfasting glucose level of 7.8–11.0 mmol/L (140–199 mg/dL). Total cholesterol and triglycerides were determined using an enzymatic assay, and HDL cholesterol levels were determined by direct measurement. Dyslipidemia was defined as follows: (1) total cholesterol of ≥ 5.7 mmol/L (≥ 220 mg/dL), (2) triglycerides of ≥ 1.7 mmol/L (≥ 150 mg/dL) for both fasting and nonfasting, (3) HDL cholesterol of <1.0 mmol/L (<40 mg/dL), and/or (4) use of medication for dyslipidemia. Creatinine levels were assayed using an enzymatic method. The estimated glomerular filtration rate (eGFR) was calculated using the following equation proposed by the working group of the Japanese Chronic Kidney Disease (CKD) initiative[16]: eGFR (mL/min/1.73 m^2) = 194 × [creatinine (an enzymatic method)]$^{-1.094}$ × (age)$^{-0.287}$ × (0.739 for women).

After the participants were seated and had rested for 5 min, systolic and fifth-phase diastolic blood pressures in the right arm were measured by trained physicians or technicians using standard mercury sphygmomanometers according to the unified epidemiological methods[17]. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, and/or use of antihypertensive medication. Height was measured with the participants in stocking feet and weight while wearing light clothing. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). During baseline surveys, we interviewed participants to determine their medical history, smoking status, number of cigarettes per day, usual alcohol intake per week, and medication use for hypertension and diabetes.

Statistical Analysis

Analysis of covariance was used to test differences in means and proportions of baseline characteristics by hs-cTnT quartiles among controls. Odds ratios (ORs) and 95% confidence intervals (CIs) for the risk of incident CHD were calculated using conditional logistic regression analyses. We calculated the ORs for each quartile of hs-cTnT among controls against the lowest quartile (Q1) as a reference. In addition, multivariable ORs were calculated and adjusted for BMI, diastolic blood pressure, antihypertensive medication use (yes or no), diabetes mellitus, serum non-HDL cholesterol, antidyslipidemic medication use (yes or no), serum HDL cholesterol, current

