

# Non-High-Density Lipoprotein Cholesterol and Risk of Stroke Subtypes and Coronary Heart Disease

## The Japan Public Health Center-Based Prospective (JPHC) Study

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**Aim:** A positive association between non-high-density lipoprotein cholesterol (non-HDL-C) and coronary heart disease (CHD) has been established; however, associations between non-HDL-C and stroke subtypes have not been determined.

**Methods:** We conducted a prospective study of 30,554 individuals aged 40–69 yrs with no history of cardiovascular disease (CVD) in Japan. Sex-specific hazard ratios (HRs) and 95% confidence intervals (CIs) for the incidence of stroke subtypes and CHD were estimated according to quintiles of non-HDL-C, using Cox proportional hazard models adjusted for other established risk factors.

**Results:** We identified 1,705 stroke and 296 CHD events over a median 15 yrs of follow-up. The fractional polynomials analysis revealed a U-shaped association between non-HDL-C and stroke risk in men. When analyzed for stroke subtypes, the data revealed an inverse relationship between non-HDL-C and intracerebral hemorrhage (ICH), primarily with lobar ICH, and a positive association between non-HDL-C and large-artery occlusive infarction in men [adjusted HR 0.55 (95% CI, 0.35–0.87) and 2.05 (95% CI, 1.07–3.93) for the highest and lowest quintile of non-HDL-C, respectively]. The lowest risk of ICH in women was observed in the fourth quintile, and the lowest risk of embolic infarction was observed in the third quintile. In contrast, non-HDL-C was positively associated with CHD in both sexes.

**Conclusions:** In Japanese men, lower non-HDL-C levels were associated with a decreased risk of large-artery occlusive infarction and an increased risk of ICH, particularly lobar ICH.

**Key words:** Non-HDL-C, Coronary heart disease, Lacunar infarction, Intracerebral hemorrhage, Epidemiology

### Introduction

Elevated non-high-density lipoprotein cholesterol (non-HDL-C) is an established risk factor for coronary heart disease (CHD)<sup>1</sup>. Randomized controlled trials of lipid-lowering drugs provided strong

evidence of a causal connection between non-HDL-C and CHD<sup>2, 3</sup>. In contrast, the association between non-HDL-C and stroke and stroke subtypes remains unknown. Indeed, epidemiological studies in Japan showed inconsistent results, i.e., some found a positive association between non-HDL-C and atherothrom-

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botic infarction<sup>4</sup>), while others found no associations<sup>5,6</sup> or even an inverse relationship with ischemic stroke<sup>7</sup>.

Unlike CHD, stroke can be subdivided into several subtypes, and the proportion of each subtype differs among populations and ethnic groups<sup>8</sup>. In Japan, intracerebral hemorrhage and lacunar infarction are major subtypes of stroke<sup>9</sup>. These subtypes are characterized by different lipid profiles<sup>10, 11</sup>. Conversely, lower lipid levels in Japanese adults are shown to be associated with an increased risk of atrial fibrillation<sup>12, 13</sup>. Together, these factors may have concealed associations between non-HDL-C and stroke risk.

Given the potentially complex associations between lipid profile and stroke risk, we conducted a large-scale prospective study to clarify these associations, focusing on stroke subtypes, in approximately 31,000 individuals in nine population-based cohorts. Non-HDL-C can be calculated simply using a well standardized algorithm regardless of the fasting triglyceride level, which is needed to estimate low density lipoprotein (LDL) cholesterol using the Friedewald equation. This study investigated the relationships between the incidence of CHD, stroke, and stroke subtypes and baseline levels of non-HDL-C over a median follow-up period of 15 yrs.

