Table 4. Multivariable-adjusted hazard ratios for cardiovascular disease according to sex, age group, and quartile of WC: The Suita Study, Japan

	Q1 (low)	Q2	Q3	Q4 (high)	*P* for trend
Men					
Age 50–69 years					
Person-years	4078	4004	3872	3806	
CVD, no. of cases	32	33	29	44	
HRs	1	1.07 (0.66–1.75)	0.97 (0.58–1.61)	1.63 (1.03–2.59)	0.06
CHD, no. of cases	13	17	12	23	
HRs	1	1.28 (0.62–2.63)	0.96 (0.44–2.12)	2.02 (1.02–4.02)	0.07
Stroke, no. of cases	19	16	17	21	
HRs	1	0.97 (0.50–1.88)	0.96 (0.49–1.86)	1.43 (0.76–2.67)	0.31
Ischemic stroke, no. of cases	13	9	13	17	
HRs	1	0.80 (0.34–1.87)	1.07 (0.49–2.31)	1.64 (0.79–3.41)	0.15
Age ≥70 years					
Person-years	999	1208	1200	1124	
CVD, no. of cases	25	28	27	27	
HRs	1	0.94 (0.55–1.62)	0.91 (0.53–1.58)	1.06 (0.61–1.84)	0.87
CHD, no. of cases	14	11	12	12	
HRs	1	0.67 (0.30–1.47)	0.65 (0.30–1.43)	0.82 (0.38–1.78)	0.60
Stroke, no. of cases	11	17	15	15	
HRs	1	1.29 (0.60–2.77)	1.21 (0.55–2.66)	1.36 (0.62–2.99)	0.52
Ischemic stroke, no. of cases	5	10	10	12	
HRs	1	1.70 (0.58–4.98)	1.82 (0.62–5.37)	2.26 (0.79–6.47)	0.14
Women					
Age 50–69 years					
Person-years	4669	4685	5046	4221	
CVD, no. of cases	15	18	25	30	
HRs	1	1.19 (0.60–2.36)	1.43 (0.75–2.71)	1.87 (1.00–3.51)	0.04
CHD, no. of cases	7	5	5	13	
HRs	1	0.74 (0.24–2.34)	0.65 (0.21–2.08)	1.86 (0.73–4.72)	0.18
Stroke, no. of cases	8	13	20	17	
HRs	1	1.56 (0.65–3.77)	2.06 (0.90–4.70)	1.93 (0.82–4.54)	0.11
Ischemic stroke, no. of cases	4	6	9	10	
HRs	1	1.44 (0.41–5.10)	1.70 (0.52–5.54)	2.00 (0.62–6.52)	0.23
Age ≥70 years					
Person-years	1175	1234	1046	1157	
CVD, no. of cases	16	16	15	20	
HRs	1	1.05 (0.52–2.11)	1.11 (0.54–2.25)	1.45 (0.74–2.83)	0.28
CHD, no. of cases	8	6	7	6	
HRs	1	0.85 (0.29–2.49)	1.21 (0.43–3.43)	0.88 (0.30–2.59)	0.98
Stroke, no. of cases	8	10	8	14	
HRs	1	1.24 (0.49–3.14)	1.10 (0.41–2.93)	2.00 (0.83–4.87)	0.15
Ischemic stroke, no. of cases	5	4	4	9	
HRs	1	0.85 (0.23–3.21)	0.93 (0.25–3.47)	1.86 (0.61–5.61)	0.24

Multivariable adjustment was performed for age, smoking, and drinking status. Parentheses indicate 95% CIs for HRs.
Abbreviations: WC, waist circumference; Q, quartile; CVD, cardiovascular disease; CHD, coronary heart disease; HR, hazard ratio.

Our study has several limitations. First, the number of cases of CVD among participants aged 30 to 49 years was insufficient for statistical analysis. Further study is required to confirm an association between WHtR and CVD risk among younger adults. Second, the effect of visceral fat could not be estimated because we did not use computed tomography to measure abdominal fat distribution. Third, changes in WHtR during the follow-up period were not considered in the present study. Finally, because WC was measured once, the estimated risks might have been underestimated because of regression dilution bias.[31]

In conclusion, the present findings suggest that WHtR is useful in identifying middle-aged Japanese at higher risk of CVD and is more predictable than WC in determining CVD risk, especially among men. In addition, the data indicate that WHtR cut-off points should be set according to sex and age. This study enrolled a limited Japanese population, and further studies with larger and more ethnically diverse samples are required to confirm our findings.

ONLINE ONLY MATERIALS

eTable 1. Baseline characteristics and CVD incidence among men and women aged 30–49 years according to quartile of waist-to-height ratio: the Suita Study, Japan.

eTable 2. Multivariable-adjusted hazard ratios for cardiovascular disease in the upper and lower fourth quartile of WHtR according to sex and age group: the Suita Study, Japan.

eTable 3. Multivariable-adjusted hazard ratios for cardiovascular disease according to sex, age group, and quartile of WHtR: the Suita Study, Japan.
Abstract in Japanese.

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Conflicts of interest: None declared.

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ORIGINAL ARTICLE

Blood Pressure, Low-Density Lipoprotein Cholesterol, and Incidences of Coronary Artery Disease and Ischemic Stroke in Japanese: The Suita Study

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BACKGROUND
Blood pressure (BP) and low-density lipoprotein cholesterol (LDL-C) are risk factors for coronary artery disease (CAD) and ischemic stroke. However, the hazards of their coexistence are not fully understood in Asian populations. We investigated whether the relationship between BP and cardiovascular disease (CVD) outcomes are modified by LDL-C level in a Japanese population.

METHODS
Individuals aged 30–79 years (n = 5,151) were classified into 6 groups according to LDL-C levels (<140 and ≥140 mg/dL or lipid medication) and BP levels (optimal BP, prehypertension, and hypertension; reference: low LDL-C and optimal BP). Hazard ratios (HRs) were calculated after adjusting for age, high-density lipoprotein cholesterol, diabetes, smoking status, and alcohol consumption. The effect modification of LDL-C on BP–CVD association was assessed using likelihood ratio tests.

RESULTS
There were 264 CAD and 215 ischemic stroke events during 13 years of follow-up. With low LDL-C, the HRs of prehypertension and hypertension for CAD were 2.01 and 4.71, respectively. Similar trends of HRs were observed with high LDL-C (optimal BP = 2.09, prehypertension = 3.45, hypertension = 5.94). However, the HRs for ischemic stroke did not differ between normal and high LDL-C levels at the same BP level. The apparent effect modification of LDL-C was not observed in the BP–CVD association in either CAD ($P = 0.48$) or ischemic stroke ($P = 0.39$).

CONCLUSIONS
The HRs for CAD in prehypertensive and hypertensive groups were higher than those in the optimal BP group at the same LDL-C levels in a Japanese population; however, there was no statistical effect modification of LDL-C on the BP–CAD association.

Keywords: Asian; blood pressure; cohort study; coronary artery disease; hypertension; incidence; ischemic stroke; low-density lipoprotein cholesterol; Suita Study.

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Cardiovascular disease is a leading cause of mortality and morbidity in Asian countries.[1] Elevated blood pressure (BP)[1–5] and hypercholesterolemia[1,6–10] are well-established independent cardiovascular risk factors. Moreover, the combination of these risk factors is a better predictor of the risk of cardiovascular disease in Western populations.[11,12] In Japan, the Japan Lipid Intervention Trial (J-LIT) study showed that Japanese hypercholesterolemia patients with high systolic BP (SBP; ≥130 mm Hg) and high total cholesterol levels (≥220 mg/dl) treated with low-dose simvastatin had an increased risk of cardiovascular disease events.[13] In Asia, the Asia Pacific Cohort Studies Collaborations (APCSC) demonstrated that the combination of high SBP (≥130 mm Hg) and high total cholesterol (≥212 mg/dl) increased the risks of fatal and nonfatal cardiovascular disease among both Western and Asian populations.[14] However, the J-LIT and APCSC studies have some drawbacks, including relatively short follow-up periods (mean follow-up period

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of approximately 6 years) and lipid profiles based on total cholesterol and not low-density lipoprotein cholesterol (LDL-C). Furthermore, the J-LIT study was a patient-based clinical trial,[13] and the APCSC study[14] did not exclusively involve Asian populations, which have a higher incidence of stroke and lower incidence of coronary artery disease (CAD) than Western populations.[1]

The purpose of our study was to examine whether the relationship between BP and CVD outcomes (CAD and ischemic stroke) is modified by LDL-C levels in a community-based cohort study in a Japanese population.