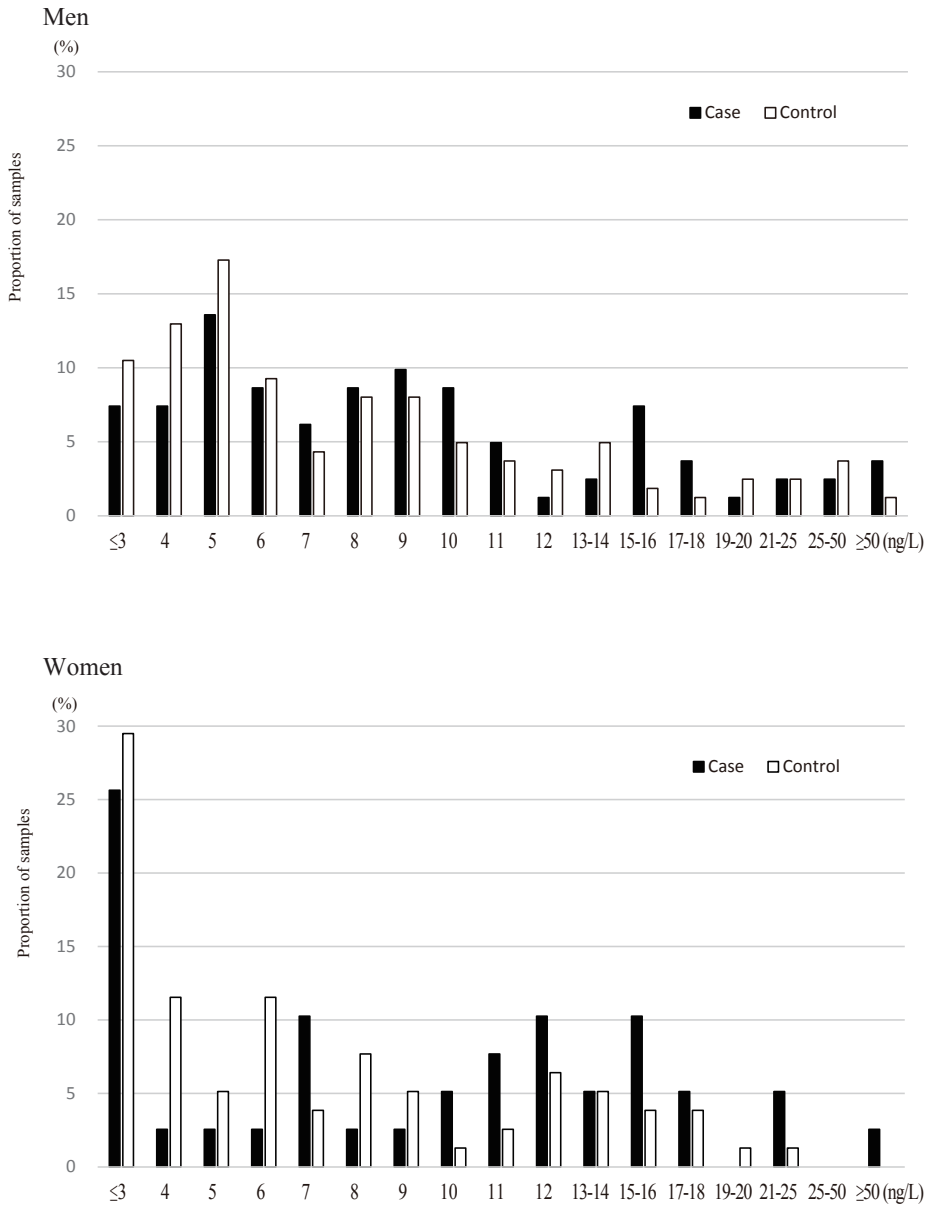

Fig. 1. Sex-specific distributions of serum high-sensitivity cardiac troponin T concentrations according to incident coronary heart disease case and control in the Circulatory Risk in Communities Study

drinker (yes or no), current smoker (yes or no), and menopause status for women (yes or no) in Model 1 and further adjusted for eGFR in Model 2, considering kidney function, which may affect serum hs-cTnT level[18]. Corresponding ORs were analyzed stratified by median age, i.e., <70 years and ≥ 70 years, and the median time between blood sampling and CHD incidence, i.e., <2 years (4–724 days) and ≥ 2 years (755–3,473 days). Further, we excluded participants with CKD (eGFR <45 mL/min/1.73 m^2) and analyzed similarly to the sensitivity analysis. All statistical analyses were performed using the SAS System for Windows (version 9.4). All *p*-values for statistical tests were two-tailed, and *p*-values of <0.05 were regarded as statistically significant.

Results

Fig. 1 presents the distribution of hs-cTnT in men and women. Based on our findings, hs-cTnT distributed ranged between ≤ 3 (undetectable due to measurement limit) and ≥ 50 ng/L (maximum 155 ng/L). Among men, the proportion of undetectable (below the assay detection limits) values was 10.5%

Table 1. Mean values (standard deviations) or prevalence of risk characteristics at baseline according to the serum high-sensitivity cardiac troponin T (hs-cTnT) quartiles among controls in a nested case-control study

