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)

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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-

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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.

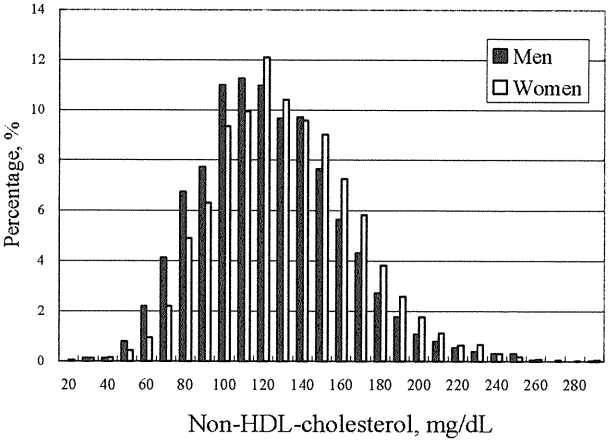

Fig. 1. Sex-specific histogram for distribution of non-HDL-cholesterol.

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

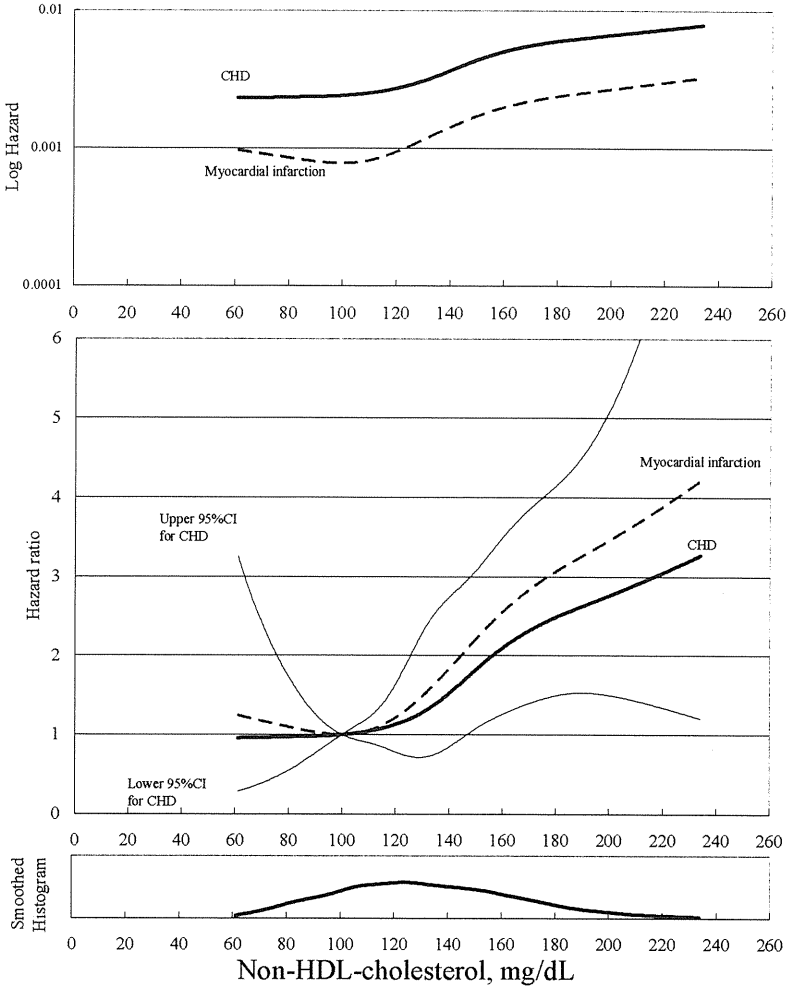

Fig. 2. Multivariable log hazard and multivariable HR for CHD and MI in relation to non-HDL-cholesterol levels.