METHODS

Population

The Suita Study, a cohort study evaluating cardiovascular disease risk in an urban Japanese population, was established in 1989. This cohort study has been extensively used to evaluate risk factors associated with the incidences of CAD and stroke.[4,15–18] The details of this study have been described previously.[4,15–18] Briefly, 6,483 men and women aged 30–79 years underwent a baseline survey at the National Cerebral and Cardiovascular Centre (Japan) between September 1989 and March 1994. Subjects older than 80 years were excluded because it remains unconfirmed whether LDL-C is a risk factor for cardiovascular disease in the elderly population (aged ≥80 years).[19] A total of 1,332 participants were excluded for the following reasons: history of CAD or stroke (n = 208); loss to follow-up (n = 535); lack of participation in the baseline survey (n = 78); nonfasting visit (n = 239); triglyceride level >400 mg/dl (n = 86); LDL-C ≤0 (n = 1); missing total cholesterol, high-density lipoprotein cholesterol (HDL-C), or triglyceride data (n = 30); aged ≥80 years (n = 12); and other missing data (n = 145). Therefore, data from the remaining 5,151 participants (men: n = 2,399; women: n = 2,752) were included in our analysis.

This study was approved by the institutional review board of the National Cerebral and Cardiovascular Centre. Informed consent was obtained from all participants by health professions at the baseline examination. The collected data were anonymized.

Baseline examination

Blood samples were collected at the National Cerebral and Cardiovascular Centre after the participants had fasted for at least 10 hours. The samples were immediately centrifuged, and a routine blood examination that included serum total cholesterol, HDL-C, triglyceride, and glucose levels was performed. LDL-C was estimated for both men and women using the Friedewald formula.[20] Participants with triglyceride levels >400 mg/dl were excluded because LDL-C estimates are inaccurate among such persons.[19,21,22]

BP was measured by well-trained physicians using a standard mercury sphygmomanometer. After the participant had been in the seated position for 5 minutes, BP was measured 3 times on the right arm, and the average of the second and third measurements was used in the analyses to avoid bias due to white coat hypertension. Because HbA1c data from before 1995 were unavailable, diabetes was defined according to the American Diabetes Association 2013 guidelines as a fasting serum glucose level ≥126 mg/dl, the use of diabetes medication, or both.[23,24] Height and weight were measured while the subjects wore socks and light clothing. Public health nurses obtained information about smoking status, alcohol consumption, and medical history of the participants.

The information about smoking and alcohol consumption have been reported previously.[4,15–18] Well-trained nurses obtained information on smoking and alcohol consumption. Smoking status was classified as never, ex-smoker, or current smoker. If a participant responded yes to "current smoker," the number of cigarettes smoked per day was ascertained. Alcohol consumption was categorized as never drinker, ex-drinker, or current drinker (i.e., >1 time per week).

Endpoint determination

The endpoint determination in the Suita Study has been described previously.[4,15–18] The Suita Study is an ongoing cohort study, and the latest endpoint determination was performed on 31December 2007. The endpoints in our follow-up study were as follows: (i) the date of the first CAD or stroke event, (ii) the date of death, (iii) the date of leaving Suita City, and (iv) 31 December 2007.

The first step in the CAD and stroke survey involved checking the health status of all participants at biennial clinical visits every 2 years and through annual questionnaires sent by mail or administered by telephone. The second step involved the review of the in-hospital medical records of participants suspected of having had CAD or stroke; the reviews were performed by registered hospital physicians or research physicians blinded to the baseline information. The diagnosis of stroke was based on the US National Survey of Stroke criteria.[25] Stroke subtypes, including ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage, were diagnosed on the basis of computed tomography, magnetic resonance imaging, or autopsy results. Definite and probable acute myocardial infarction were defined according to the criteria of the Monitoring Trends and Determinants of Cardiovascular Disease (MONICA) Project.[26] In addition to acute myocardial infarction, the criteria for CAD diagnosis included sudden cardiac death within 24 hours from symptom onset or CAD followed by coronary artery bypass or angioplasty. Furthermore, myocardial infarction and stroke fatalities were recorded by searching for systematic death certificates.

Statistical analysis

BP was categorized into 3 groups; optimal BP (SBP <120 mm Hg and diastolic blood pressure (DBP) <80 mm Hg), prehypertension (SBP = 120–139 mm Hg, DBP = 80–89 mm Hg, or both), and hypertension (SBP ≥140 mm Hg, or DBP ≥90 mm Hg, or the use of antihypertensive agents). LDL-C was categorized into 2 groups; normal (LDL-C <140 mg/dl) or high (LDL-C ≥140 mg/dl or lipid medication) according to the diagnostic criteria for screening of the Japan Atherosclerosis Society Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases.[19]

This guideline has set the cutoff point of LDL-C to 140 mg/dl as diagnostic criteria of dyslipidemia. Using the abovementioned BP and LDL-C categories, combinations of BP and LDL-C (3 × 2 groups) were made to estimate hazard ratios (HRs) with optimal BP and normal LDL-C as the reference group. Analysis of variance and the Bonferroni test were used to compare continuous variables, and the χ^2 test was used to compare dichotomous variables.

Sex-stratified Cox proportional hazard models, accounting for different baseline hazards in men and women, were used to estimate the HRs of the combination of BP and LDL-C on cardiovascular disease outcomes. Age, HDL-C, smoking status, alcohol consumption, and diabetes were included in the models as confounders. For the primary analysis, HRs and 95% confidence intervals (CIs) were estimated for CAD and stroke events by analyzing BP as a categorical variable within each LDL-C group. Moreover, the association between BP and LDL-C was examined by comparing the HRs for CAD and stroke events across the 6 groups, adjusting for age, HDL-C, diabetes, smoking status, and alcohol consumption. The interaction between BP and LDL-C on cardiovascular outcomes was assessed using likelihood ratio tests.[27] The level of significance was set at $P < 0.05$. All statistical analyses were performed using STATA release 12 (Stata Corp LP, College Station, TX).

RESULTS

Overall, 5,151 individuals (men: n = 2,399; women: n = 2,752) were analyzed. Table 1 shows the baseline characteristics of groups with BP and LDL-C combination in men. In both LDL-C groups, men with hypertension had the highest mean age, body mass index, and fasting blood glucose, as well as the most cases of diabetes and medications. There were fewer current drinkers in the high LDL-C group than the normal LDL-C group ($P < 0.001$). Moreover, there were more current smokers in the normal LDL-C group than the high LDL-C group ($P < 0.001$).

Table 2 shows the means and prevalence of baseline characteristics with respect to BP and LDL-C groups in women. As with the men, in both LDL-C groups, women with hypertension had the highest mean age, body mass index, and fasting blood glucose, as well as the most cases of diabetes and medications. There were fewer current drinkers in the high LDL-C group than the normal LDL-C group ($P < 0.001$). Moreover, there were more current smokers in the normal LDL-C group than in high LDL-C group ($P < 0.001$).

The associations of alcohol consumption and smoking status with LDL-C levels were similar in both sexes. In addition, the rates of current smokers and drinkers were obviously higher in men than women (Tables 1 and 2).

