Original Article

Association between Non-High-Density Lipoprotein Cholesterol Levels and the Incidence of Coronary Heart Disease among Japanese: The Circulatory Risk in Communities Study (CIRCS)

Akihiko Kitamura[1], Hiroyuki Noda[2], Masakazu Nakamura[1], Masahiko Kiyama[1], Takeo Okada[1], Hironori Imano[3], Tetsuya Ohira[3], Shinichi Sato[4], Kazumasa Yamagishi[5], and Hiroyasu Iso[3]

[1]Osaka Medical Center for Health Science and Promotion, Osaka, Japan
[2]Osaka University Hospital Medical Center for Translational Research, Osaka, Japan
[3]Public Health Department of Social and Environmental Medicine, Osaka University Graduate School of Medicine, Osaka, Japan
[4]Chiba Prefectural Institute of Public Health, Chiba, Japan
[5]Department of Public Health Medicine, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Ibaragi, Japan

***Aim*: The aim of this study was to identify the threshold level for non-high-density lipoprotein cholesterol (non-HDL-cholesterol) to raise the risk of coronary heart disease (CHD) incidence in a Japanese general population.**
***Methods*: A total of 8,132 men and women, aged 40 to 69 years with no history of stroke or CHD, completed the baseline risk factor surveys between 1975 and 1987. Systematic surveillance of cardiovascular disease incidence was performed through 2003 (the median follow-up period was 21.9 years), and 155 incidents of CHD were identified.**
***Results*: We found a statistically significant association between non-HDL-cholesterol levels and the risk of CHD with a threshold around 140 mg/dL. After adjustment for potential confounding factors, this association did not change materially. The multivariable hazard ratio of CHD compared with that for levels of <100 mg/dL was 2.49 (95% confidence interval: 1.35 to 4.61) for 140-159 mg/dL and 3.13 (1.58-6.21) for ≥180 mg/dL. Setting the cut-off point at ≥140 mg/dL non-HDL-cholesterol resulted in the greatest improvement of integrated discrimination.**
***Conclusions*: Higher concentrations of non-HDL-cholesterol are associated with an increased risk of CHD with a threshold around 140 mg/dL, suggesting that the optimal cut-off point for healthy persons to prevent increasing the risk of CHD might be around 140 mg/dL non-HDL-cholesterol.**

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Key words; Non-HDL-cholesterol, Coronary heart disease, Epidemiology, Primary prevention

Introduction

Non-high-density-lipoprotein cholesterol (non-HDL-cholesterol) as well as low-density-lipoprotein cholesterol (LDL-cholesterol) is a major risk factor for artherosclerotic disease[1-10], and management of these lipids is important for the prevention of coronary heart disease (CHD)[11, 12]; however, current guidelines in the United States and Japan do not stress the importance of non-HDL-cholesterol as much as that of LDL-cholesterol[11-13]. In fact, the National Cholesterol Educational Program (NCEP) Expert Panel recommended the use of LDL-cholesterol as the primary indicator of therapy and primary prevention of CHD, while non-HDL-cholesterol was only a secondary target of therapy for patients with hypertriglyceridemia[11, 12]. The Japan Atherosclerosis Society's guidelines also use a cut-off point for LDL-cholesterol, but not for non-HDL-cholesterol, as an indicator for atherogenic lipid management[13].

However, a recent study has shown that direct measurements of LDL-cholesterol as well as triglycer-

Address for correspondence: Akihiko Kitamura, Osaka Medical Center for Health Science and Promotion, 1-3-2 Nakamichi, Higashinari-ku, Osaka 537-0025, Japan
E-mail: xkita-2008@kenkoukagaku.jp
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ides may not be fully standardized in many clinical laboratories[14]. This indicates that LDL-cholesterol estimated with the Friedewald formula[15] as well as directly measured may include measurement errors, which may jeopardize satisfactory lipid monitoring and control in clinical practice.

Non-HDL-cholesterol is easily calculated by using total and HDL-cholesterol concentrations, the determinations of which are well standardized[14, 16]. It has been shown that the predictive value of non-HDL-cholesterol is similar to or better than that of LDL-cholesterol from epidemiological studies[1, 3, 5, 6, 8]; therefore, non-HDL-cholesterol could be a more reliable indicator than LDL-cholesterol for the prevention of CHD in community-based preventive strategies. In Japan, two prospective studies, the Suita study[8] and the JALS-ECC[10], showed a positive association between non-HDL-cholesterol and the incidence of CHD; however, the optimal cut-off point of non-HDL-cholesterol for the primary prevention of CHD remained unclear.

We therefore examined the threshold level of non-HDL-cholesterol to increase the risk of CHD by a prospective cohort study in a Japanese general population in order to estimate the optimal cut-off point for healthy persons to prevent increasing the risk of CHD.

Methods

Study Cohort

The participants consisted of a population-based sample aged 40 to 69 years living in four communities in Japan included in the Circulatory Risk in Communities Study (CIRCS)[17]. They participated in the cardiovascular risk surveys conducted between 1975 and 1980 in Ikawa and Noichi, between 1975 and 1984 in Yao, and between 1981 and 1987 in Kyowa, from which we obtained data for lipid profiles and confounding variables. The proportion of subjects who participated in the surveys was 77% for the total census population.