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

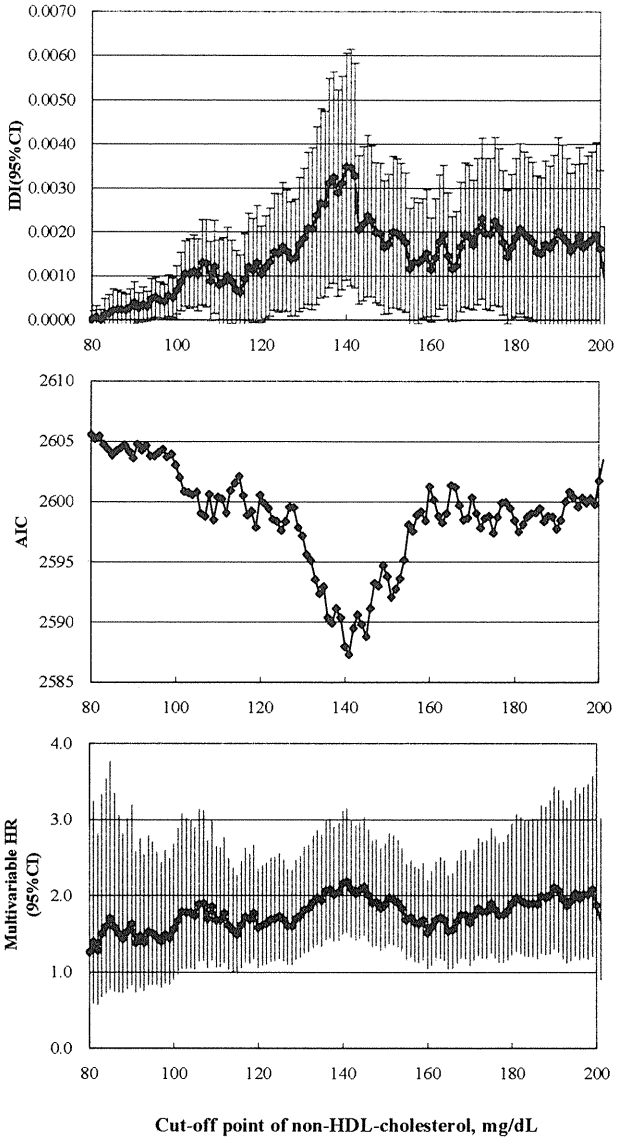

Fig. 3. Cut-off point for non-HDL-cholesterol and integrated discrimination improvement (IDI) of CHD, Akaike's Information Criteria (AIC) and multivariable HR.

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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Low-density lipoprotein cholesterol and risk of coronary heart disease among Japanese men and women: The Circulatory Risk in Communities Study (CIRCS)

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ABSTRACT

Objective. The objective of this study was to assess the association between serum LDL-cholesterol levels and risk of coronary heart disease (CHD) among Japanese who have lower means of LDL-cholesterol than Western populations.

Methods. The predictive power of estimated serum LDL-cholesterol levels in casual blood samples for risk of CHD was evaluated among residents from four Japanese communities participating in the Circulatory Risk in Communities Study (CIRCS). A total of 8131 men and women, aged 40 to 69 years with no history of stroke or CHD, completed baseline risk factor surveys between 1975 and 1987. By 2003, 155 cases of incident CHD (myocardial infarction, angina pectoris and sudden cardiac death) had been identified.

Results. Mean LDL-cholesterol values were 99.4 mg/dL for men and 109.4 mg/dL for women. The crude incidence rate (per 100,000 person-years) of CHD was 152.0 for men and 51.9 for women. The respective multivariable hazard ratios for ≥140 mg/dL versus <80 mg/dL LDL-cholesterol were 2.80 (95% confidence interval: 1.59 to 4.92) for total CHD, 3.83 (1.78–8.23) for myocardial infarction, 4.07 (2.02–8.20) for non-fatal CHD, and 1.24 (0.44–3.47) for fatal CHD.

Conclusion. Serum LDL-cholesterol levels ranging from around 80 mg/dL to 200 mg/dL were positively associated with risk of CHD in a Japanese population.

Introduction

Low-density lipoprotein cholesterol (LDL-cholesterol) is one of the major atherogenic lipoproteins and has been identified by the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP-ATPIII) (2002) as a primary target for prevention of coronary heart disease (CHD).

Associations of high concentrations of LDL-cholesterol with increased risk of CHD have been examined mainly in high cholesterol populations, but lower cholesterol populations have been the subject of only a few studies (Chien et al., 2007; Law et al., 2003; Liu et al., 2006; NCEP-ATPIII, 2002). It has therefore remained a matter of debate whether serum LDL-cholesterol levels are associated with risk of CHD for populations with low to moderate mean LDL-cholesterol levels.

A review article (O'Keefe et al., 2004) showed that the optimal levels of LDL-cholesterol are 50 to 70 mg/dL, because the range of LDL-cholesterol was estimated to be 50 to 70 mg/dL among hunter–gatherer humans as well as wild primates and mammals, none of whom has atherosclerosis, and because atherosclerosis progression and CHD events were minimal among participants in a cholesterol lowering trial whose LDL-cholesterol level were less than 70 mg/dL. However, the NCEP-ATPIII (2002) has recommended clinical management and dietary therapy even for low-risk persons with ≥160 mg/dL of LDL-cholesterol, because few studies have examined whether the aforementioned associations are also observed when LDL-cholesterol levels are in the lower ranges.