During the 13-year follow-up (total = 67,287 person-years), 164 CAD cases (men: n = 110; women: n = 54) and 215 stroke cases (ischemic: n = 126; hemorrhagic: n = 48; subarachnoid hemorrhage: n = 22; and unclassified stroke: n = 19) were documented. The adjusted HRs for CAD in hypertension were highest in both the normal and the high LDL-C groups. The high HRs were observed as both BP and LDL-C upgraded in CAD (Figure 1). In the high LDL-C group, the HRs of CAD with optimal BP, prehypertension, and hypertension were 2.09 (95% CI = 0.88–4.98), 3.45 (95% CI = 1.59–7.51), and 5.94 (95% CI = 2.88–12.27), respectively. In the normal LDL-C group, the HR of CAD with prehypertension (2.01; 95% CI = 0.92–4.42) was almost the same as those with optimal BP and high LDL-C, whereas the HR with hypertension (2.95; 95% CI = 1.45–5.9) was significantly higher (Figure 1). The HR for ischemic stroke was 2.70 (95% CI = 1.37–5.35) in the hypertension and normal LDL-C group and 2.95 (95% CI = 1.47–5.90) in the hypertension and high LDL-C group. No apparent interaction between BP and LDL-C was detected with either CAD ($P = 0.48$) or ischemic stroke ($P = 0.39$).

These results have almost no differences when medication use (lipid-lowering medicine and BP-lowering medicine) is not considered the BP and LDL classification.

DISCUSSION

This study showed that the HRs for CAD in prehypertensive and hypertensive groups were higher than those in the optimal BP group at the same LDL-C levels in the Japanese population; however, 95% CIs for these groups almost overlapped, and no apparent modification by LDL-C was observed in the BP–CVD relationship. Furthermore, the HRs for ischemic stroke were not different between normal and higher LDL-C levels at the same BP levels.

Our results support the results from the APCSC, which demonstrated that the combination of elevated BP and elevated total cholesterol increases the risks of fatal and nonfatal cardiovascular disease in Asian, Australian, and New Zealand populations.[14] The APCSC showed that cardiovascular disease events are particularly increased in individuals with SBP ≥130 mm Hg and the highest total cholesterol levels (≥212 mg/dl). Furthermore, the relative risk of cardiovascular disease events in individuals with an SBP of 130–144 mm Hg and total cholesterol levels of 212–241 mg/dl is similar to that of individuals with an SBP of 145–159 mm Hg and total cholesterol levels <212 mg/dl. The J-LIT study, which was an observational study among Japanese patients that investigated the relationship between total cholesterol and BP on cardiovascular disease, also found that the relative risk of cardiovascular disease events was significantly higher in patients with poorly controlled hypercholesterolemia patients (total cholesterol >220 mg/dl), prehypertension (SBP = 130–139 mm Hg; DBP = 80–89 mm Hg), and hypertension (SBP >140 mm Hg; DBP >90 mm Hg) compared with the reference group (SBP <130 mm Hg; DBP <80 mm Hg).[13] Thus, our findings are concordant with those of the APCSC and J-LIT studies. However, it should be emphasized that our study cohort consisted exclusively of a general Asian population in contrast with the APCSC. In addition, hypercholesterolemia patients in the J-LIT study were treated with low-dose simvastatin.

The HRs for ischemic stroke did not differ between the normal and high LDL-C groups at the same BP levels. However, most cohort studies in Japan report that total cholesterol and LDL-C are not risk factors for total stroke[28] despite their

Table 1. Baseline characteristics of men with respect to blood pressure and serum low-density lipoprotein categories

	Normal LDL-C						High LDL-C						
	Optimal BP		Prehypertension		Hypertension		Optimal BP		Prehypertension		Hypertension		*P* value
No.	543		593		491		232		269		271		
Age, y	49.5	(13.2)	54.8	(13.2)**	61.3	(11.4)**	52.4	(12.5)*	56.2	(11.5)**	60.7	(10.8)**	<0.001
Systolic blood pressure, mm Hg	107.6	(7.5)	126.1	(7.3)**	150.8	(17.6)**	108.3	(7.4)*	126.3	(7.7)**	149.3	(16)**	<0.001
Diastolic blood pressure, mm Hg	67.9	(7)	67.9	(7)**	90.1	(10.6)**	69.3	(6.3)	79.5	(6.8)**	90.1	(10.3)**	<0.001
LDL-C, mg/dl	108.7	(20.5)	109.2	(20.7)*	108.6	(21.6)**	159.9	(18.5)**	159.8	(19.4)**	161.5	(22.5)**	<0.001
Fasting blood glucose, mg/dl	96.5	(13)	100.6	(17.8)*	102.6	(19.4)**	98.0	(20.7)**	102.9	(22.7)**	104.2	(21.2)**	<0.001
Body mass index, kg/m^2	21.8	(2.7)	22.7	(2.7)**	23.1	(3)**	22.6	(2.5)*	23.3	(2.6)**	23.8	(2.7)**	<0.001
Diabetes, %	3.5		5.4		7.9		3.4		4.8		10		0.004
Medication for hypertension, %	0		0		49.7		0		0		34.3		
Medication for hypercholesterolemia, %	0		0		0		2.6		5.6		8.5		
Medication for diabetes, %	0.9		2		2		1.3		1.9		5.2		0.001
Smoking, %													<0.001
Current smoker	60.6		49.7		43.6		32.8		44.2		41.7		
Ex-smoker	22.7		29.3		36.9		67.8		32.7		40.6		
Never smoker	16.8		20.9		19.6		43.3		23		17.7		
Alcohol consumption, %													<0.001
Current drinker	74.2		78.8		79.6		65.1		72.9		73.1		
Ex-drinker	2.2		3.9		3.1		3.9		4.8		6.6		
Never drinker	23.6		17.4		17.3		31		22.3		20.3		

Age, systolic blood pressure, diastolic blood pressure, low-density lipoprotein cholesterol (LDL-C), fasting blood glucose, and body mass index were analyzed by analysis of variance. The percentages of diabetes, medication for hypertension, medication for hypercholesterolemia, medication for diabetes, smoking, and alcohol consumption were analyzed by the χ^2 test. Data are expressed as mean (SD) or percentages. Optimal BP: systolic blood pressure <120 mm Hg and diastolic blood pressure <80 mm Hg. Prehypertension: systolic blood pressure 120–139 mm Hg or diastolic blood pressure 80–89 mm Hg. Hypertension: systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or the use of antihypertensive medication. Normal LDL-C: fasting LDL-C <140 mg/dl. High LDL-C: fasting LDL-C ≥140 mg/dl or the use of medication for hypercholesterolemia. Diabetes: fasting plasma glucose ≥126 mg/dl or the use of antidiabetic medication.

Abbreviations: BP, blood pressure; LDL-C, low-density lipoprotein cholesterol.

*P < 0.05, **P < 0.001: Bonferroni test (with normal LDL-C and optimal BP as the reference).

Table 2. Baseline characteristics of women with respect to blood pressure and serum low-density lipoprotein categories

	Normal LDL-C						High LDL-C						
	Optimal BP		Prehypertension		Hypertension		Optimal BP		Prehypertension		Hypertension		*P* value
No.	837		427		311		364		403		410		
Age, y	44.9	(11.3)	53.2	(12.4)**	61.9	(10.4)**	53.3	(10.8)**	57.9	(10.1)**	62.5	(8.9)**	<0.001
Systolic blood pressure, mm Hg	104.8	(8.1)	126.3	(7.1)**	151.8	(16.9)**	106.9	(7.5)	127.5	(6.8)**	151.4	(16.6)**	<0.001
Diastolic blood pressure, mm Hg	66	(6.6)	77.4	(6.8)**	86.3	(11.2)**	67	(6.8)	77.7	(7)**	86.8	(11.3)**	<0.001
LDL-C, mg/dl	108.9	(19.4)	114.2	(18.2)	115.4	(18.1)	163.3	(23.6)**	167.2	(26.6)**	168	(26.3)**	<0.001
Fasting blood glucose, mg/dl	91.3	(8.3)	96.2	(14.7)**	100.1	(20.5)**	93.5	(11.4)	98.6	(22.7)**	101.9	(18.3)**	<0.001
Body mass index, kg/m^2	20.9	(2.65)	22.2	(3.03)**	23.2	(3.81)**	21.7	(2.82)*	22.9	(3.08)**	23.8	(3.43)**	<0.001
Diabetes, %	1.2		2.3		6.1		1.4		4.5		6.3		<0.001
Medication for hypertension, %	0		0		37.6		0		0		39.3		
Medication for hypercholesterolemia, %	0		0		0		3.6		5.2		7.6		
Medication for diabetes, %	0.6		0.9		2.3		0.5		1.5		2		0.09
Smoking, %													<0.001
Current smoker	16.4		9.8		8.7		13.7		10.2		7.6		
Ex-smoker	3.8		3.5		2.3		2.7		3.2		5.6		
Never smoker	79.8		86.7		89.1		83.5		86.6		86.8		
Alcohol consumption, %													<0.001
Current drinker	41.1		33		29.3		26.1		29.3		27.8		
Ex-drinker	2		1.6		1.9		1.6		1.7		1.7		
Never drinker	56.9		65.3		68.8		72.3		69		70.5		