From the 8,158 participants (3,201 men and 4,957 women), we excluded 26 persons with a confirmed history of CHD and/or stroke at the time of baseline inquiry, because our purpose was to examine the association between non-HDL-cholesterol and the primary incidence of CHD. As a result, 8,132 persons (3,178 men and 4,954 women) were enrolled in the present analysis. The Ethics Committee of Osaka Medical Center for Health Science and Promotion approved this study.

Measurement of Risk Factors

Serum total cholesterol, HDL-cholesterol and triglycerides were measured with enzymatic methods using an automatic analyzer (Hitachi 7250; Hitachi Medical Corp., Hitachi, Japan). These measurements were performed at Osaka Medical Center for Cancer and Cardiovascular Diseases, which has been standardized since April 1975 by the U.S. Centers for Disease Control (CDC)-National Heart, Lung, and Blood Institute (NHLBI) Lipid Standardization Program[14, 16]. Non-HDL-cholesterol was calculated as follows: Non-HDL-cholesterol = Total cholesterol - HDL-cholesterol.

Diabetes was defined as a plasma glucose level of ≥126 mg/dL during fasting or ≥200 mg/dL during non-fasting, or use of medication for diabetes, while borderline diabetes was defined as a plasma glucose level of 110-125 mg/dL at fasting or 140-199 mg/dL at non-fasting, and no use of medication for diabetes. As for blood pressure, mild hypertension was categorized as systolic blood pressure 140-159 mmHg or diastolic blood pressure 90-99 mmHg, while the corresponding values for moderate hypertension were 160-179 mmHg or 100-109 mmHg, and for severe hypertension ≥180 mmHg or ≥110 mmHg, based on World Health Organization-International Society of Hypertension (WHO-ISH) Guidelines[18]. Height in stocking feet and weight in light clothing were measured, and body mass index (BMI) was calculated as weight (kg)/height $(m)^2$. An interview was conducted to ascertain the smoking status, the number of cigarettes smoked per day, and usual alcohol intake per week.

Follow-Up Study

The follow-up was conducted by annual cardiovascular risk surveys to obtain information on incident CHDs from the participants. For non-participants in any of the surveys, these endpoints were ascertained by means of a mailed questionnaire or a death certificate to establish the underlying cause of death (International Classification for Diseases, 9th edition: 410 to 414, 428, 429 and 430 to 438). We also used national insurance claims, ambulance records, reports by local physicians and public health nurses for case ascertainment. To confirm the diagnosis, all living patients were telephoned or visited to obtain their medical history, and their medical records at hospitals were also reviewed. In the case of death, we obtained histories from the deceased's family and reviewed the medical records.

The criteria for CHD used in our study were modified from those of the World Health Organiza-

tion Expert Committee[19]. Definite myocardial infarction (MI) was defined as the presence of typical chest pain lasting for ≥30 minutes accompanied by the appearance of abnormal and persistent Q or QS waves, or changes in cardiac enzyme activity or both. Probable MI was defined as the presence of typical chest pain but for which the findings of electrocardiogram or enzyme activity were not available. Angina pectoris was defined as repeated episodes of chest pain during effort, especially when walking, usually disappearing rapidly after the cessation of effort or the use of sublingual nitroglycerin. The date of the first episode was identified as the date of angina pectoris incidence. We did not include cases whose clinical examination data were negative for MI or angina pectoris, even if clinical symptoms corresponded to our criteria. Sudden cardiac death was defined as death within 1 hour of onset, a witnessed cardiac arrest, or abrupt collapse not preceded by ≥1 hour of symptoms. We excluded sudden cardiac death cases whose cause of death had been diagnosed as lethal arrhythmia, cardiomyopathy, stroke, and other organic heart diseases. CHD was defined as including definite or probable MI, angina pectoris, and sudden cardiac death. The final diagnosis of CHD was made by a panel of three or four physicians, blinded to the baseline data.

For each of the participants, the person-years of follow-up were calculated from the date of the baseline survey to the date of CHD incidence, death, exit from the community, or the end of 2003, whichever occurred first. Participants who moved away from the community (5.9%) were treated as censored. The total person-years studied were 173,025 with a median follow-up period of 21.9 years.

Statistical Analysis

First, sex- and age-adjusted means and proportions of selected cardiovascular risk factors at the baseline survey were identified according to non-HDL-cholesterol categories. Analysis of covariance and Mantel-Haenszel chi-square tests were used to examine differences among non-HDL-cholesterol categories in terms of sex- and age-adjusted mean values and proportions of baseline characteristics.

Second, we examined, non-parametrically and with restricted cubic splines[20], possible non-linear associations between non-HDL-cholesterol levels and risk of CHD. Because sparse tail data may lead to a visual influence (i.e. overestimation of risk difference), predictions from the top and bottom 1% of the analytical distribution are not included in the graph. We used 5 knots, the values of which corresponded to 81 mg/dL, 110 mg/dL, 130 mg/dL 152 mg/dL and 193 mg/dL of non-HDL-cholesterol levels.