The Seven Countries Study demonstrated that the association between total cholesterol and mortality from CHD holds only for high cholesterol populations such as Americans, but not for low cholesterol populations such as the Japanese (Verschuren et al., 1995). On the other

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hand, a recent increase in CHD incidence rates detected among urban Japanese men shows the need for controlling an upward shift of population distributions of serum cholesterol levels (Iso et al., 1999). It is therefore of the utmost importance to determine whether LDL-cholesterol levels are associated with risk of CHD among Japanese.

To this purpose, we conducted a population-based cohort study of Japanese men and women with lower means of LDL-cholesterol levels than seen in Western populations (Verschuren et al., 1995).

Methods

Study cohort

The participants were recruited from population-based samples obtained under the Circulatory Risk in Communities Study (CIRCS) (Imano et al., 2009). They were aged 40 to 69 years, living in four Japanese communities and participated in cardiovascular risk surveys between 1975 and 1987, from which we obtained data related to lipid profiles and confounding variables. The participation rate in the study presented here was 77% for a total of census population.

From the 8157 participants (3201 men and 4956 women), we excluded 26 persons with a history of CHD and/or stroke at the time of the baseline inquiry, so that a total of 8131 persons (3178 men and 4953 women) were enrolled in the analysis.

Informed consent was obtained for conducting this epidemiological study, which was based on the guidelines of the Council for International Organizations of Medical Science (1991). The Ethics Committee of Osaka Medical Center for Health Science and Promotion approved this study.

Measurement of risk factors

Serum total cholesterol was measured with the Liebermann–Burchard direct method using Autoanalyzer II (Technicon, Tarrytown, NY) for 1975–1979 and Autoanalyzer SMA-6/60 (Technicon) for 1979–1986, and with the enzymatic method using Autoanalyzer SMAC (Technicon) since 1986. Serum triglycerides were measured with the fluorometric method using Autoanalyzer II for 1975–1986, and with the enzymatic method using Autoanalyzer SMAC since 1986. After precipitation by heparin–manganese, serum high-density lipoprotein cholesterol (HDL-cholesterol) was measured with the Liebermann–Burchard method using Autoanalyzer II. These measurements were performed at the laboratory of the Osaka Medical Center for Health Science and Promotion, an international member of the US National Cholesterol Reference Method Laboratory Network (Nakamura et al., 2003).

LDL-cholesterol was calculated with the Friedewald formula as follows: LDL-cholesterol (mg/dL) = total cholesterol (mg/dL) − HDL-cholesterol (mg/dL) − 0.2 × triglycerides (mg/dL) (Friedewald et al., 1972). A previous study showed no bias related to LDL-cholesterol levels among persons with <781 mg/dL of triglycerides in fasting blood samples (Tremblay et al., 2004). Since 77% of the subjects enrolled in the present study, were not fasting, we compared LDL-cholesterol estimated with the Friedewald formula and values measured by direct method as the gold standard in 14,072 men and 10,479 women aged 40–69 years who participated in health check-ups by the Osaka Medical Center for Health Science and Promotion between 2001 and 2009. We found that the LDL-cholesterol values determined with those two methods were comparable when triglycerides were <781 mg/dL in both fasting and non-fasting blood samples. The Spearman's rank correlation coefficients for estimated and directly measured LDL-cholesterol values were 0.96 (0.96 for men and 0.97 for women) for fasting and 0.94 (0.93 and 0.95, respectively) for non-fasting subjects. Mean values ± standard deviations for estimated and directly measured LDL-cholesterol were 129 ± 33 mg/dL and 130 ± 32 mg/dL, respectively, for fasting subjects, and 125 ± 33 mg/dL and 129 ± 32 mg/dL, respectively, for non-fasting subjects.

The details of other baseline examinations have been described in a previous report of ours (Iso, et al. 2001). Mild hypertension was defined as systolic blood pressure 140–159 mm Hg or diastolic blood pressure 90–99 mm Hg; the corresponding values for moderate hypertension were 160–179 mm Hg or 100–109 mm Hg and ≥180 mm Hg or ≥110 mm Hg for severe hypertension, regardless of antihypertensive medication use. Diabetes was defined as a serum glucose level ≥126 mg/dL in the fasting or ≥200 mg/dL in the non-fasting state, or as use of medication for diabetes. Borderline diabetes was defined as serum glucose level 110–125 mg/dL in the fasting or 140–199 mg/dL in the non-fasting state, and as no use of medication for diabetes. An interview was conducted to ascertain smoking status, number of cigarettes smoked per day, and usual alcohol intake per week.