Age, systolic blood pressure, diastolic blood pressure, low-density lipoprotein cholesterol (LDL-C), fasting blood glucose, and body mass index were analyzed by analysis of variance. The percentages of diabetes, medication for hypertension, medication for hypercholesterolemia, medication for diabetes, smoking, and alcohol consumption were analyzed by the χ^2 test. Data are expressed as mean (SD) or percentages. Optimal BP: systolic blood pressure <120 mm Hg and diastolic blood pressure <80 mm Hg. Prehypertension: systolic blood pressure 120–139 mm Hg or diastolic blood pressure 80–89 mm Hg. Hypertension: systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or the use of antihypertensive medication. Normal LDL-C: fasting LDL-C <140 mg/dl. High LDL-C: fasting LDL-C ≥140 mg/dl or the use of medication for hypercholesterolemia. Diabetes: fasting plasma glucose ≥126 mg/dl or the use of antidiabetic medication. When mean body mass index was examined in women, there were 836 women with normal blood pressure and normal LDL-C.

Abbreviation: BP, blood pressure.

*P < 0.05, **P < 0.001: Bonferroni test (with normal LDL-C and optimal BP as the reference).

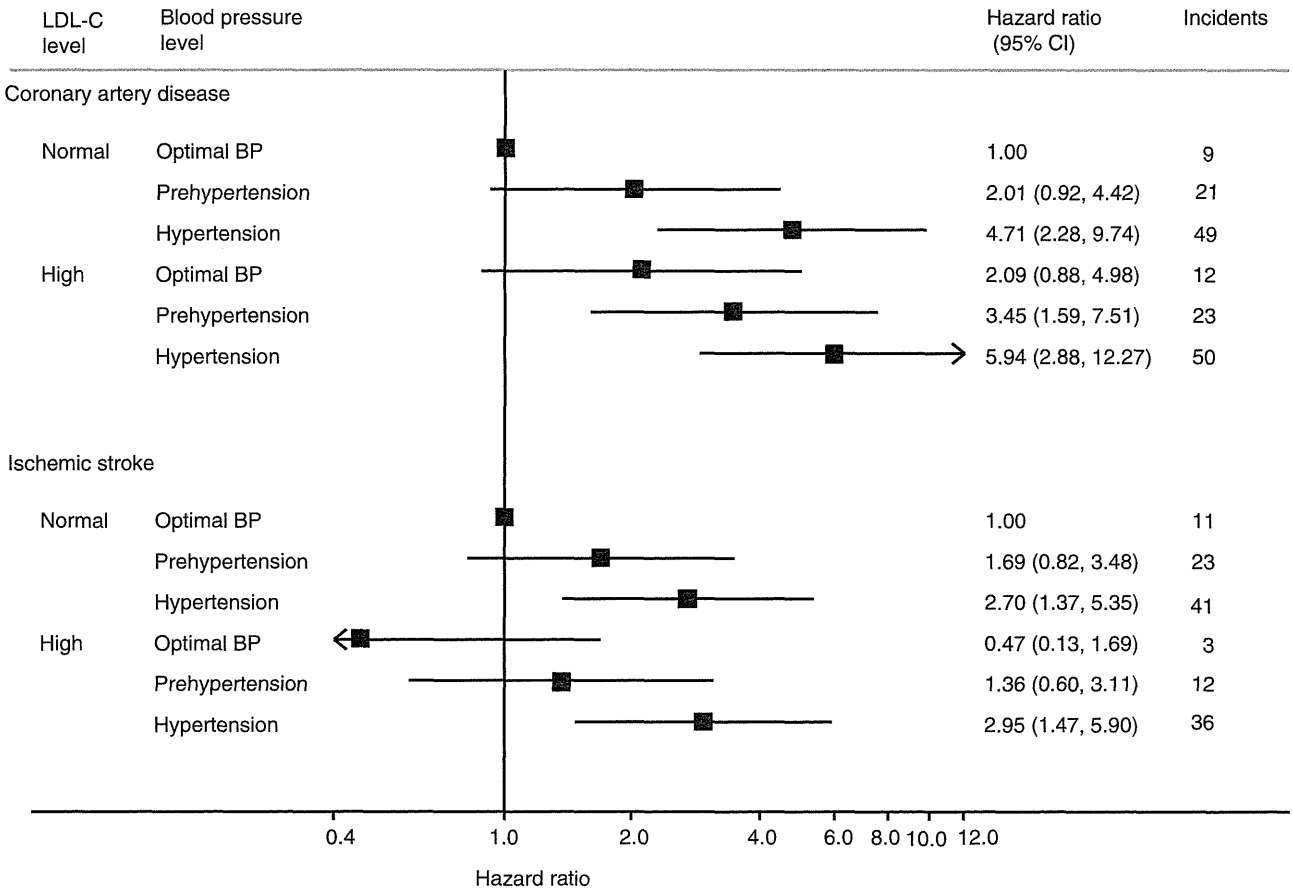

Figure 1. Hazard ratios (HRs) for coronary artery disease and stroke by blood pressure (BP) group with respect to low-density lipoprotein cholesterol (LDL-C; mg/dl) categories adjusted for age, high-density lipoprotein cholesterol, diabetes, smoking status, and alcohol consumption. ■ indicate HR estimates: ▬ indicate 95% confidence intervals (CIs) by Cox proportional hazard model stratified by sex. The reference group had optimal BP (systolic BP <120 mm Hg and diastolic BP <80 mm Hg) and normal LDL-C levels (LDL-C <140 mg/dl). $P = 0.48$ for CAD; $P = 0.39$ for ischemic stroke.

weak association with ischemic stroke.[29] Given these contradictory results between clinical trials and cohort studies, the effects of statins on the prevention of stroke should be interpreted cautiously. Several studies report cholesterol-lowering statins are beneficial for the prevention of stroke in hypertensive patients.[30,31] The post hoc analysis of the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese study revealed that pravastatin effectively reduced the incidence of cardiovascular disease, particularly ischemic stroke, in individuals with both hypertension and mildly elevated cholesterol.[30] Meanwhile, the Anglo–Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm showed that atorvastatin significantly reduces CAD, stroke, and cardiovascular disease even in hypertensive patients without dyslipidemia.[31] Although there have been numerous clinical trials for statin therapy, the primary endpoint of these studies was CAD, with ischemic stroke as the secondary endpoint. Furthermore, statins have pleiotropic effects that help prevent cardiovascular disease, including anti-inflammatory effects, improved vascular endothelial function, and plaque stabilization. These factors may explain the significant discrepancy between cohort studies and clinical trials with respect to the efficacy of statins in stroke prevention. Therefore, further investigation is required to clarify the role of statin therapy in stroke prevention. However, BP management should be the first priority in ischemic stroke prevention irrespective of LDL-C level.

Our study used a stratified Cox model that included 3 BP and 2 LDL-C categories, as well as their interaction terms and confounders. This combined model is statistically appropriate for the investigation of interactions between risk factors and disease outcomes. Furthermore, LDL-C and hypertension, which were the main targets of this study, and the abovementioned confounding factors encompass all major risk factors in the Framingham risk score,[22] the European SCORE chart,[21] and the Japanese Atherosclerosis Society risk chart[19] for predicting future coronary events.