	Q1	Q2	Q3	Q4	*p* for trend
Range of hs-cTnT, ng/L	≤ 4	5-6	7-10	11-155	
Median of hs-cTnT, ng/L	≤ 3	5	8	15	
Control, *n* (%)	70 (75.3)	56 (73.7)	55 (61.1)	59 (58.4)	
Case (CHD), *n* (%)	23 (24.7)	20 (26.3)	35 (38.9)	42 (41.6)	
Total, *n* (%)	93 (100)	76 (100)	90 (100)	101 (100)	
Age, years	61.2 (10.0)	67.1 (7.5)	71.7 (6.8)	74.3 (6.9)	<.0001
Men, %	53.8	80.3	75.6	63.4	.895
Body mass index, kg/m^2	23.2 (3.1)	23.3 (2.8)	23.6 (3.7)	24.1 (3.1)	.026
Systolic blood pressure, mmHg	130 (17)	133 (17)	132 (17)	136 (18)	.016
Diastolic blood pressure, mmHg	80 (11)	81 (11)	76 (10)	74 (12)	<.0001
Hypertension, %	44.1	52.6	60.0	77.2	<.0001
Hypertension (medication), %	23.7	26.3	43.3	64.4	<.0001
Glucose, mmol/L	5.7 (1.0)	6.0 (1.9)	6.6 (2.9)	6.4 (2.0)	.050
Hyperglycemia, %	10.8	17.1	23.3	26.7	.036
Diabetes mellitus, %	4.3	7.9	15.6	18.8	.002
Diabetes mellitus (medication), %	3.2	3.9	12.2	14.9	.002
Total cholesterol, mmol/L	5.5 (0.9)	5.4 (1.0)	5.2 (0.9)	5.2 (0.9)	.036
Triglycerides, mmol/L	1.6 (2.1)	1.5 (0.9)	1.4 (1.0)	1.4 (0.8)	.341
Non-high-density lipoprotein cholesterol, mmol/L	3.9 (0.9)	3.9 (0.9)	3.8 (0.9)	3.8 (0.8)	.208
High-density lipoprotein cholesterol, mmol/L	1.6 (0.4)	1.5 (0.4)	1.4 (0.4)	1.4 (0.3)	.026
Dyslipidemia (medication), %	3.2	6.6	14.4	11.9	.044
Drinker, %	49.5	60.5	45.6	32.7	.001
Smoker, %	35.5	31.6	23.3	24.8	.103
Menopause for women, %	83.7	93.3	100.0	100.0	.099
eGFR, mL/min per 1.73 m^2	83.1 (18.0)	79.4 (17.8)	72.2 (13.4)	66.1 (18.0)	<.0001
Chronic kidney disease (eGFR <60), %	5.4	7.9	18.9	36.6	<.0001
Chronic kidney disease (eGFR <45), %	0.0	0.0	4.4	13.9	<.0001

In parentheses: standard deviations except for control, case, and total. hs-cTnT; high-sensitivity cardiac troponin T, CHD; coronary heart disease, eGFR; estimated glomerular filtration rate.

and 7.4% for controls and cases; for women, these values were 29.5% and 25.6%, respectively. Men exhibited higher hs-cTnT levels than women. Cases presented higher hs-cTnT levels than controls, especially among women.

Table 1 shows the baseline characteristics according to the hs-cTnT quartiles of the controls. The proportion of CHD cases in the lowest quartile (Q1) was 24.7%, increasing in stages until 41.6% in the highest quartile (Q4). The mean age increased in stages as hs-cTnT levels increased. The proportion of men was highest in the second quartile (Q2) (80.3%) and the lowest in Q1 (53.8%). The means of BMI and systolic blood pressure, the proportions of hypertension, medication for hypertension, hyperglycemia, diabetes mellitus, medication for diabetes mellitus, medication for dyslipidemia, and CKD tended to be higher with higher hs-cTnT levels. Higher hs-cTnT levels were correlated with lower diastolic blood pressure, serum total cholesterol, serum HDL cholesterol, eGFR, and the proportion of drinkers.

Table 2 presents the age, sex, and community-matched and multivariable ORs for incident CHD according to hs-cTnT quartiles. Serum hs-cTnT levels were positively associated with the risk of CHD. After adjusting for conventional cardiovascular risk factors in Model 1, the association with the risk of incident CHD attenuated but remained statistically significant. Multivariable ORs (95% CIs) of CHD for Q2–Q4 versus Q1 of hs-cTnT were 1.30 (0.57–2.95, p=0.54), 2.48 (1.09–5.64, p=0.03), and 3.01 (1.27–7.12, p=0.01), respectively (p for trend=0.01). Similar associations were detected after adjusting for eGFR (Model 2). After excluding 18 matched groups including participants with CKD, the corresponding ORs showed a similar tendency, namely, the multivariable ORs (95% CIs) of CHD for Q2–Q4 versus Q1 of

Table 2. Multivariable odds ratios (ORs, 95% CI) of coronary heart disease according to quartiles of serum high-sensitivity cardiac troponin T (hs-cTnT) among controls in the nested case-control study