Follow-up study

The details of endpoint determination have been described in a previous report of ours (Shimamoto, et al. 1989). Briefly, to validate the diagnosis, all living patients were telephoned or visited or invited to attend annual cardiovascular risk factor surveys or a medical history was obtained from their families. In addition, relevant medical records at local clinics and hospitals were reviewed. In cases of death, history was obtained from the family and/or attending physician and medical records were reviewed.

The criteria for coronary heart disease were modified from those established by the World Health Organization Expert Committee (1962). Definite myocardial infarction was diagnosed as typical severe chest pain (lasting for ≥30 min) together with the appearance of new abnormal and persistent Q or QS waves, consistent changes in cardiac enzyme levels, or both. Probable myocardial infarction was indicated by typical chest pain, but for which no electrocardiographic findings or findings related to enzyme activity were available. Myocardial infarction was considered present if either definite or probable myocardial infarction was diagnosed. Angina pectoris was defined as repeated episodes of chest pain during effort, especially when walking, usually disappearing rapidly after the cessation of effort or by the use of sublingual nitroglycerin. Sudden cardiac death was defined as death within 1 h of onset, a witnessed cardiac arrest, or abrupt collapse not preceded by ≥1 h of symptoms. CHD was defined as including myocardial infarction, angina pectoris, and sudden cardiac death. We also defined incident CHD death within 28 days as fatal CHD.

For each of the participants, the person-years of follow-up were calculated from the date of completion of the baseline survey to the date of cardiovascular incidence, death, exit from the community, or the end of 2003, whichever occurred first. The participants who moved away from the community (5.8%) were treated as censored.

Statistical analysis

ANCOVA and Mantel–Haenszel chi-square tests were used to examine differences between persons with and those free of incident CHD in terms of sex- and age-adjusted mean values and proportions of baseline characteristics.

The sex- and age-adjusted, sex-specific age-adjusted, and multivariable hazard ratios (HR) and 95% confidence intervals (95% CI) were calculated with the Cox proportional hazards model after adjustment for potentially confounding factors. The reference was <80 mg/dL LDL-cholesterol at baseline. The potentially confounding factors included blood pressure category, antihypertensive medication use, glucose category, body mass index (sex-specific quartiles), smoking status (never, ex- and current smokers of cigarette smoking 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), category of HDL-cholesterol (<40, 40–49, 50–59, 60–69, and ≥70 mg/dL) and triglycerides (<100, 100–149, 150–199, 200–249, and ≥250 mg/dL), fasting status (<8 or ≥8 h), year of baseline survey, and study area. We also calculated the HR per 30 mg/dL increment in LDL-cholesterol. We tested the assumption of proportional hazards (Ng'andu, 1997), and found no violation of proportionality.

We also examined, non-parametrically and with restricted cubic splines (Durrleman and Simon, 1989), possible non-linear associations between LDL-cholesterol levels and risk of CHD. Tests for non-linearity used the likelihood ratio test to compare the model with only the linear term to the model with the linear and the cubic spline terms.

All statistical tests were two-sided and a p-value <0.05 was regarded as statistically significant. SAS, version 9.1.3 (SAS Institute, Inc., Cary, NC, USA) was used for all statistical analyses.

Results

Table 1 shows selected cardiovascular risk factors at the baseline survey for persons developing/free of incident CHD. The mean of LDL-cholesterol was 105.5 mg/dL for all participants, 99.4 mg/dL for men and 109.4 mg/dL for women at baseline. Compared with persons free of incident CHD, those who were developing CHD, myocardial infarction or non-fatal CHD were more likely to be male and older. They also tended to have higher means of total and LDL-cholesterol

Table 1
Baseline characteristics of participants developing incident coronary heart disease (CHD) and those remaining free of it.