We found that the HRs for CAD in high LDL-C group were higher than those in normal LDL-C at the same BP levels in the Japanese population. However, the apparent effect modification of LDL-C was not detected in the relation between BP and CAD. There are 3 possibilities to explain these results; no interaction, low statistical power, and bias. Our results suggested that BP and LDL-C were mutually independent risk factors and no interaction exist between them. This result was not as similar to other previous studies, and explanations were needed to claim the independence. A second possibility is that lack of statistical power induces

the results; a very small number of events was assigned in each category. The third possibility is that the single assessment of BP and LDL-C at the baseline survey and the fact that we did not evaluate the longitudinal trend for each risk factor may have underestimated the relationship between these conditions and CAD because of regression dilution bias.[32] All of these misclassification diluted the HRs and made the effect modification obscure. We are not quite sure which is the correct answer for this issue, but we believe our description of the BP, LDL-C, and CAD relationship among an Asian population gives important insight to future epidemiological studies.

In conclusion, to the best of our knowledge, this study is the first epidemiological study to examine the combined association between BP and LDL-C on the incidences of cardiovascular disease subtypes in an Asian population only. The results show that risk for CAD due to hypertension or prehypertension in the high LDL-C group was higher than those in the normal LDL-C group, although there were no statistical interaction between BP and LDL-C. Accordingly, BP and LDL-C should be managed for the early prevention of CAD in Japanese and other Asian individuals with hypertension, prehypertension, and high LDL-C levels. Furthermore, large-scale epidemiological studies should carefully assess the association between BP and LDL-C with the incidence of cardiovascular disease subtypes among Asian populations.

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DISCLOSURE

The authors declared no conflict of interest.

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Original Article

Predicting Coronary Heart Disease Using Risk Factor Categories for a Japanese Urban Population, and Comparison with the Framingham Risk Score: The Suita Study

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Aim: The Framingham risk score (FRS) is one of the standard tools used to predict the incidence of coronary heart disease (CHD). No previous study has investigated its efficacy for a Japanese population cohort. The purpose of this study was to develop new coronary prediction algorithms for the Japanese population in the manner of the FRS, and to compare them with the original FRS.
Methods: Our coronary prediction algorithms for Japanese were based on a large population-based cohort study (Suita study). The study population comprised 5,521 healthy Japanese. They were followed-up for 11.8 years on average, and 213 cases of CHD were observed. Multiple Cox proportional hazard model by stepwise selection was used to construct the prediction model.
Results: Our coronary prediction algorithms for Japanese patients were based on a large population-based cohort study (the Suita study). A multiple Cox proportional hazard model by stepwise selection was used to construct the prediction model. The C-statistics showed that the new model had better accuracy than the original and recalibrated Framingham scores. The net reclassification improvement (NRI) by the Suita score with the inclusion of CKD was 41.2% ($P<0.001$) compared with the original FRS. The recalibration of the FRS slightly improved the efficiency of the prediction, but it was still worse than the Suita score with the CKD model. The calibration analysis suggested that the original FRS and the recalibrated FRS overestimated the risk of CHD in the Japanese population. The Suita score with CKD more accurately predicted the risk of CHD.
Conclusion: The FRS and recalibrated FRS overestimated the 10-year risk of CHD for the Japanese population. A predictive score including CKD as a coronary risk factor for the Japanese population was more accurate for predicting CHD than the original Framingham risk scores in terms of the C-statics and NRI.

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Key words: Coronary heart disease, Risk score, Japanese cohort, Framingham risk score, Suita study

Introduction

The Framingham Heart Study identified the classic risk factors for coronary heart disease (CHD)[1], and it developed multivariable predictive instruments, which enable clinicians to estimate the 10-year individual risk of developing CHD[2, 3]. These findings have also been widely adopted in clinical guidelines[4, 5]. However, the FRS cannot be generalized for other populations, since 99% of the Framingham cohort participants were Caucasian[5]. For example, the use of the FRS in some other populations resulted in an overestimation of the CHD risk[6-8].

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There has been relatively little attention paid to the validity of the FRS in the Japanese population, which constitutes a unique population in many aspects, with a markedly lower incidence of CHD than Western populations[9]. To our knowledge, no previous Japanese cohort study has been performed to evaluate the original and recalibrated FRS.

Several Japanese cohort studies developed risk prediction tools for Japanese patients. The NIPPON DATA 80 prediction tool has been used as the standard prediction tool in Japan[10], and has been adopted by some clinical guidelines for the stratification of risk in Japanese subjects[11]. However, the NIPPON DATA 80's outcome measure was coronary death, not the incidence of CHD. The Hisayama study predicted a composite outcome of stroke and CHD[12]. Noda's prediction score also applied to cardiac mortality[13]. The JALS study group developed a prediction tool for acute myocardial infarction (AMI), but their prediction period was relatively short (five years)[14]. The JMS-cohort study chart was also targeted for AMI, but the population was limited to rural residents[15]. These tools are all associated with some advantages and disadvantages. However, additional tools for the prediction of CHD are needed that can accurately assess the risk of the longer-term incidence of CHD in the Japanese population.

In this context, we have developed a new algorithm, named the Suita Score, for predicting the 10-year probability of developing CHD, which is based on the findings of a large population-based cohort study performed in an urban area in Japan.

Furthermore, chronic kidney disease (CKD) has recently been advocated as an independent risk factor for CHD, and patients with CKD tend to possess multiple CVD risk factors, and thus represent a major public health problem[16, 17]. A recent CHD risk assessment tool based on 2.3 million patients, the QRISK2, included CKD as a necessary component for the risk prediction[18]. Moreover, CKD patients tend to have an underestimated CHD risk based on the FRS[19]. In addition, we previously reported that CKD leads to an increased risk of both MI and stroke[20]. Hence, the objective of this study was;

1) To incorporate established classic coronary risk factors into newly developed coronary prediction algorithms for the Japanese population,

2) To compare the discriminatory properties of this approach with those of the original and recalibrated FRS

Methods

Populations

The Suita study, a cohort study of urban residents in Japan, was started in 1989. It was based on a random sampling of 12,200 Japanese residents living in Suita. As a baseline, participants between the ages of 30 and 79 years of age were randomly selected from the municipality population registry in 1989. Of these, 6485 males and females underwent regular health checkups between September 1989 and March 1994. The subjects have continued to visit the National Cerebral and Cardiovascular Center (NCVC) every two years for regular health checkups[21-24]. A total of 1,546 subjects were excluded from the study based on a past history of CHD or stroke, non-fasting blood collections, missing data or because they were lost to follow-up. The data from the remaining 5,866 participants (2,788 males and 3,078 females) were used for the analyses. After exclusion of subjects with missing values, total 5,521 (male 2,796 and female 2,725) subjects were used to construct the risk scores. This cohort study was approved by the Institutional Review Board of the National Cerebral and Cardiovascular Center.

Baseline Examinations

Blood samples were collected after the participants had fasted for at least 10 hours. The samples were centrifuged immediately, and a routine blood examination was performed that included the serum total cholesterol (TC), high density lipoprotein cholesterol (HDLC), triglycerides (TG), serum creatinine (Cre) and fasting blood glucose (FBG) levels. The blood pressure was measured three times on the right arm after five minutes of rest by well-trained physicians using a standard mercury sphygmomanometer. The average of the second and third measurements was used for the analyses. Public health nurses obtained information on the smoking and drinking habits and medical histories. To ensure comparability with the FRS, the categorization of the BP, diabetes, TC and HDL-C in this study were done in accordance with the criteria used in the FRS model3. DM was defined as an FBG level ≥ 7.0 mmol/L (126 mg/dl) and/or current use of anti-diabetic medication. Cigarette smoking was dichotomized as current versus non-current. The LDL-C was determined by the Freidewald equation.