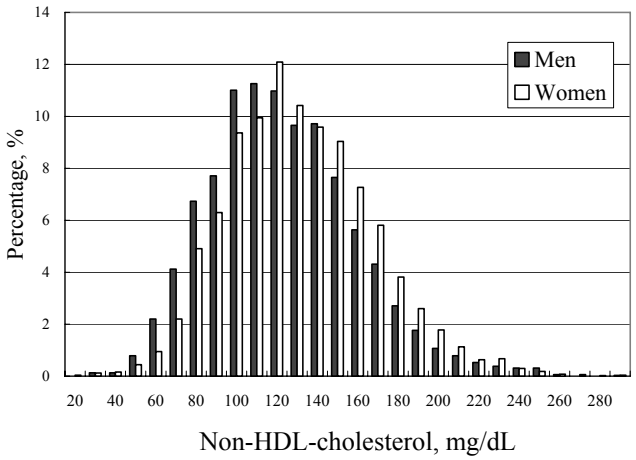

Fig. 1. Sex-specific histogram for distribution of non-HDL-cholesterol.

The distribution percentages for men were 35% for ≥140 mg/dL, 18% for ≥160 mg/dL, 8% for ≥180 mg/dL, and 3% for ≥200 mg/dL. The corresponding percentages for women were 43%, 24%, 11%, and 5%.

Third, categorical analysis was based on the incidence rates of CHD divided by clinical categories of non-HDL-cholesterol (<100, 100-120, 120-139, 140-159, 160-179, ≥180 mg/dL). The Cox proportional hazards model was used to calculate the sex- and age-adjusted and multivariable hazard ratios (HRs) and 95% confidence intervals (95%CI) after adjustment for sex, age and potential confounding factors, which included the blood pressure category (normal, mild, moderate, and severe hypertension), antihypertensive medication use (yes or no), glucose category (normal, borderline diabetes, and diabetes), BMI category (sex-specific quartiles), smoking status (never, ex- and current cigarette smokers at <20 and ≥21 cigarettes per day), alcohol intake category (never, ex-drinker, and current drinker of ethanol at 1 to 22, 23 to 45, 46 to 68, and ≥69 g per day), lipid-lowering medication use (yes or no), HDL-cholesterol category (<40, 40-49, 50-59, 60-69, and ≥70 mg/dL) and triglyceride category (<100, 100-149, 150-199, 200-249, and ≥250 mg/dL), fasting status (<8 hours versus ≥8 hours after last meal), entry year of baseline survey, and study area. We tested the assumption of proportional hazards and found no violation of the proportionality principle. Tests for effect modification by sex or other cardiovascular risk factors were conducted with an interaction term generated by multiplying the continuous variable of non-HDL-cholesterol by sex or other cardiovascular risk factors.

Finally, to confirm whether the threshold of non-

Table 1. Sex- and age-adjusted mean and prevalence as baseline characteristics of participants according to non-HDL-cholesterol categories

	Non-HDL-cholesterol, mg/dL					
	<100	100-119	120-139	140-159	160-179	180+
Median, mg/dL	86	110	129	149	168	197
Range, mmol/L	<2.59	2.59-3.09	3.10-3.61	3.62-4.13	4.14-4.64	4.65+
Number of persons	1,442	1,665	1,771	1,475	964	815
Men, %	48.1	42.5†	37.0†	37.4†	32.8†	31.0†
Age, year	49.9	50.8†	51.9†	52.4†	53.3†	53.9†
Total cholesterol, mg/dL	147.9	168.9†	185.6†	203.1†	221.0†	252.4†
HDL-cholesterol, mg/dL	64.1	59.0†	56.5†	54.1†	52.4†	49.5†
Triglycerides, mg/dL	94.7	110.4†	128.9†	152.4†	173.9†	208.1†
Lipid-lowering medication use, %	0.0	0.0	0.1	0.1	0.1	0.5†
Body mass index, kg/m^2	22.1	22.7†	23.2†	23.7†	24.1†	24.7†
Systolic blood pressure, mmHg	133.1	132.8	133	134.3	135.3†	136.5†
Diastolic blood pressure, mmHg	79.1	79.4	80.1*	81.4†	82.7†	83.4†
Non-hypertension, %	66.2	65.6	65.8	61.4†	58.8†	55.5†
Mild hypertension, %	21.7	22.1	22.3	24.3	24.9	28.9†
Moderate hypertension, %	8.5	8.8	9.2	11.0*	12.3†	12.7†
Severe hypertension, %	3.6	3.5	2.7	3.2	4.0	2.8
Antihypertensive medication use, %	10.1	9.1	9.4	12.4*	10	13.9†
Non-diabetes, %	80	77.8	79.5	78.2	81.4	78
Borderline diabetes, %	4.6	6.4*	6.2	8.2†	7.2*	9.7†
Diabetes, %	2.8	2.3	3.0	3.4	2.8	4.8†
Current smoker, %	29.7	29.1	26.0†	28.6	28.6	32.3
Current drinkers, %	50.6	49.5	45.9†	44.1†	43.6†	37.4†

Test for difference from persons in lowest category; *$p<0.05$, †$p<0.01$

HDL-cholesterol shown in the categorical analysis is the optimal cut-off level, we examined changes in integrated discrimination improvement (IDI)[21] and Akaike's Information Criteria (AIC)[22] at different cut-off points. We selected non-HDL-cholesterol values on the basis of primarily a higher IDI and secondarily a smaller AIC in multivariable Cox proportional hazard models with potential confounding factors as better cut-off points for the prediction of CHD, and used these cut-off points to reduce the misclassification of risk prediction.