	Participants free of incident CHD	Participants developing incident CHD	Participants developing myocardial infarction	Participants developing non-fatal CHD	Participants developing fatal CHD
Total (men and women)					
Number of persons	7976	155	91	115	40
Men, %	38.6	63.9†	69.2†	67.8†	52.5
Age, year	51.7	55.5†	55.1‡	54.4‡	58.4†
Total cholesterol, mg/dL	188.3	200.6†	203.2†	202.3‡	195.7
LDL-cholesterol, mg/dL	104.2	114.2‡	114.0‡	117.3‡	105.3
HDL-cholesterol, mg/dL	56.6	54.7	56.1	53.6‡	57.9
Triglycerides, mg/dL	137.3	158.2‡	165.5‡	156.7†	162.5
Lipid lowering medication use, %	0.1	0.0	0.0	0.0	0.0
Body mass index, kg/m^2	23.2	23.6	23.6	23.5	23.8
Systolic blood pressure, mmHg	134.0	141.6‡	140.1†	141.6‡	141.7†
Diastolic blood pressure, mmHg	80.9	85.2‡	84.5‡	84.9‡	85.9‡
Antihypertensive medication use, %	10.4	15.2†	13.9	11.9	24.8†
Diabetes, %	3.3	2.4	4.6	2.7	1.5
Current smoker, %	35.1	39.9	44.4†	41.4	35.6
Current drinkers, %	45.2	42.8	44.5	44.4	36.3
Fasting blood samples, %	22.5	27.5	26.8	28.2	25.6
LDL- to total cholesterol ratio	0.55	0.56	0.55	0.57	0.53
Men					
Number of persons	3079	99	63	78	21
Age, year	52.0	53.9‡	53.3	52.9	57.5†
Total cholesterol, mg/dL	183.6	195.9†	197.6†	196.9†	192.1
LDL-cholesterol, mg/dL	99.1	109.7†	107.2	111.3†	103.8
HDL-cholesterol, mg/dL	56.0	54.1	55.6	53.5	56.2
Triglycerides, mg/dL	142.2	160.5	173.9†	160.4	161.1
Lipid lowering medication use, %	0.1	0.0	0.0	0.0	0.0
Body mass index, kg/m^2	22.9	23.4	23.4	23.5	23.3
Systolic blood pressure, mmHg	135.5	142.1†	140.8‡	143.1†	138.1
Diastolic blood pressure, mmHg	82.4	86.1†	85.5‡	86.6†	84.0
Antihypertensive medication use, %	10.3	17.0‡	15.0	16.1	20.1
Diabetes, %	4.4	2.9	4.6	3.8	0.0
Current smoker, %	64.4	66.5	71.8	70.7	50.6
Current drinkers, %	79.9	77.1	78.5	78.4	71.8
Fasting blood samples, %	22.0	26.9	22.0	28.0	22.8
Women					
Number of persons	4897	56	28	37	19
Age, year	51.5	58.3†	59.2†	57.7†	59.4†
Total cholesterol, mg/dL	193.0	204.2‡	208.0‡	206.4‡	199.9
LDL-cholesterol, mg/dL	109.3	117.6	121.5	123.0‡	107.0
HDL-cholesterol, mg/dL	57.2	55.5	56.8	53.3	59.7
Triglycerides, mg/dL	132.3	155.7‡	148.7	150.5	166.0
Lipid lowering medication use, %	0.1	0.0	0.0	0.0	0.0
Body mass index, kg/m^2	23.5	23.6	23.6	23.2	24.5
Systolic blood pressure, mmHg	132.5	141.9†	140.1†	139.8‡	146.0†
Diastolic blood pressure, mmHg	79.4	84.6†	84.1†	82.7	88.2†
Antihypertensive medication use, %	10.6	12.0	11.2	2.8	30.0†
Diabetes, %	2.2	2.5	5.9	1.7	4.0
Current smoker, %	5.8	15.4†	19.3†	11.8	22.3†
Current drinkers, %	10.5	9.6	15.6	12.0	1.1
Fasting blood samples, %	22.9	27.8	36.4	27.4	28.6

Participants developing myocardial infarction constitute a subset of participants developing incident CHD. Participants developing incident CHD are divided into those developing non-fatal and fatal CHD.
Test for difference from participants free of incident coronary heart disease.
To convert values for LDL-cholesterol to millimoles per liter, multiply by 0.02586. The convert values for triglycerides to millimoles per liter, multiply by 0.01129.
† $p<0.01$.
‡ $p<0.05$.

and triglycerides and systolic and diastolic blood pressures, whereas there was no difference in total and LDL-cholesterol and triglycerides for those who were developing fatal CHD.

A total of 8131 persons (3178 men and 4953 women) were followed up for a median of 21.9 years, during which time, we identified 155 incidences of CHD (including 115 non-fatal and 40 fatal CHDs). LDL-cholesterol levels correlated linearly with risk of myocardial infarction for men and with total CHD, myocardial infarction and non-fatal CHD for all participants (Table 2). Adjustment for potentially confounding factors did not alter these associations materially. The multivariable hazard ratios for ≥140 mg/dL versus <80 mg/dL LDL-cholesterol for all participants were 2.80 (95% CI: 1.59–4.92) for total CHD, 3.83 (1.78–8.23) for myocardial infarction, 4.07 (2.02–8.20) for non-fatal CHD, and 1.24 (0.44–3.47) for fatal CHD. The corresponding multivariable hazard ratios (95% CI) associated with a 30 mg/dL increment in LDL-cholesterol were 1.30 (1.14–1.49), 1.33 (1.12–1.59), 1.36 (1.17–1.58), and 1.16 (0.87–1.55). These positive associations were similar for men and women with no sex interaction ($p=0.89$ for total CHD, $p=0.45$ for myocardial infarction, $p=0.78$ for non-fatal CHD, and $p=0.55$ for fatal CHD). We also did not observe any fasting status interaction ($p=0.67$, $p=0.67$, $p=0.91$ and $p=0.67$, respectively).