Definition of CKD

The serum Cre level was measured using the noncompensated kinetic Jaffe′ method. The estimated

glomerular filtration rate (eGFR) of each participant was calculated from Cre value and the age, using the MDRD equation below, modified with the Japanese coefficient (0.881)[25]:

eGFR (ml/min/1.73 m2) = $0.881*186*age^{-0.203}*Cre^{-1.154}$ (for males)

eGFR = $0.881*186*age^{0.203}*Cre^{-1.154}*0.742$ (for females).

The CKD stage was defined by the K/DOQI clinical practice guidelines[26]. CKD was categorized into Stage 3 CKD (eGFR 30-60 ml/min/1.73m^2) and Stage 4 or 5 CKD (eGFR < 30 ml/min/1.73m^2).

Endpoint Determination

The follow-up method used in the Suita study has been reported previously[20-24]. The endpoints for the current follow-up study were: (1) the date of the first diagnosis of CHD (2) the date of death, (3) the date when the subject left Suita or (4) censoring by December 31, 2007.

The first step in the survey for CHD involved checking the health status of all the participants at clinical visits carried out every two years, and by yearly questionnaires sent by mail or conducted by telephone. The second step involved the review of in-hospital medical records of participants who were suspected to have developed CHD. The criteria for definite or probable acute myocardial infarction were the same as the criteria used for the MONICA project[27].

In order to complete the surveillance for fatal MI, we also conducted a systematic search of death certificates. In addition to acute myocardial infarction, the criteria for a diagnosis of CHD included sudden cardiac death within 24 hours after the onset of acute symptoms, or CHD followed by coronary artery bypass or angioplasty.

Statistical Analysis

First, we evaluated the validity of categorical variables in the Suita Score to compare them with the original FRS[3]. Then, we conducted a multiple Cox proportional hazard model using the same categories as those in the FRS. Subsequently, we developed a new CHD risk score for Japanese subjects based on the Cox model for the Suita cohort. Other risk factors were calculated using the same categories as the FRS. A stepwise selection with a p-value of 0.1 for backward elimination was used to select the best predictive model.

After selection of the best Cox model, we fitted the hazard functions developed by the Framingham investigators from the previously published data[6] for predicting the 10-year probability of developing CHD in the Suita cohort. The probability function was: $P = 1 - S(t)^{\exp(X, M)}$; $f(X, M) = \beta_1*(X_1 - M_1) + \ldots + \beta_n*(X_n - M_n)$,

where S(t) is the survival rate for the mean values of the risk factors at 10 years in the Suita study; $\beta_1 \ldots \beta_n$ are the regression coefficients of the Cox model (β) shown in **Table 3** ; $X_1 \ldots X_n$ represent the individual risk factor values of each study participant and $M_1 \ldots M_n$ are the mean values of the risk factors in the Suita cohort. In the recalibrated Framingham functions, the coefficients were taken from the Framingham Cox model, but the mean values from the Suita cohort were used for the risk factors and the mean incidence rates[6].

Discrimination and calibration were used to evaluate the predictive capabilities of the models. We evaluated the discriminatory ability of this model by comparing the means of the C-statistics and Bayesian information criteria (BIC). Furthermore, we measured the model improvement as indicated by the clinical reclassification of the FRS by the Suita Score, which is considered to be more important indicator for predictive ability using the net reclassification improvement (NRI)[28]. Since the inclusion of a new biomarker in a prediction tool , such as the FRS, minimally improves the predictive ability, the evaluation based on the NRI is considered to be a valid approach for evaluating the new biomarker[29]. The NRI measures the reclassification of people from one risk category to another resulting from the addition of the new risk factor to a prediction model with established risk. If all of the people end up in a more correct risk class based on the model with the new marker, the NRI is positive. We calculated the category-free NRI[30].

The third approach was calibration, which measured how closely the predicted risk fit the actual risk. The Suita participants were divided into quintiles of 10-year CHD risk predicted by the Suita score functions, the original Framingham functions and the recalibrated Framingham functions[6]. The predicted and actual risk in each quintile were compared, and the differences were assessed by the Hosmer-Lemeshow chi-square tests. The SAS software program, version 9.3. (SAS Institute Inc), and the STATA software program, version 12 (STATA Corp LP), were used for all of the statistical analyses.

Results

Population Characteristics

The number of person-years studied consisted of 75,776 (34,480 for males and 41,296 for females), with a mean follow-up period of 11.8 years. During

Table 1. Population characteristics of the study cohort

	Males (n=2796)	Females (n=2725)
Age (years, mean ± SD)	56.1 ± 13.3	54.5 ± 12.9
DM (%)	6	5.8
Current smoker (%)	49.67	11.91
Blood pressure (mmHg, %)		
Optimal (SBP < 120, DBP < 80)	30.74	41.68
Normal (SBP < 130, DBP < 85)	19.31	17.30
High normal (SBP < 140, DBP < 90)	17.98	15.69
Stage I HT (SBP < 160, DBP < 100)	20.39	15.94
Stage II to IV HT (SBP > = 160, DBP ≥ 100)	11.59	9.40
Total cholesterol (mg/dl, %)		
< 160	10.12	6.88
160-199	39.75	30.52
200-239	37.41	39.60
240-279	10.98	18.51
≥ 280	1.74	4.49
LDL cholesterol (mg/dl, %)		
> 130	55.54	45.78
130-159	28.19	30.86
> 160	16.26	23.34
HDL cholesterol (mg/dl, %)		
< 35	11.40	3.28
35-44	28.71	16.36
45-49	15.87	12.25
50-59	23.82	29.95
≥ 60	20.20	38.14
Creatinine (mg/dl, mean ± SD)	0.91 ± 0.21	0.69 ± 0.22
eGFR (mean ± SD)	64.7 ± 24.9	90.6 ± 29.3
CKD (≥ Stage 3) (%)	46.2	11.3

LDL, Low-density lipoprotein; HDL, high-density lipoprotein;
eGFR, estimated glomerular filtration rate (ml/min/1.73 m^2); CKD, chronic kidney disease; HT, hypertension

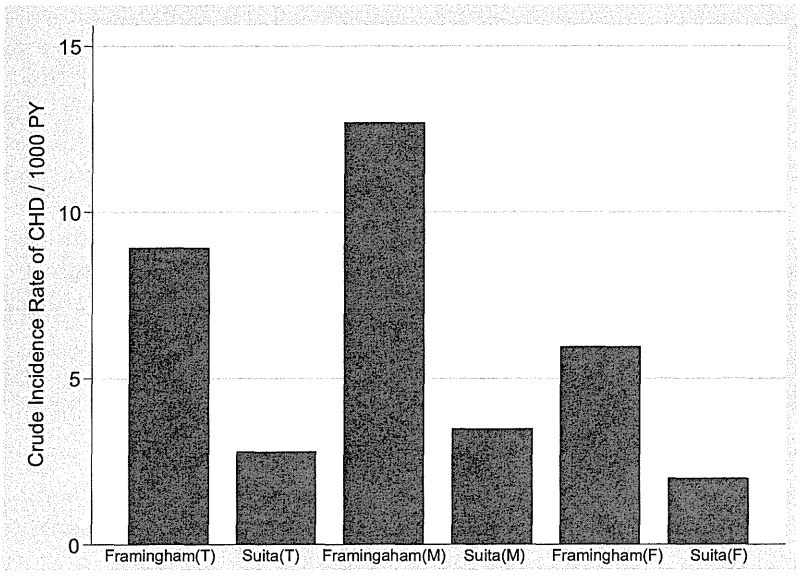

Fig. 1. The absolute risk difference of the Framingham cohort and Suita Study cohort

The Framingham cohort data were adopted from Wilson's study
CHD, coronary heart disease; PY, person-years; Framingham(T), total Framingham cohort; Framingham(M), Male Framingham cohort; Framingham(F), Female Framingham cohort; Suita(T), total Suita cohort; Suita (M), Male Suita cohort; Female Suita (F), Suita cohort

Table 2. The multivariable-adjusted hazard ratios for coronary heart disease based on the FRS categories