All statistical tests were two-sided and $p<0.05$ was regarded as statistically significant. SAS, version 9.13 (SAS Institute, Inc., Cary, NC, USA) was used for all statistical analyses.

Results

Fig. 1 shows a sex-specific histogram of non-HDL-cholesterol distribution at the baseline survey. The percentages were 35% for men with ≥140 mg/dL and 8% for men with ≥180 mg/dL. The corresponding percentages for women were 43% and 11%. The mean value (±standard deviation) was 128.0 mg/dL (±36.1) for men and 136.0 mg/dL (±36.4) for women.

Table 1 shows selected cardiovascular risk factors at the baseline survey according to non-HDL-cholesterol categories. The median value of non-HDL-cholesterol categories was 86mg/dL, 110 mg/dL, 129 mg/dL, 149 mg/dL, 168 mg/dL and 197 mg/dL in each category. Compared with persons in the lowest category of non-HDL-cholesterol (<100 mg/dL), persons in the highest category (≥180 mg/dL) tended to have higher means of total cholesterol levels, triglycerides, body mass index, and systolic and diastolic blood pressures, and lower means of HDL-cholesterol. Also, they were more likely to be female, older, hypertensive, with diabetes, to use of medication for hypertension and hyperlipidemia, and less likely to drink.

During the follow-up period, we identified 155 incidences of CHD, comprising 91 MI, 36 angina pectoris and 28 sudden cardiac death. Higher non-HDL-cholesterol levels were associated with increased

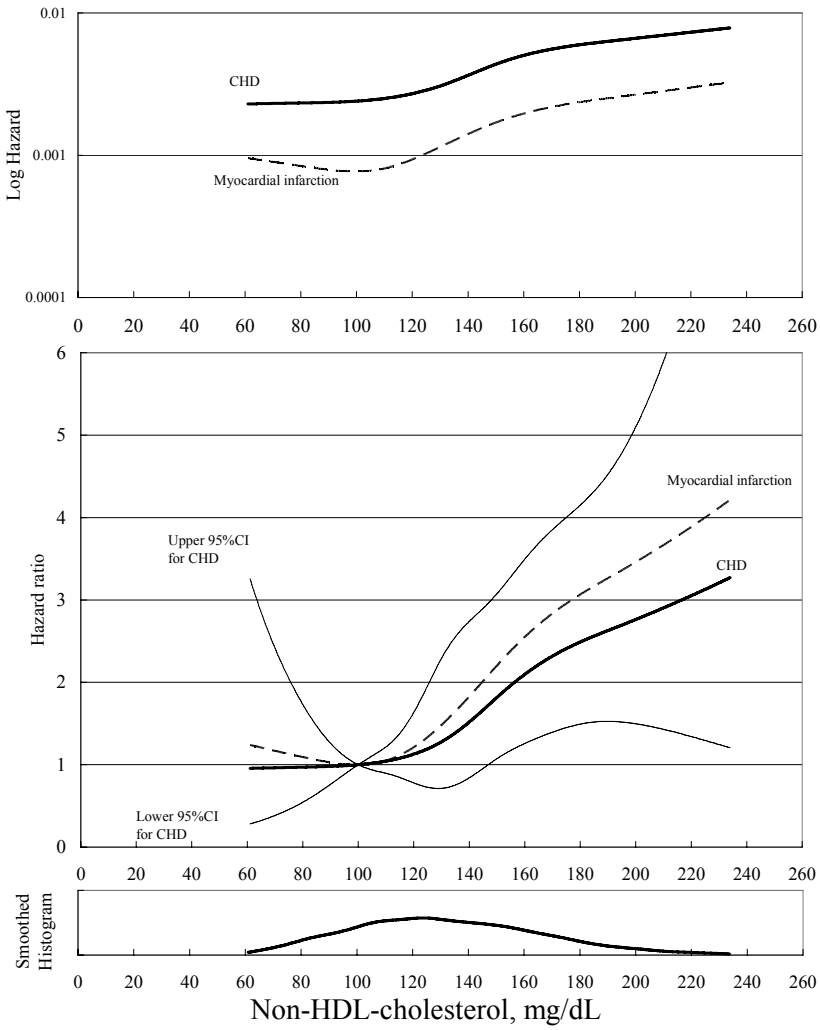

Fig. 2. Multivariable log hazard and multivariable HR for CHD and MI in relation to non-HDL-cholesterol levels.

100 mg/dL of non-HDL-cholesterol was selected as a reference for HR. The values of the five knots corresponded to 81 mg/dL, 110 mg/dL, 130 mg/dL 152 mg/dL and 193 mg/dL of non-HDL-cholesterol levels. The *p*-values for linearity were $p=0.0002$ for CHD and $p=0.001$ for MI. The smoothed histogram shows the distribution of non-HDL-cholesterol levels.

risks of CHD and MI, with a threshold between 120 mg/dL and 140 mg/dL (**Fig. 2**). The HR was fairly flat for non-HDL-cholesterol levels less than 120 mg/dL. The graph suggests that the risk of CHD and MI may start to increase at non-HDL-cholesterol levels between 120 mg/dL and 140 mg/dL.