Further, these associations did not alter substantially after the exclusion of persons with hypertriglyceridemia (triglycerides ≥300 mg/dL, 193 men and 172 women, not shown in the table). The multivariable hazard ratios (95% CI) for LDL-cholesterol ≥140 mg/dL versus <80 mg/dL LDL-cholesterol were 2.81 (1.55–5.07) for total CHD, 3.53 (1.60–7.80) for myocardial infarction, 3.97 (1.93–8.17) for non-fatal CHD, and 1.19 (0.38–3.70) for fatal CHD.

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

Range, mg/dL (mmol/L)	LDL-cholesterol					HR per 30 mg/dL increment
	<80 (<2.06)	80–99 (2.06–2.57)	100–119 (2.58–3.09)	120–139 (3.10–3.61)	140+ (3.62+)	
Total (men and women)						
Persons	1774	1899	1949	1302	1207	8131
Person-years	38,175	40,754	41,474	27,513	25,109	173,024
Total CHD						
No	23	29	35	31	37	155
Crude incidence rate	60.2	71.2	84.4	112.7	147.4	89.6
Sex- and age-adjusted HR	1.0	1.22 (0.71–2.12)	1.48 (0.87–2.51)	2.09 (1.22–3.61)	2.76 (1.62–4.70)	1.34 (1.17–1.53)
Multivariable HR[a]	1.0	1.35 (0.77–2.36)	1.66 (0.96–2.86)	2.15 (1.22–3.81)	2.80 (1.59–4.92)	1.30 (1.14–1.49)
Myocardial infarction						
No	12	17	20	21	21	91
Crude incidence rate	31.4	41.7	48.2	76.3	83.6	52.6
Sex- and age-adjusted HR	1.0	1.41 (0.67–2.96)	1.69 (0.82–3.47)	2.89 (1.42–5.91)	3.28 (1.59–6.74)	1.33 (1.12–1.59)
Multivariable HR[a]	1.0	1.67 (0.78–3.55)	2.07 (0.98–4.34)	3.42 (1.62–7.26)	3.83 (1.78–8.23)	1.33 (1.12–1.59)
Non-fatal CHD						
No	13	23	24	26	29	115
Crude incidence rate	34.1	56.4	57.9	94.5	115.5	66.5
Sex- and age-adjusted HR	1.0	1.77 (0.90–3.50)	1.89 (0.96–3.72)	3.30 (1.69–6.45)	4.22 (2.17–8.20)	1.43 (1.23–1.66)
Multivariable HR[a]	1.0	1.95 (0.98–3.90)	2.06 (1.03–4.13)	3.25 (1.61–6.53)	4.07 (2.02–8.20)	1.36 (1.16–1.58)
Fatal CHD						
No	10	6	11	5	8	40
Crude incidence rate	26.2	14.7	26.5	18.2	31.9	23.1
Sex- and age-adjusted HR	1.0	0.52 (0.19–1.43)	0.89 (0.37–2.12)	0.62 (0.21–1.84)	0.98 (0.37–2.57)	1.07 (0.81–1.42)
Multivariable HR[a]	1.0	0.57 (0.20–1.64)	1.04 (0.41–2.60)	0.72 (0.23–2.28)	1.24 (0.44–3.47)	1.16 (0.87–1.55)
Men						
Persons	881	795	728	440	334	3,178
Person-years	18,296	16,490	14,921	8901	6522	65,130
Total CHD						
No	20	23	18	16	22	99
Crude incidence rate	109.3	139.5	120.6	179.8	337.3	152.0
Age-adjusted HR	1.0	1.25 (0.69–2.27)	1.07 (0.57–2.02)	1.68 (0.87–3.24)	3.05 (1.66–5.59)	1.34 (1.13–1.59)
Multivariable HR[a]	1.0	1.34 (0.72–2.49)	1.17 (0.60–2.28)	1.72 (0.85–3.48)	2.90 (1.51–5.57)	1.30 (1.09–1.55)
Myocardial infarction						
No	11	15	14	10	13	63
Crude incidence rate	60.1	91.0	93.8	112.3	199.3	96.7
Age-adjusted HR	1.0	1.49 (0.69–3.25)	1.53 (0.69–3.37)	1.91 (0.81–4.49)	3.30 (1.48–7.37)	1.26 (1.01–1.56)
Multivariable HR[a]	1.0	1.79 (0.80–4.01)	1.83 (0.80–4.20)	2.26 (0.90–5.66)	3.59 (1.51–8.55)	1.24 (1.00–1.53)
Women						
Persons	893	1104	1221	862	873	4953
Person-years	19,878	24,264	26,553	18,612	18,588	107,895
Total CHD						
No	3	6	17	15	15	56
Crude incidence rate	15.1	24.7	64.0	80.6	80.7	51.9
Age-adjusted HR	1.0	1.26 (0.31–5.05)	2.84 (0.83–9.75)	3.20 (0.92–11.18)	2.78 (0.79–9.75)	1.26 (1.01–1.56)
Multivariable HR[a]	1.0	1.21 (0.30–4.95)	3.41 (0.98–11.95)	3.80 (1.06–13.58)	3.05 (0.84–11.07)	1.25 (1.00–1.55)
Myocardial infarction						
No	1	2	6	11	8	28
Crude incidence rate	5.0	8.2	22.6	59.1	43.0	26.0
Age-adjusted HR	1.0	1.22 (0.11–13.50)	2.85 (0.34–23.86)	6.67 (0.85–52.20)	4.11 (0.50–33.44)	1.38 (1.02–1.85)
Multivariable HR[a]	1.0	1.26 (0.11–14.26)	3.69 (0.43–31.83)	8.93 (1.11–71.72)	5.43 (0.64–45.92)	1.42 (1.05–1.91)