MALES				
Variable	Relative Risk	*P*-value	95% CI	Framingham Cohort
Age, y	1.07	<0.001	1.05-1.09	1.05
TC, mg/dl				
<200	Reference			
200-239	1.30	0.172	0.89-1.88	1.31
≥ 240	2.15	0.001	1.38-3.34	1.9
HDL-C mg/dl				
<35	2.06	0.001	1.37-3.10	1.47
35-59	Reference			
≥ 60	0.67	0.103	0.42-1.08	0.56
Blood Pressure				
Normal (including optimal)	Reference			
High normal	1.52	0.104	0.92-2.51	1.31
Stage I hypertension	2.24	<0.001	1.45-3.46	1.67
Stage II hypertension	2.34	0.001	1.41-3.86	1.84
Diabetes (y/n)	1.39	0.234	0.81-2.40	1.5
Smoking	1.25	0.193	0.89-1.76	1.68
CKD	1.34	0.109	0.94-1.92	N.A
FEMALES				
Variable	Relative Risk	*P*-value	95% CI	Framingham Cohort
Age, y	1.10	<0.001	1.07-1.13	1.04
TC, mg/dl				
<200	Reference			
200-239	0.58	0.097	0.30-1.10	1.51
≥ 240	1.38	0.272	0.78-2.46	1.72
HDL-C mg/dl				
<35	1.94	0.102	0.88-4.31	2.02
35-59	Reference			
≥ 60	1.04	0.881	0.61-1.79	0.58
Blood Pressure				
Normal (including optimal)	Reference			
High normal	1.60	0.222	0.75-3.38	1.3
Stage I hypertension	1.82	0.089	0.91-3.61	1.73
Stage II hypertension	3.86	<0.001	1.99-7.48	2.12
Diabetes (y/n)	2.59	0.013	1.23-5.49	1.77
Smoking	3.22	<0.001	1.74-5.97	1.47
CKD	1.38	0.247	0.80-2.40	N.A

FRS, Framingham risk score; All variables were adjusted for all FRS variables by a Cox proportional hazard model. CKD, chronic kidney disease; 95% CI, 95% confidence interval; N.A, not available

the follow-up period, there were 213 incidents of CHD. The population characteristics are summarized in **Table 1**. The univariate Cox regression analysis indicated all variables in FRS were statistically significant (data not shown).

Fig. 1 depicts the difference in the absolute risk for CHD between the Framingham cohort and Suita study cohort. The crude incidence rate of CHD in the original Framingham cohort was 8.94 per 1000 person-years, while that of the Suita cohort was 2.81 per 1000 person-years. The risk of developing CHD is nearly one-third of both the males and females in this study cohort.

The results of the multiple Cox proportional

hazard model using the same categories as those used in the FRS are shown in **Table 2**. All hazard ratios (HRs) of categorical hypertension were higher than those of the original FRS. The HRs of smoking and DM for females were also higher than those of the original FRS (2.59 and 3.22, respectively). The HR of a TC between 200 and 239 for females was 0.58, which was lower than that of the FRS. The HRs of other variables were similar to those of the original FRS.

Prediction Model Development and the Simplified Prediction Model for Clinical Use

Table 3 shows the best Cox model for the Suita cohort selected by a stepwise method with the total cholesterol categories. (TC Suita score) The multivariable adjusted HR for the association between CHD and Stage 3 CKD was 1.39 and that for Stage 4 and 5 CKD was 3.72, respectively. The HRs of the other predictors were similar between the with CKD and without CKD models.

Table 4 shows the best Cox model for the Suita Score with CKD according to the cut-off levels of LDL-C and HDL-C proposed in the Japan Atherosclerosis Society (JAS) Guidelines for the Prevention of Atherosclerotic Cardiovascular Diseases 2012[11, 31] (LDL Suita Score). For convenient clinical use, we developed prediction sheets based on the TC and LDL Suita Scores (**Table 5**). The beta coefficients corresponding to the Cox model were multiplied 10 times for categorical covariates and were rounded. For the age category, the midpoint of each category was multiplied by the β coefficients in **Table 4**, and then multiplied 10 times. We added all these values corresponding to each individual risk, divided the number by 10, and then the corresponding probability of CHD was calculated from the equation: P=1−S(t)^exp((sum of the points)/10) where S(t) is the baseline survival function of the Suita cohort.

The C-statistics of the LDL Suita Score with CKD in **Table 4**, which corresponded to the AUC of the Cox proportional hazard model, was 0.831. This was very similar to the TC Suita Score shown in **Table 3**, which had a C-index of 0.835 (**Table 6a**). The likelihood ratio test was not conducted, since the categorical variables were different and these two models were not nested. The NRI between TC Suita Score with CKD and the LDL Suita Score with CKD was not significant (P=.0.256; **Table 6b**). These findings suggest that the two models predict CHD with similar efficiency.

Validation of the Inclusion of CKD

The C-static of the Suita Score without CKD was slightly lower than the Suita Score with CKD (0.835 vs. 0.833). The comparison between the TC Suita Scores with and without CKD suggested that the addition of CKD improved the risk classification of CHD by 40%. This suggested that the inclusion of CKD in the risk prediction tool improves the prediction of the development of CHD, making it a more appropriate predictive tool.

Comparison of the Suita Score and Framingham Risk Scores

Table 7a shows the model fit, C-statistics and BIC of the Cox regression for the TC Suita Score, the original FRS and the recalibrated score for the mean value of each of the covariates. The TC Suita Score with CKD showed the best goodness-of-fit by the likelihood ratio test, and the C-statistics of the TC Suita Score with CKD were also the highest. The BIC was the lowest for the TC Suita Score with CKD, which supported its better predictive ability. The C-statistics were not changed by the recalibration of the FRS. The C-statistics of the recalibrated FRS were still smaller than the TC Suita Score with CKD.

The results of the clinical reclassification measured by the NRI are shown in **Table 7b**. The NRI for the TC Suita Score with CKD compared to the original FRS was 46.8% (P<0.001). In both the CHD and non-CHD groups, the risk categories tended to be increased by the TC Suita Score with CKD. The NRI between the TC Suita Score with CKD and the recalibrated model was lower (25.4%), but the difference remained significant (P=0.003). These associations also held for the TC Suita Score without CKD, the FRS and the recalibrated FRS.

Fig. 2 depicts the actual and predicted probabilities of the 10-year risk of cardiac events by calibration. The FRS consistently overestimated the cardiac events in all quintiles. The overall 10-year calibration of the FRS and recalibrated FRS were worse than the TC Suita Score with CKD as determined by the Hosmer-Lemeshow chi-square test (both p<0.001). The largest difference between the actual rate and the predicted rate after recalibration was 13.9% (in the fifth quintile in males), compared with the difference of 14.5% for the FRS. The difference between the actual probability and the TC Suita Score with CKD was not significant (P=0.18). The TC Suita Score with CKD model underestimated the risk of CHD in the fourth quintile, but the difference was only 2.2%. These findings consistently indicated that the FRS overestimates the CHD risk in the Japanese population.