## Methods

### Study Population

The Japan Public Health Center-based Prospective (JPHC) Study began in 1990 (Cohort I) and 1993-1994 (Cohort II), included 140,420 Japanese residents aged 40–59 yrs (Cohort I) or 40–69 yrs (Cohort II), and it included 11 public health-centers that hold information on incident CVD events<sup>14</sup>. Participants were asked about lifestyle 5 and 10 yrs after the baseline examination. Because non-HDL-C was not available at baseline in Cohort I, we used data after 5 yrs in Cohort I ( $n=45,019$ ) and at baseline in Cohort II ( $n=63,216$ ). Excluding two communities without CVD registration, we selected individuals who received baseline blood examinations ( $n=31,296$ ). After exclusion of patients with a history of CVD or extreme hypertriglyceridemia ( $\geq 600$  mg/dl)<sup>15</sup>, 30,554 individuals were included in the analyses.

The study protocol, including the procedure for obtaining informed consent in the JPHC study, was approved by the Human Ethics Review Committees of the National Cancer Center and Faculty of Medicine, Oita University.

### Baseline Surveys

A self-administered questionnaire was used to

obtain a medical history, smoking and alcohol-drinking habits, sports during leisure time, menopause (for women), and time since the last meal ( $\geq 8$  hours or not). Sports during leisure time was determined by a validated question<sup>16, 17</sup>, i.e., “How many times did you participate in sports and physical activity other than during working hours,” with 5 predefined categories: almost never, 1–3 days per month, 1–2 days per week, 3–4 days per week, and almost daily.

Blood pressure was measured in the right arm using a standard mercury sphygmomanometer, with the patient in the sitting position after resting for at least 5 minutes. Body mass index (BMI, kg/m<sup>2</sup>) was calculated as weight divided by the square of height, and overweight was defined as BMI  $\geq 25$  kg/m<sup>2</sup>. Hypertension was defined as systolic and diastolic blood pressures  $\geq 140/90$  mmHg or the use of medication to treat hypertension. Diabetes was defined as a fasting plasma glucose  $\geq 7.0$  mmol/L, a non-fasting glucose  $\geq 11.0$  mmol/L, or the use of medication to treat diabetes. The concentrations of total cholesterol, HDL-C, triglycerides, and glucose in the blood were measured by conventional enzyme methods. External quality control for the measurement of serum lipids and plasma glucose was provided by the Standardization Program of the Japan Medical Association. For international quality control, the laboratories joined the program of the Osaka Medical Center for Health Science and Promotion, a member of the Cholesterol Reference Method Laboratory Network to standardize total cholesterol and HDL-C<sup>18</sup>.

### Ascertainment of Stroke and CHD Incidence Rates

Subjects were followed-up for a median of 15.0 yrs from 1995 to December 31, 2009 (Cohort I) and from 1993 to December 31, 2012 (Cohort II). Person-yrs were calculated from the date of entry to the date of the first endpoint (death, emigration, or lost to follow-up) or to the study end-date.

CVD outcomes were determined as mentioned previously<sup>19</sup>. In brief, physicians systematically reviewed the medical records of possible stroke hospitalizations at 81 major community hospitals. Strokes were confirmed by medical records, including computed tomography scans, magnetic resonance images, and autopsy findings. All strokes met the criteria of the National Survey of Stroke<sup>20</sup>, which requires symptoms related to neurological deficits of sudden or rapid onset lasting at least 24 h or until death. Strokes were classified as subarachnoid hemorrhage, intracerebral hemorrhage (ICH), or ischemic stroke, which included lacunar infarction, large-artery occlusive infarction, embolic infarction, and unclassified<sup>21</sup>. ICH was further classified into two groups: “deep

only” included ICH in the deep brain regions (basal ganglia, thalamus, internal capsules, and brainstem), and “lobar” included ICH in the cortex, subcortical white matter, and cerebellum. Mixed type (deep and lobar regions) was included in the latter group. Infarcts  $\leq 1.5$  cm in diameter in the deep brain regions were defined as lacunar infarctions, while infarcts  $> 1.5$  cm involving cortical areas were classified as large-artery occlusive infarctions. The definition of embolic infarction required the same criteria as ischemic infarction plus the presence of an embolus in the brain, atrial fibrillation, or medical record evidence of a possible embolic source. A stroke that was diagnosed clinically but exhibited no lesions on CT, MRI, or autopsy was classified as a stroke of undetermined type.