In the categorical analysis, higher non-HDL-cholesterol levels were found to be associated with increased risks of CHD and MI, with a threshold at around 140 mg/dL (**Table 2**). Adjustment for potential confounding factors did not alter these associations materially. The multivariable HR of CHD compared with that for levels of <100 mg/dL was 2.49 (95% confidence interval (95%CI): 1.35 to 4.61) for 140-159 mg/dL and 3.13 (1.58-6.21) for ≥180 mg/dL. The respective multivariable HR of MI was 3.17 (1.40-7.22) and 4.09 (1.64-10.21). These positive associations were similar for men and women with no sex interaction ($p=1.00$ for total CHD, and $p=0.70$ for MI). These results did not alter after exclusion of triglycerides in potential confounding factors (not shown in the tables). There was no interaction of years at entry (1970s versus 1980s) on an association between non-HDL-cholesterol and CHD risk

Table 2. Crude incidence rate (per 100,000 person-years), sex- and age-adjusted and multivariable hazard ratio (HR) and 95% confidence interval (95%CI) of coronary heart disease (CHD) according to categories of non-HDL-cholesterol

	Non-HDL-cholesterol, mg/dL					
	<100	100-119	120-139	140-159	160-179	180+
Persons	1,442	1,665	1,771	1,475	964	815
Person-years	31,161	35,899	38,027	31,076	20,296	16,566
CHD						
No	17	24	21	42	21	30
Crude incidence rate	55	67	55	135	103	181
Sex- and age-adjusted HR	1.0	1.32 (0.71-2.45)	1.09 (0.57-2.07)	2.79 (1.58-4.91)	2.22 (1.16-4.23)	3.90 (2.13-7.13)
Multivariable HR*	1.0	1.25 (0.66-2.36)	1.06 (0.54-2.06)	2.49 (1.35-4.61)	1.81 (0.90-3.63)	3.13 (1.58-6.21)
MI						
No	9	14	12	26	11	19
Crude incidence rate	29	39	32	84	54	115
Sex- and age-adjusted HR	1.0	1.48 (0.64-3.43)	1.23 (0.52-2.92)	3.42 (1.60-7.32)	2.34 (0.97-5.68)	5.07 (2.27-11.30)
Multivariable HR*	1.0	1.44 (0.61-3.38)	1.23 (0.50-3.03)	3.17 (1.40-7.22)	2.01 (0.77-5.23)	4.09 (1.64-10.21)

*HR (95%CI) adjusted for age and potential confounding factors.
Potential confounding factors: blood pressure category, antihypertensive medication use, glucose category, BMI category, smoking status, alcohol intake category, lipid-lowering medication use, categories of HDL-cholesterol and triglycerides, fasting status, years at entry and study area.

(p for interaction was 0.43).

The associations between non-HDL-cholesterol and the risk of CHD were different according to the presence of glucose abnormality or HDL-cholesterol levels, although gender and other risk factors did not affect the associations (**Table 3**). The multivariable HR (95% CI) for ≥180 mg/dL versus <100 mg/dL of non-HDL-cholesterol was 5.83 (2.48-13.71) for persons with normal glucose, 0.53 (0.07-3.91) for those with borderline diabetes or diabetes (p for interaction=0.04). The corresponding HR was 1.12 (0.29-4.26) for those with ≥56 mg/dL HDL-cholesterol, and 5.73 (1.88-17.46) for those with <56 mg/dL HDL-cholesterol (p for interaction=0.002).

Fig. 3 supports that the optimal cut-off point appears to be around 140 mg/dL non-HDL-cholesterol. Setting this cut-off point yielded the highest IDI for the range between 80 mg/dL and 200 mg/dL of non-HDL-cholesterol levels, suggesting a major improvement in misclassification with this cut-off point. The IDI (95% CI) was highest at non-HDL-cholesterol 140 mg/dL with a value of 0.0035 (0.0010-0.0060; p=0.007), mainly due to an increase in integrated sensitivity (+0.0033; p=0.009), but not in integrated specificity (+0.0001; p=0.27). The respective multivariable HR (95% CI) was 2.16 (1.51-3.11; p<0.0001) and the largest was 2.19 (1.53-3.14; p<0.0001) for ≥141 mg/dL versus <141 mg/dL. We also obtained the lowest AIC for a similar level of non-HDL-cholesterol (141 mg/dL).

Discussion

In the present population-based prospective study of Japanese, we observed a statistically significant association between non-HDL-cholesterol levels and risks of CHD and MI with a threshold around 140 mg/dL. Non-parametric analysis showed that the risk of CHD and MI started to increase around 140 mg/dL non-HDL-cholesterol. Although the existence of a threshold does not always mean that the optimal cut-off level should be the same value, the absence of an increase in risk below this threshold suggests that the optimal cut-off point for Japanese to prevent increasing the risk of CHD may be around 140 mg/dL non-HDL-cholesterol.