Range of hs-cTnT, ng/L	≤ 4	5-6	7-10	11-155	*p* for trend
Men and Women (case, *n* = 120 / control, *n* = 240)					
Control, *n*	70	56	55	59	
Case, *n*	23	20	35	42	
Total, *n*	93	76	90	101	
Odds ratio	ref.	1.42 (0.66-3.07)	2.76 (1.29-5.91)†	3.20 (1.48-6.94)†	.003
Multivariable odds ratio, Model 1	ref.	1.30 (0.57-2.95)	2.48 (1.09-5.64)*	3.01 (1.27-7.12)*	.011
Multivariable odds ratio, Model 2	ref.	1.34 (0.59-3.04)	2.40 (1.05-5.47)*	2.67 (1.10-6.47)*	.039
Age < 70 yrs (case, *n* = 59 / control, *n* = 118)					
Control, *n*	58	31	18	11	
Case, *n*	18	16	14	11	
Total, *n*	76	47	32	22	
Odds ratio	ref.	2.15 (0.88-5.29)	3.15 (1.19-8.38)*	3.93 (1.35-11.43)*	.015
Multivariable odds ratio, Model 1	ref.	1.97 (0.73-5.33)	2.86 (0.92-8.85)	4.77 (1.24-18.39)*	.024
Multivariable odds ratio, Model 2	ref.	2.22 (0.80-6.15)	2.78 (0.90-8.60)	3.76 (0.92-15.38)	.064
Age ≥ 70 yrs (case, *n* = 61 / control, *n* = 122)					
Control, *n*	12	25	37	48	
Case, *n*	5	4	21	31	
Total, *n*	17	29	58	79	
Odds ratio	ref.	0.39 (0.08-1.84)	1.42 (0.41-4.87)	1.55 (0.46-5.22)	.068
Multivariable odds ratio, Model 1	ref.	0.31 (0.06-1.64)	1.17 (0.30-4.52)	1.27 (0.33-4.95)	.122
Multivariable odds ratio, Model 2	ref.	0.30 (0.06-1.57)	1.10 (0.28-4.34)	1.15 (0.28-4.68)	.184
The time of < 2.0 years between blood sampling and CHD incidence (case, *n* = 60 / control, *n* = 120)					
Control, *n*	37	28	21	34	
Case, *n*	11	11	19	19	
Total, *n*	48	39	40	53	
Odds ratio	ref.	1.84 (0.57-5.96)	4.11 (1.35-12.51)†	2.85 (0.92-8.83)	.152
Multivariable odds ratio, Model 1	ref.	0.77 (0.20-3.02)	3.27 (0.84-12.74)	3.07 (0.71-13.15)	.063
Multivariable odds ratio, Model 2	ref.	0.87 (0.22-3.48)	3.18 (0.80-12.65)	2.39 (0.54-10.57)	.190
The time of ≥ 2.0 years between blood sampling and CHD incidence (case, *n* = 60 / control, *n* = 120)					
Control, *n*	33	28	34	25	
Case, *n*	12	9	16	23	
Total, *n*	45	37	50	48	
Odds ratio	ref.	1.13 (0.39-3.23)	1.87 (0.63-5.54)	4.06 (1.32-12.56)*	.005
Multivariable odds ratio, Model 1	ref.	1.40 (0.44-4.44)	2.19 (0.67-7.14)	4.89 (1.37-17.46)*	.010
Multivariable odds ratio, Model 2	ref.	1.41 (0.45-4.44)	2.10 (0.63-6.94)	4.53 (1.23-16.63)*	.017

†; $p < 0.01$, *; $p < 0.05$. Cases and controls were matched with age, sex, communities and sampling term. Multivariable odds ratio adjusted for body mass index, diastolic blood pressure, antihypertensive medication use, diabetes mellitus, serum non-high-density lipoprotein cholesterol, serum high-density lipoprotein cholesterol, dyslipidemia medication use, drinking, smoking status and menopause status for women in Model 1, and further adjusted for eGFR in Model 2.