Myocardial infarction meeting the criteria of the MONICA project, which required typical chest pain and evidence of infarction from an electrocardiogram, cardiac enzymes, or autopsy records<sup>22</sup>, was confirmed from medical records. Sudden cardiac death was defined as a death of unknown cause that occurred within one hour of the onset of the cardiovascular event. CHD was defined as a composite outcome of myocardial infarction and sudden cardiac death.

### Statistical Analysis

Sex-specific and age-adjusted incidence rates of CHD, total stroke, subarachnoid hemorrhage, ICH, and ischemic stroke were calculated by quintile of non-HDL-C using the Poisson regression analysis stratified by study community. A Cox proportional hazards model was used to calculate sex-specific hazard ratios (HRs) and 95% confidence intervals (CIs) using data grouped according to non-HDL-C quintile, with the lowest quintile serving as a reference stratified by study community. Model 1 was adjusted for age (continuous). Model 2 was additionally adjusted for smoking status (never, ex-,  $< 20$ , or  $\geq 20$  cigarettes/day for men; or current smoker or not for women), alcohol intake (0, 1–150, 151–300, or  $\geq 301$  g/wk for men; or  $\geq 1$  day/week alcohol or not for women), sports at leisure time (rarely, 1–2, 3–4 times/week, or almost every day), BMI, menopause in women (yes/no), systolic blood pressure (continuous), use of antihypertensive agents (yes/no), diabetes (yes/no), HDL-C (continuous), and use of antilipemic agents (yes/no). A linear trend was examined using continuous values of non-HDL-C in the Cox regression models. We tested the non-linear trend based on the fractional polynomials analysis to determine the significance of the trend when the linearity was denied<sup>23</sup>. Analyses stratified by the presence of overweight, hypertension, and hypertriglyceridemia (fast-

ing triglycerides  $\geq 150$  mg/dl or non-fasting triglycerides  $\geq 300$  mg/dl) were also performed. Statistical significance was assumed at  $p < 0.05$ . Analyses were performed with SAS software, version 9.4 (SAS Institute, Inc., Cary, North Carolina, USA).

## Results

**Table 1** shows the baseline characteristics of study participants according to sex and non-HDL-C quintile. Non-HDL-C was significantly associated with several other variables, except current smoking and mean intake of alcohol in women.

Incidence rates of CHD, stroke, and stroke subtype were analyzed according to sex and non-HDL-C quintile (**Fig. 1**). In contrast to CHD, stroke incidence rates demonstrated a U-shaped association with non-HDL-C quintile. Trends in the incidence of ICH and ischemic stroke according to non-HDL-C quintile level were significantly different.

As for stroke occurrences in men (**Table 2**), the lowest multivariable adjusted HR was in the fourth non-HDL-C quintile, compared with the lowest non-HDL-C quintile [0.78 (95% CI, 0.62–0.98) in men and 0.80 (95% CI, 0.64–0.99) in women]. Furthermore, the fractional polynomial models showed significant non-linear associations between stroke risk and non-HDL-C quintile in men ( $p < 0.001$ ) but not in women. The age-adjusted HRs for CHD in the highest quintile were 6.55 (95% CI, 3.45–12.4) in men and 2.88 (95% CI, 1.43–5.80) in women, stratified by the study community. Linear trend tests were significant in both sexes. After adjustment for smoking status, alcohol intake, sports during leisure time, BMI, menopause (in women), systolic blood pressure, use of antihypertensive agents, diabetes, HDL-C, and use of antilipemic agents (model 2), the association with CHD remained significant in both sexes.