This cut-off point resulted in improvement of the misclassification of risk prediction. The selection of ≥140 mg/dL of non-HDL-cholesterol as the cut-off point yielded higher values for IDI, suggesting a major improvement in misclassification. The model fitting AIC was also better for a similar value (141 mg/dL non-HDL-cholesterol). Although few studies have examined the target value for non-HDL-cholesterol levels, the NCEP Expert Panel has suggested that a reasonable goal for non-HDL-cholesterol is 30 mg/dL higher than the LDL-cholesterol goal[11]. The NCEP Expert Panel suggested that the LDL-cholesterol goal could be <100 mg/dL, so the non-HDL-cholesterol goal for healthy persons may be <130 mg/dL. Our results constitute additional epidemiological evidence for this advice, which suggests that the

Table 3. Crude incidence rate (per 100,000 person-years), multivariable hazard ratio (HR)* and 95% confidence interval (95%CI) of coronary heart disease according to non-HDL-cholesterol levels, stratified by gender and other risk factors

	Non-HDL-cholesterol, mg/dL						HR per 30 mg/dL increment	*p* for interaction
	<100	100-119	120-139	140-159	160-179	180 +		
Men								
No	15	19	11	25	11	18	99	
Crude incidence rate	103	130	81	225	172	370	152	
Multivariable HR*	1.0	1.18 (0.59-2.37)	0.78 (0.34-1.75)	2.05 (1.00-4.19)	1.45 (0.62-3.39)	3.43 (1.53-7.71)	1.31 (1.10-1.56)	
Women								
No	2	5	10	17	10	12	56	
Crude incidence rate	12	24	41	85	72	103	52	
Multivariable HR*	1.0	1.67 (0.32-8.70)	2.75 (0.59-12.84)	5.88 (1.31-26.50)	4.30 (0.90-20.57)	5.90 (1.23-28.32)	1.40 (1.15-1.70)	1.00
Non-hypertension								
No	12	7	10	16	7	10	62	
Crude incidence rate	57	29	41	86	61	123	58	
Multivariable HR*	1.0	0.54 (0.21-1.40)	0.81 (0.34-1.93)	1.67 (0.75-3.72)	1.28 (0.47-3.50)	2.70 (1.02-7.11)	1.43 (1.14-1.78)	
Hypertension §								
No	5	17	11	26	14	20	93	
Crude incidence rate	49	141	81	209	158	238	142	
Multivariable HR*	1.0	2.90 (1.05-8.04)	1.82 (0.61-5.45)	4.37 (1.57-12.13)	3.38 (1.13-10.07)	5.01 (1.71-14.72)	1.28 (1.08-1.52)	0.72
Normal glucose								
No	9	15	14	27	13	26	104	
Crude incidence rate	36	54	47	112	78	201	76	
Multivariable HR*	1.0	1.51 (0.65-3.49)	1.43 (0.60-3.42)	3.20 (1.43-7.18)	2.10 (0.84-5.21)	5.83 (2.48-13.71)	1.47 (1.26-1.72)	
Borderline diabetes/Diabetes								
No	3	5	3	4	3	2	20	
Crude incidence rate	136	171	90	115	159	88	124	
Multivariable HR*	1.0	1.28 (0.26-6.19)	0.66 (0.12-3.76)	0.77 (0.15-4.04)	1.60 (0.25-10.29)	0.53 (0.07-3.91)	0.87 (0.58-1.31)	0.04
Non-smoker								
No	10	10	9	23	10	14	76	
Crude incidence rate	49	40	32	103	67	119	62	
Multivariable HR*	1.0	0.80 (0.33-1.95)	0.63 (0.25-1.59)	2.04 (0.91-4.55)	1.14 (0.44-2.92)	2.17 (0.87-5.41)	1.30 (1.07-1.57)	
Current smoker								
No	7	13	11	15	10	15	71	
Crude incidence rate	69	125	127	185	218	359	154	
Multivariable HR*	1.0	1.73 (0.67-4.43)	1.77 (0.66-4.78)	2.44 (0.92-6.49)	2.81 (0.99-7.96)	4.93 (1.74-13.97)	1.36 (1.11-1.67)	0.32
Non-drinker								
No	3	3	9	10	7	9	41	
Crude incidence rate	35	32	72	94	99	135	75	
Multivariable HR*	1.0	1.11 (0.22-5.72)	2.15 (0.53-8.68)	2.65 (0.65-10.71)	2.26 (0.53-9.69)	2.99 (0.71-12.62)	1.26 (0.99-1.62)	
Current drinker								
No	13	16	6	16	6	9	66	
Crude incidence rate	106	139	60	194	130	308	133	
Multivariable HR*	1.0	1.21 (0.57-2.57)	0.52 (0.19-1.42)	1.65 (0.73-3.71)	1.16 (0.41-3.29)	3.02 (1.11-8.22)	1.22 (0.96-1.54)	0.96
BMI < 23.0 kg/m^2 ¶								
No	12	16	13	13	8	8	70	
Crude incidence rate	60	79	69	95	105	163	82	
Multivariable HR*	1.0	1.34 (0.62-2.88)	1.28 (0.56-2.92)	1.77 (0.77-4.10)	1.76 (0.68-4.58)	2.75 (1.02-7.41)	1.24 (1.01-1.53)	
BMI ≥ 23.0 kg/m^2 ¶								
No	4	8	7	29	12	21	81	
Crude incidence rate	38	52	37	170	96	183	94	
Multivariable HR*	1.0	1.31 (0.39-4.43)	0.96 (0.27-3.36)	3.67 (1.23-11.02)	2.09 (0.64-6.84)	4.18 (1.32-13.27)	1.40 (1.16-1.68)	0.41