Potential confounding factors: blood pressure category, antihypertensive medication use, glucose category, body mass index, smoking status, alcohol intake category, lipid lowering medication use, categories of HDL-cholesterol and triglycerides, fasting status, years at entry and study area.

[a] HR (95% CI) adjusted for sex, age and potential confounding factors.

The dose–response patterns of total CHD, as well as non-fatal CHD, corroborated the results of the categorical analysis (Fig. 1).

Discussion

In the population-based prospective study of Japanese reported here, we found positive relationships between LDL-cholesterol levels and risks of total CHD and myocardial infarction. The risk of total CHD started to increase when the serum LDL-cholesterol level was above 80 mg/dL (corresponding to 167 mg/dL of total cholesterol levels).

Previous cohort studies of an American population (mean LDL-cholesterol levels: 139 mg/dL for men 138 mg/dL for women at baseline) (Liu et al., 2006), a Chinese population (133 mg/dL and 142 mg/dL, respectively) (Chien et al., 2007) and high-risk patients enrolled in cholesterol lowering clinical trials (162 mg/dL for all participants) (Sacks et al., 2000) showed positive relationships between LDL-cholesterol and risk of CHD. Because the lowest category of LDL-cholesterol levels in these previous studies was ≥100 mg/dL, which represented the middle and higher categories in the current study, it was not clear whether a similar relationship holds true for populations with moderate cholesterol levels, the men and women in our study with means of LDL-cholesterol of 99.4 mg/dL and 109.4 mg/dl, respectively. These values corresponded to the optimal individual levels, addressed by the Japan Atherosclerosis Society Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases in 2007. A previous Japanese population-based cohort study showed a non-linear association: a 1.68 times higher multivariable hazard ratio for persons with 126–150 mg/dL of LDL-cholesterol in comparison with men and women with ≤102 mg/dL and the risk plateaued at less than 125 mg/dL (Imamura et al., 2009). Our findings, however, corroborated the evidence for a linear association between LDL-cholesterol levels and the risk of incident CHD among Japanese with lower ranges of LDL-cholesterol levels.