Next, we compared the risk of stroke subtype in men according to non-HDL-C quintile, adjusted for multiple variables, relative to the lowest non-HDL-C quintile (**Table 3**). The HRs for SAH and ICH decreased by 0.30 (95% CI, 0.10–0.92) in the fourth quintile and by 0.57 (95% CI, 0.37–0.87) in the fifth quintile (Model 1). When adjusted for confounders, the association between non-HDL-C and SAH diminished, but the association with ICH was unchanged and suggested an inverse trend. Non-HDL-C was positively associated with an increased risk of large-artery occlusive infarction, independent of several other risk factors. The lowest risk of embolic infarction was observed in the fourth non-HDL-C quintile.

Similar to our findings in men, the age-adjusted HRs for SAH and ICH in women in the higher non-

**Table 1.** Baseline characteristics according to non-HDL cholesterol (non-HDL-C) quintile

Sex	Variables	Non-HDL-C quintile					P for difference
		Q1	Q2	Q3	Q4	Q5	
Men	<i>n</i>	2,079	2,059	2,116	2,093	2,112	
	Range of non-HDL-C, mmol/L (mg/dL)	<2.87 (111)	2.87-3.34 (111-129)	3.37-3.81 (130-147)	3.83-4.38 (148-169)	≥ 4.40 (170)	
	Age	58.3	57.7	57.5	57.0	56.6	<0.001
	Body mass index, kg/m <sup>2</sup>	22.2	23.2	23.7	24.1	24.7	<0.001
	Systolic blood pressure, mmHg	132.2	132.9	132.9	133.5	134.5	0.001
	Diastolic blood pressure, mmHg	79.0	80.0	79.9	80.8	81.5	<0.001
	Total cholesterol, mmol/L	4.02	4.60	4.99	5.42	6.24	<0.001
	HDL cholesterol, mmol/L	1.58	1.48	1.40	1.33	1.27	<0.001
	Triglycerides <sup>†</sup> , mmol/L	0.90	1.08	1.27	1.51	1.89	<0.001
	Overweight, %	14.1	24.3	29.9	36.3	43.6	<0.001
	Current smokers, %	47.3	41.3	40.4	40.7	38.9	<0.001
	Alcohol intake ≥ 1 day/week, %	73.9	70.9	68.4	66.2	60.3	<0.001
	Mean intake of alcohol <sup>‡</sup> , g/week	325.9	294.5	278.8	285.4	271.1	<0.001
	Sports during leisure time ≥ 1 time/week, %	15.6	19.3	19.4	20.5	20.4	<0.001
	Hypertension, %	43.8	45.3	44.5	46.1	48.5	0.026
	Diabetes, %	5.9	5.9	5.5	6.8	8.5	0.001
	Antilipemic agents use, %	0.6	0.8	1.1	1.9	4.0	<0.001
Women	<i>n</i>	3,972	3,979	4,159	4,004	3,981	
	Range of non-HDL-C, mmol/L (mg/dL)	<3.16 (122)	3.16-3.63 (122-140)	3.65-4.12 (141-159)	4.14-4.69 (160-181)	≥ 4.71 (182)	
	Age	54.0	56.1	57.0	57.7	58.1	<0.001
	Body mass index, kg/m <sup>2</sup>	22.7	23.5	23.9	24.3	24.7	<0.001
	Systolic blood pressure, mmHg	126.0	128.7	130.3	131.7	133.4	<0.001
	Diastolic blood pressure, mmHg	75.0	76.7	77.3	78.0	79.0	<0.001
	Total cholesterol, mmol/L	4.39	4.96	5.38	5.83	6.65	<0.001
	HDL cholesterol, mmol/L	1.65	1.56	1.50	1.43	1.36	<0.001
	Triglycerides <sup>†</sup> , mmol/L	0.83	1.02	1.19	1.37	1.65	<0.001
	Overweight, %	20.4	28.7	33.3	38.3	42.2	<0.001
	Current smokers, %	3.5	2.9	2.6	3.3	2.7	0.055
	Alcohol intake ≥ 1 day/week, %	10.4	8.7	9.3	7.7	6.5	<0.001
	Mean intake of alcohol <sup>‡</sup> , g/week	92.8	78.8	100.1	81.2	70.4	0.084
	Sports during leisure time ≥ 1 time/week, %	16.7	19.4	20.0	22.0	22.1	<0.001
	Menopause, %	64.4	64.4	76.0	76.0	82.8	<0.001
	Hypertension, %	29.4	36.2	39.6	43.6	46.7	<0.001
	Diabetes, %	1.9	2.5	2.7	3.8	4.8	<0.001
Antilipemic agents use, %	0.6	1.9	3.6	4.7	8.2	<0.001	