Table 3. The Cox regression coefficients for the Suita cohort adjusted for the original FRS variables (TC Suita Score)

3a. TC Suita Score with CKD

	β	HR	*P*-value	95% CI
Age, years	0.0766382	1.08	<0.001	1.06-1.10
Female	−0.5866078	0.56	0.001	0.39-0.78
Smoking	0.4865127	1.63	0.002	1.20-2.21
DM	0.4557071	1.59	0.042	1.02-2.45
Blood Pressure				
Optimal	−0.7183575	0.49	0.003	0.31-0.78
Normal and high normal	Referent	Reference	Reference	Reference
Stage I hypertension	0.3330895	1.40	0.055	0.99-1.96
Stage II hypertension	0.59332684	1.81	0.002	1.25-2.63
TC (mg/dl)				
<160	−1.112393	0.33	0.008	0.14-0.74
160-239	Referent	Reference	Reference	Reference
240-279	0.5110573	1.67	0.003	1.19-2.32
Over 280	0.8511397	2.34	0.002	1.36-4.04
HDL(mg/dl)				
<35	0.6173452	1.85	0.001	1.27-2.71
35-50	Referent	Reference	Reference	Reference
50-59	−0.5096169	0.60	0.008	0.41-0.87
Over 60	−0.4322771	0.65	0.022	0.45-0.94
CKD				
Stage 3	0.3278965	1.39	0.035	1.02-1.88
Stage 4 or 5	1.315004	3.72	0.005	1.48-9.38

3b. TC Suita Score without CKD

	β	HR	*P*-value	95% CI
Age, years	0.0806456	1.08	<.0001	1.07-1.10
Female	−0.7401036	0.48	<.0001	0.35-0.66
Smoking	0.4527364	1.57	0.004	1.16-2.14
DM	0.424255	1.52	0.059	0.98-2.37
Blood Pressure				
Optimal	−0.7017837	0.50	0.004	0.31-0.79
Normal and high normal	Referent	Reference	Reference	Reference
Stage I hypertension	0.3607005	1.43	0.037	1.02-2.01
Stage II hypertension	0.6305927	1.87	0.001	1.30-2.72
TC (mg/dl)				
<160	−1.073273	0.34	0.010	0.16-0.78
160-239	Referent	Reference	Reference	Reference
240-279	0.5408852	1.71	0.001	1.23-2.40
Over 280	0.8678275	2.38	0.002	1.38-4.10
HDL(mg/dl)				
<35	0.6742382	1.96	<.0001	1.35-2.86
35-50	Referent	Reference	Reference	Reference
50-59	−0.5011838	0.61	0.009	0.44-0.93
Over 60	−0.4464421	0.64	0.018	0.15-0.93

CKD, chronic kidney disease; TC, total cholesterol; LDL, low density lipoprotein; 95% CI, 95% confidence interval; CKD, chronic kidney disease; HR, hazard ratio; all other abbreviations are the same as in Table 1. The gender difference was incorporated into the model as a covariate to improve the predictability of the model.

Table 4. The LDL Suita Score with CKD model according to the JAS Guideline 2012 LDL/HDL cut-off (n=5,727) (LDL Suita Score)

4a. The LDL Suita Score with CKD

	β	HR	P-value	95% CI
Age, years	0.0760078	1.08	<0.001	1.06-1.10
Female	−0.6619839	0.52	<0.001	0.36-0.74
Smoking	0.5031949	1.65	0.002	1.20-2.28
DM	0.5533678	1.74	0.031	1.05-2.88
Blood Pressure				
Optimal	−0.6763825	0.51	0.005	0.32-0.82
Normal and high normal	Reference	Reference	Reference	Reference
Stage I hypertension	0.4189501	1.52	0.019	1.07-2.16
Stage II hypertension	0.5935986	1.81	0.001	1.22-2.68
LDL (mg/dl)				
<100	Reference	Reference	Reference	Reference
100-140	0.5319015	1.70	0.039	1.03-2.81
140-160	0.6837867	1.98	0.015	1.14-3.43
160-180	1.021015	2.78	<0.001	1.57-4.91
Over 180	1.128479	3.09	<0.001	1.69-5.66
HDL(mg/dl)				
<40	Reference	Reference	Reference	Reference
40-59	−0.4730423	0.62	0.005	0.45-0.87
≥ 60	−0.5822414	0.56	0.007	0.37-0.85
CKD				
Stage 3	0.2893668	1.34	0.071	0.98-1.83
Stage 4 or 5	1.388216	4.01	0.008	1.43-11.25

4b. The LDL Suita Score without CKD

	β	HR	P-value	95% CI
Age, years	0.0795083	1.08	<0.001	1.06-1.10
Female	−0.804252	0.45	<0.001	0.32-0.62
Smoking	0.4642934	1.59	0.004	1.16-2.19
DM	0.3955565	1.48	0.106	0.91-2.40
Blood Pressure				
Optimal	−0.6602255	0.52	0.006	0.32-0.83
Normal and high normal	Reference	Reference	Reference	Reference
Stage I hypertension	0.4467296	1.56	0.012	1.10-2.21
Stage II hypertension	0.6256262	1.87	0.002	1.27-2.76
LDL (mg/dl)				
<100	Reference	Reference	Reference	Reference
100-140	0.5040579	1.66	0.049	1.00-2.74
140-160	0.664678	1.94	0.017	1.57-4.90
160-180	1.01949	2.77	<0.001	1.73-4.90
Over 180	1.151674	3.16	<0.001	1.73-5.80
HDL (mg/dl)				
<40	Reference	Reference	Reference	Reference
40-59	−0.4798994	0.62	0.004	0.45-0.86
≥ 60	−0.6092216	0.54	0.005	0.36-0.83

JAS Guideline 2012, Japan Atherosclerosis Society(JAS) Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2012; CKD, chronic kidney disease; LDL, low density lipoprotein; 95% CI, 95% confidence interval; CKD, chronic kidney disease; HR, hazard ratio; all other abbreviations are the same as in Table 1. Stage 3 and Stage 4 or 5 CKD were defined by estimated GFR levels of 30-60 ml/min/1.73 m^2 and less than 30 ml/min/1.73 m^2, respectively.

Table 5. Prediction score sheets for TC/ LDL Suita score

5a. TC Suita scoore

Risk Factor	
Variable	Score
Age	
36-45	30
46-55	39
56-65	46
>65	58
Female	−6
Current Smoker	5
DM	5
Blood pressure	
Optimal blood pressure	−7
Normal and high normal	0
Stage 1 hypertension	3
Stage 2 hypertension	6
TC (mg/dl)	
<160	−11
160-239	0
240-279	5
>280	9
HDL (mg/dl)	
<35	6
36-49	0
50-59	−5
>=60	−5
CKD	
eGFR>60	0
Stage 3	3
Stage 4 or 5	15
Total Score	A

Predicted Probability of CHD in 10 years	
Total Score	Probability (%)
30<=	<1
31-35	1
36-40	2
41-45	4
46-50	6
51-55	10
56-60	15
>=61	24

5b. LDL Suita Score

Risk Factor	
Variable	Score
Age	
35-44	30
45-54	38
55-64	45
65-69	51
>=70	53
Female	−7
Current Smoker	5
DM	6
Blood pressure	
Optimal blood pressure	−7
Normal and high normal	0
Stage 1 hypertension	4
Stage 2 hypertension	6
LDL (mg/dl)	
<100	0
100-139	5
140-159	7
160-179	10
>=180	11
HDL (mg/dl)	
<40	0
40-59	−5
>=60	−6
CKD	
eGFR>60	0
Stage 3	3
Stage 4 or 5	14
Total Score	A

Predicted Probability of CHD in 10 years	
Total Score	Probability (%)
35<=	<1
36-40	1
41-45	2
46-50	3
51-55	5
56-60	9
61-65	14
66-70	22
71<=	>28

Estimates risk for CHD over a period of 10 years based on Suita Cohort experience at baseline. Summation of risk factor category points yield total score. JAS Guideline 2012, Japan Atherosclerosis Society (JAS) Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2012. LDL cholesterol was derived by Fridewald's equation. Those who have triglycerides>400 were omitted for the calculation.

Discussion

In this study, we demonstrated the predictive ability of newly developed coronary prediction algorithms for Japanese subjects developed in the manner of the FRS. Our findings can be summarized as follows: 1) the risk profile for CHD of a Japanese population was considerably different from that of the original Framingham Heart Study cohort; 2) The prediction of CHD obtained with the risk score based on the Suita cohort with CKD variables was superior to that of the FRS or recalibration of the FRS; 3) Clinical reclassification revealed that the FRS overestimates the CHD risk in the Japanese population.

First, the risk profile of the Suita cohort proved to be considerably different from that of a Western population. The crude incidence rate of CHD in the original Framingham Cohort was 8.94 per 1000 person-years, while that of the Suita cohort was only 2.81 per 1000 person-years. The risks of hypertension, low HDL-C for males, and diabetes and smoking for females, in the Suita cohort were weighted higher than the risks in the Framingham cohort. This difference between the Suita and the Framingham cohorts constitutes a major concern for the application of the FRS in Japanese subjects, where the lower CHD incidence