	Non-HDL-cholesterol, mg/dL						HR per 30 mg/dL increment	*p* for interaction
	<100	100-119	120-139	140-159	160-179	180 +		
(Cont Table 3)								
HDL-cholesterol ≥56 mg/dL ¶								
No	13	18	12	15	4	3	65	
Crude incidence rate	59	85	61	115	53	64	74	
Multivariable HR*	1.0	1.49 (0.72-3.10)	1.12 (0.50-2.54)	2.16 (0.98-4.78)	0.92 (0.29-3.00)	1.12 (0.29-4.26)	1.04 (0.82-1.31)	
HDL-cholesterol <56 mg/dL ¶								
No	4	6	9	27	17	27	90	
Crude incidence rate	44	41	49	149	133	227	106	
Multivariable HR*	1.0	0.90 (0.25-3.22)	1.27 (0.38-4.19)	3.46 (1.17-10.21)	2.96 (0.95-9.17)	5.73 (1.88-17.46)	1.55 (1.32-1.81)	0.002
Triglycerides <114 mg/dL ¶								
No	13	13	8	13	5	3	55	
Crude incidence rate	57	58	41	109	78	89	64	
Multivariable HR*	1.0	1.19 (0.54-2.61)	1.10 (0.44-2.72)	2.72 (1.19-6.22)	1.96 (0.67-5.77)	3.02 (0.80-11.46)	1.46 (1.13-1.88)	
Triglycerides ≥114 mg/dL ¶								
No	4	11	13	29	16	27	100	
Crude incidence rate	49	82	70	151	115	205	116	
Multivariable HR*	1.0	1.61 (0.51-5.10)	1.51 (0.48-4.71)	3.34 (1.14-9.77)	2.39 (0.77-7.42)	4.28 (1.43-12.86)	1.31 (1.12-1.53)	0.96
Fasting (≥8 hours after last meal)								
No	6	7	4	12	5	10	44	
Crude incidence rate	78	90	53	176	98	213	111	
Multivariable HR*	1.0	1.45 (0.47-4.47)	0.85 (0.23-3.17)	2.78 (0.92-8.41)	1.89 (0.51-6.91)	3.72 (1.10-12.59)	1.37 (1.05-1.78)	
Non-fasting (<8 hours after last meal)								
No	11	17	17	30	16	20	111	
Crude incidence rate	47	60	56	124	105	168	83	
Multivariable HR*	1.0	1.29 (0.59-2.82)	1.22 (0.55-2.70)	2.50 (1.18-5.30)	2.00 (0.86-4.62)	3.55 (1.53-8.23)	1.36 (1.16-1.59)	0.40

*HR (95%CI) adjusted for gender, age and potential confounding factors.
**Incidence rate per 100,000 person-years
§Hypertensive was defined as systolic blood pressure ≥140 and/or diastolic blood pressure ≥90 and/or as use of medication for hypertension.
¶Median value was used for cut-off point.

optimal cut-off point may be around 140 mg/dL non-HDL-cholesterol for the general Japanese population.

Our result does not mean that all persons with ≥140 mg/dL non-HDL-cholesterol should become clinical or public health targets for interventions, because our findings were not derived from an intervention study. Approximately 40% of our study population had ≥140 mg/dL non-HDL-cholesterol. Therefore, further stratification of persons with ≥140 mg/dL non-HDL-cholesterol into several groups (e.g. mild, moderate and severe hypercholesterolemia) is needed on the basis of the results of intervention studies. In fact, non-HDL-cholesterol diagnostic criteria for healthy persons may be as high as ≥170 mg/dL (only 15% of the population in our study), suggested in the Japan Atherosclerosis Society's guidelines[13]. Clinical or public health priorities and associated strategies for interventions should be selected according to the efficacy, efficiency and total cost determined by clinical and community intervention studies.

Our findings were based on populations from 1975 to 1987, which had lower non-HDL-cholesterol levels and lower incidences of CHD than those in recent years. The situation has been changing among Japanese populations: the mean values of total cholesterol levels and the incidence rate of CHD among middle-aged men in an urban area have increased in the past half century[23]. In fact, more recent population-based cohort studies showed higher means of non-HDL-cholesterol levels[8-10]; however, these recent studies might not have examined lower cutoff-points of non-HDL-cholesterol sufficiently compared to our study, probably due to a smaller population with a low non-HDL-cholesterol level. In other words, the strength of the present study is that we could analyze the relationship between incident CHD and a lower level of non-HDL-cholesterol than recent cohort studies; therefore, our result suggesting that there was no