hs-cTnT were 1.51 (0.65–3.50, $p=0.34$), 2.57 (1.08–6.08, $p=0.03$), and 3.17 (1.28–7.86, $p=0.01$), respectively (p for trend=0.02), in Model 1 and 1.56 (0.67–3.63, $p=0.30$), 2.46 (1.03–5.87, $p=0.04$), and 2.83 (1.12–7.17, $p=0.03$), respectively (p for trend=0.04), in Model 2. Similarly, after excluding six matched groups, including cases with prior stroke, the corresponding ORs did not change materially; the multivariable ORs (95% CIs) of CHD for Q2–Q4 versus Q1 of hs-cTnT were 1.20 (0.52–2.76, $p=0.68$), 2.53 (1.10–5.83, $p=0.03$), and 2.97 (1.25–7.06, $p=0.01$), respectively (p for trend=0.01), in Model 1 and 1.22 (0.53–2.82, $p=0.64$), 2.44 (1.05–5.64, $p=0.04$), and 2.60 (1.06–6.36, $p=0.04$), respectively (p for trend=0.04), in Model 2. Furthermore, after excluding seven groups including cases with atrial

fibrillation, the corresponding ORs did not alter materially, but some were not statistically significant; the multivariable ORs (95% CIs) of CHD for Q2–Q4 versus Q1 of hs-cTnT were 1.14 (0.48–2.68, p=0.77), 2.41 (1.05–5.57, p=0.04), and 2.46 (1.03–5.88, p=0.04), respectively (p for trend=0.04), in Model 1 and 1.15 (0.49–2.70, p=0.75), 2.33 (1.00–5.41, p=0.049), and 2.22 (0.90–5.47, p=0.08), respectively (p for trend=0.095), in Model 2.

In the stratified analyses by age group **(Table 2)**, the group of <70 years showed a significant p-value for trend in Model 1, and OR (95% CIs) of Q4 was 4.89 (1.37–18.39, p=0.02); however, the older group showed no significant ORs. In addition, the interaction between hs-cTnT and age groups was not statistically significant (p=0.77, Model 1; p=0.74, Model 2).

In the stratified analyses of the time between blood sampling and CHD incidence **(Table 2)**, the time of ≥ 2.0 years group showed that ORs (95% CIs) of Q4 were 4.89 (1.37–17.46, p=0.01) in Model 1 and 4.53 (1.23–16.63, p=0.02) in Model 2, although the time of <2.0 years group showed no significant ORs. The interaction between hs-cTnT and the time was significant (p<0.0001 in both Models 1 and 2).

Discussion

In the present study, our findings revealed that serum hs-cTnT levels were an independent predictor of incident CHD using a nested case-control study in a large cohort of the Japanese general population.

According to a meta-analysis study reported in 2017 [7], the relative risk comparing the top versus the bottom categories of hs-cTn (T or I) was 1.59 (95% CI, 1.38–1.83) for CHD (death or incidence) in 16 prospective studies, involving 83,950 participants. Furthermore, a recent clinical review[6] has described that hs-cTn can be used for stratifying cardiovascular risk in the general population. However, most of these studies were based on data from Western populations. As evidence among Asian subjects, a community-dwelling prospective study evaluating 1,499 participants (aged 45–91 years) in Beijing, China has reported that 99 coronary events occurred during the median 4.8 years follow-up. The authors reported that the highest hs-cTnT group (≥ 14 ng/L, n=172) showed a significantly higher multivariable hazard ratio, 4.50 (95% CI, 2.26–9.02) for coronary events when compared with the undetectable group (<3.0 ng/L, n=679)[8], wherein the percentage of detectable hs-cTnT was lower (54.7%) than that documented in our study (84.4%). Our findings were consistent with those of previous reports.

In the present study, detectable hs-cTnT levels were ascertained in 89.5% and 92.6% of male controls and cases and 70.5% and 74.4% of female control and cases, respectively. The population with detectable hs-cTnT levels varied largely among previous studies of the general population, between 27% and 99% using the hs-cTnT assay of Roche Diagnostics KK[7]. For example, only 27% of participants exhibited detectable hs-cTnT levels in the Dallas Heart Study, which was a multiethnic cohort study (men 44%, 30–65 years including 34% 30–39 years, Black 52%, White 29%, Hispanic 17%, others 2%)[19]. Similarly, 66.5% of participants showed detectable hs-cTnT levels in the Atherosclerosis Risk in Communities Study (ARIC), which was a multiethnic cohort study (men 44%, 54–74 years, White 78%)[20]. The above meta-analysis[7] has suggested that a higher percentage of participants with detectable hs-cTnT levels can be correlated to the population mean age.