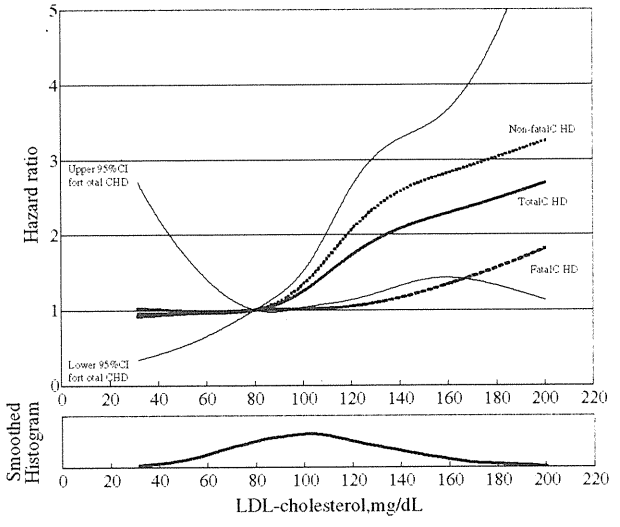

Fig. 1. Multivariable hazard ratios of total, non-fatal and fatal coronary heart diseases (CHD) in relation to LDL-cholesterol levels. 80 mg/dL of LDL-cholesterol was selected as reference level. The values of the 4 knots correspond to LDL-cholesterol levels of 57.0 mg/dL, 91.8 mg/dL, 115.6 mg/dL and 160.0 mg/dL. The smoothed histogram shows the distribution of LDL-cholesterol levels. We did not plot predictions from the top and bottom 1% of the analytical distribution to avoid an undue visual effect of sparse tail data. The p-values for non-linearity were p = 0.0006 for total CHD and p = 0.0002 for non-fatal CHD, whereas the hazard ratio was fairly flat at less than 80 mg/dL of LDL-cholesterol levels. On the other hand, we observed an increase in the risk of fatal CHD only at the upper tail of the distributions of LDL-cholesterol levels. Although the hazard ratios were still fairly flat at less than 80 mg/dL of LDL-cholesterol levels, the graph suggests that the risk of total and non-fatal CHD may start to increase a level of around 80 mg/dL of LDL-cholesterol (corresponding to 167 mg/dL of total cholesterol), whereas the risk of fatal CHD may increase at LDL-cholesterol levels over 120 mg/dL (corresponding to 202 mg/dL of total cholesterol).

It remains debatable what range of LDL-cholesterol levels is optimal for the prevention of CHD. The National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII) (2002) recommended clinical management and dietary therapy for low-risk persons with ≥160 mg/dL of LDL-cholesterol, whereas another review article suggested that the optimal level of LDL-cholesterol may be 50 to 70 mg/dL (Verschuren et al., 1995). Our findings for total and non-fatal CHD support the notion that the threshold of LDL-cholesterol for increased risks of total and non-fatal CHDs may be around 80 mg/dL (corresponding to 167 mg/dL of total cholesterol), although our LDL-cholesterol measurements may have been underestimated as discussed below.

Study limitations

One limitation of the current study is that we estimated LDL-cholesterol levels by using the Friedewald formula, which cannot be used for specific metabolic conditions such as hypertriglyceridemia (Tremblay et al., 2004). However, the association between LDL-cholesterol and risks of total and non-fatal CHDs and myocardial infarction did not alter after the exclusion of persons with hypertriglyceridemia at the baseline survey, and we observed no effect modification resulting from the presence or absence of fasting status. The second limitation is that approximately 77% of participants were non-fasting, which is likely to lead to underestimation of LDL-cholesterol calculation when using the Friedewald formula. According to a validation study conducted by our lipid reference standardization laboratory, LDL-cholesterol levels calculated with the Friedewald formula were underestimated by 4 mg/dL among non-fasting subjects. However, this did not *per se* affect the association we observed, and, as mentioned before, fasting or non-fasting status did not change the association between LDL-cholesterol and risk of CHD. Third, we found weak non-significant association between LDL-cholesterol levels and risk of fatal CHD, which corresponded to the finding from the Seven Countries Study (Verschuren et al., 1995). However, the lack of association could be due to the low statistical power resulting from only 21 fatal CHD cases among men and 19 among women. The statistical power for the association between LDL-cholesterol and risk of fatal CHD was only 15% according to our analysis.

Study strengths

The strength of the current study is the use of a population-based sample from four Japanese communities, so that our findings can probably be generalized to other Japanese populations which also have lower cholesterol levels than Western populations (O'Keefe et al., 2004). Second, the prevalence of lipid lowering medication usage was only 0.1% in the participants and serum lipid level at baseline was nearly equal to the natural state. Third, we used standardized lipid measurement values, which in turn were standardized by the CDC–NHLBI Lipid Standardized Program (Nakamura et al., 2003). This justifies our assumption that misclassification bias due to measurement errors of lipid measurement has been appropriately reduced, and that the resultant accuracy of lipid measurement allows for comparison of our results with those of previous well-standardized studies.

Conclusion

Our population-based cohort study of Japanese showed that serum LDL-cholesterol levels ranging from around 80 mg/dL to 200 mg/dL were positively associated with risk of CHD.

Conflict of interest statement
The authors declare that there are no conflicts of interest.

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