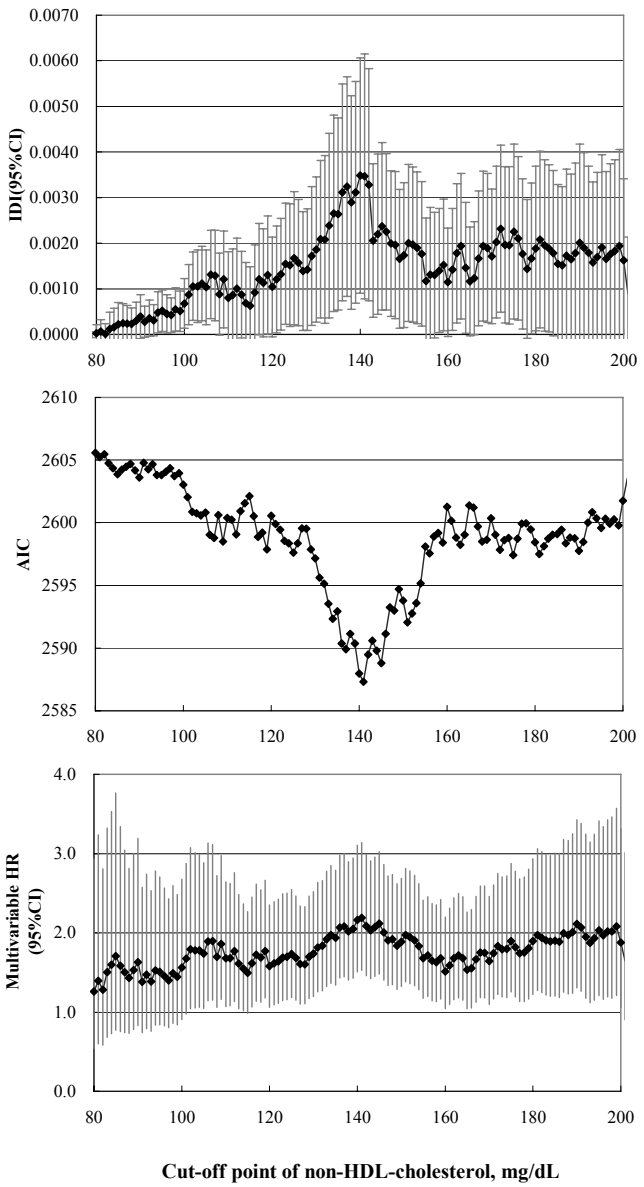

Fig. 3. Cut-off point for non-HDL-cholesterol and integrated discrimination improvement (IDI) of CHD, Akaike's Information Criteria (AIC) and multivariable HR.

Setting the cut-off point at ≥140 mg/dL of non-HDL-cholesterol yielded the highest IDI (95%CI): 0.0035 (0.0010 to 0.0060; $p=0.007$. Selection of ≥141 mg/dL non-HDL-cholesterol as the cut-off point resulted in the lowest AIC. The multivariable HR (95% CI) was 2.16 (1.51-3.11; $p<0.0001$) for ≥140 mg/dL versus <140 mg/dL, and 2.19 (1.53-3.14; $p<0.0001$) for ≥141 mg/dL versus <141 mg/dL.

cut-off point below 140 mg/dL non-HDL-cholesterol levels would not be rejected in recent populations.

We observed statistical interactions of glucose abnormality and HDL-cholesterol levels in the association between non-HDL-cholesterol and the risk of CHD. The association between higher non-HDL-cholesterol and an increased risk of CHD was observed for persons with normal glucose and low HDL-cholesterol levels, but not for cases of borderline diabetes or diabetes and high HDL-cholesterol levels. Our findings suggest that the effect of non-HDL-cholesterol on the risk of CHD may be affected by other metabolic risk factors; however, these interactions remain an issue for further investigation because a previous Japanese study on CHD mortality showed different interactions: persons with diabetes showed a stronger association between non-HDL-cholesterol and CHD death than those with normal glucose, whereas no interaction with HDL-cholesterol was observed[9].

Another strength of our study is that we used lipid measurement values standardized in a single laboratory, which in turn was standardized by the CDC-NHLBI Lipid Standardized Program[14, 16]. This justifies our assumption that the misclassification bias due to errors in lipid measurement has been sufficiently reduced, and that the resultant accuracy of lipid measurements is comparable with that of the results of previous well-standardized studies.

A limitation of the current study is the relatively small number of incident cases, which leads to wide confidence intervals of HR on the association between non-HDL-cholesterol levels and risk of CHD. Second, the cut-off point in our observational study (i.e. for prediction) may be different from in intervention studies (i.e. for intervention). Namely, we found the optimal cut-off point for prediction of CHD, but did not examine the beneficial effects after lowering non-HDL-cholesterol levels below it. In order to clarify the ideal cut-off point for lowering non-HDL-cholesterol levels in clinical practice, further interventional studies are needed. Third, we did not compare the predictive ability for CHD incidence between non-HDL-cholesterol and other lipid measurements in this study. This should be further examined to clarify whether non-HDL-cholesterol is not inferior to using total cholesterol, HDL-cholesterol, and triglyceride for the prediction of CHD events.

In conclusion, our cohort study provides epidemiological evidence that higher concentrations of non-HDL-cholesterol were associated with an increased risk of CHD with a threshold around 140 mg/dL, suggesting that the optimal cut-off point for healthy Japanese people to prevent increasing the risk of CHD might be around 140 mg/dL. Intervention studies are needed to stratify the population with ≥140 mg/dL non-HDL-cholesterol to determine clinical and public health priorities and their associated strategies.

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