Cardiac troponin is a component of the contractile apparatus of myocardial cells, existing almost exclusively in the heart[5]. Therefore, elevated cardiac troponin in the blood reflects injury leading to necrosis of myocardial cells. In addition, multiple potential mechanisms are speculated to contribute to increased hs-cTn other than myocyte necrosis. Troponin elevation occurs through six pathobiological mechanisms: myocyte necrosis, apoptosis, normal myocyte turnover, cellular release of proteolytic troponin degradation products, increased cell wall permeability, and formation and release of membranous blebs[21]. Specifically, myocardial ischemia may induce apoptosis[22], transient increases in cardiomyocyte permeability[23], membranous blebs that rupture[24], free radical overload[25], increased troponin turnover[26], and direct toxic effects of catecholamines[27].

Meanwhile, an ischemia-independent mechanism is speculated to release hs-cTnT. A computed tomography (CT) angiography study of patients with stable angina has shown that the presence and extent of coronary atherosclerosis can be correlated with blood hs-cTnT levels even in the absence of ischemia[28]. In addition, a meta-analysis of 11 studies on hs-cTn after cardiac stress (nine regarding exercise stress and two regarding pharmacological stress) has reported that hs-cTnT elevation after cardiac stress testing appears inconsistent and did not correlate with inducible myocardial ischemia[29]. Exercise stress activated the adrenergic and renin-angiotensinogen-aldosterone systems, resulting in elevated hs-cTnT levels[30].

Furthermore, a CT angiography study has revealed that high-sensitivity troponin T levels

strongly correlate with total non-calcified plaque burden (r=0.79, $p<0.001$) than with calcium scoring (r=0.45, $p<0.001$) for coronary atherosclerosis, and thus it was speculated that clinically silent ruptures of coronary plaques trigger microembolization and shedding of troponin from cardiomyocytes via membranous blebs[31].

Elevation of serum hs-cTnT levels was due to not only myocardial damage but also reduced hs-cTnT clearance[32]. Therefore, we conducted the analyses of adjusting for eGFR and excluding groups including CKD. However, the association between hs-cTnT and the risk of incident CHD did not change substantially.

A recent clinical review[6] has indicated that further investigation is needed to define optimal measurement timing and target populations for implementing cardiovascular risk stratification, and prevention strategies that incorporate hs-cTn. In the present study, the results of the stratified analysis indicated that the association between serum hs-cTnT levels and the risk of incident CHD was more evident in the time ≥ 2.0 years between blood sampling and CHD incidence than in the time <2.0 years. Therefore, the elevation of hs-cTnT had started over 2 years before the onset of CHD, and in the future, screening hs-cTnT for the general population may be more beneficial to predict the onset of CHD, which might occur after ≥ 2 years in those with elevated hs-cTnT. In our study, people under 70 years may be more practical to measure hs-cTnT for predicting incident CHD, but interactions between hs-cTnT and age groups were not statistically significant. Therefore, further investigation is needed about the target age of populations.

The strength of the current study was that it was based on a large cohort study of the general population in an Asian country that has low mortality from CHD. In addition, our study was conducted using standardized epidemiological methods for measuring risk factors and systematic surveillance for incident CHD as the target endpoint.

However, this study also has several limitations. First, the single measurement of hs-cTnT concentrations could lead to a regression dilution bias owing to misclassification. Second, our study could not exclude residual confounding or confounding by unmeasured variables such as diet[33, 34], physical activity[33], socioeconomic status[35], and psychological factors[36]. Third, we did not measure other biomarkers that have emerged as a potential adjunct to cardiovascular risk prediction, including high-sensitivity cardiac troponin I (hs-cTnI) and natriuretic peptides such as N-terminal pro-brain natriuretic peptide. A recent report from the ARIC study has shown that hs-cTnI and hs-cTnT present a modest correlation (r=0.47) and are complementary in predicting incident cardiovascular events[37]. Finally, maybe owing to insufficient sample size, some results were not statistically significant after excluding matched groups, including cases with a history of other cardiovascular diseases, although similar results.

Conclusion

In conclusion, the present study revealed that serum hs-cTnT was an independent predictor of CHD in the Japanese general population. These findings implicate a benefit of monitoring hs-cTnT to predict CHD even among populations in countries with low CHD-associated mortality rates.

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Conflict of Interest

None.

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