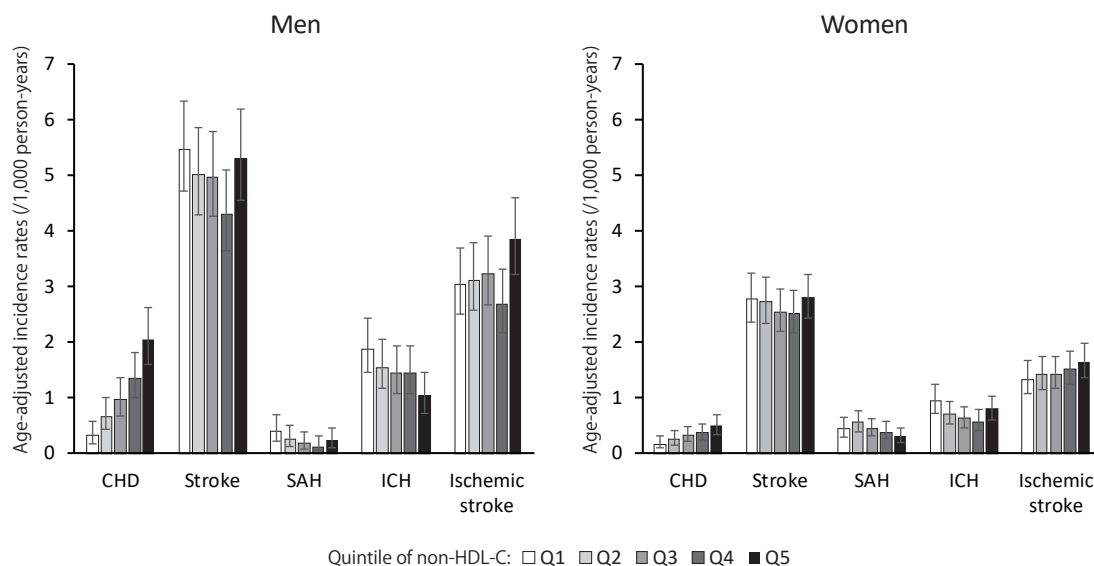
P values were calculated using ANOVA or chi-square test.

<sup>†</sup>Geometric mean, <sup>‡</sup>Among persons with alcohol intake of ≥ 1 day/week.

HDL-C quintiles were decreased relative to the lowest quintile (Table 4). The lowest HR for ICH was observed in the fourth quintile (HR=0.62, 95% CI, 0.41–0.95). The association between non-HDL-C and lacunar infarction was significant in a linear manner (*p* for trend=0.04), but it was substantially weakened after adjustment. In Model 2, the risk of embolic infarction was decreased by 0.50 (95% CI, 0.29–0.88)

in the third non-HDL-C quintile. We examined the interaction between menopausal status and non-HDL-C in women but could not find a significant interaction with any stroke subtype.

Fig. 2 shows the multivariable-adjusted HRs for deep and lobar ICH in men according to non-HDL-C quintile. An inverse linear trend was observed for lobar ICH (*p* for trend=0.01), and HRs were



**Fig. 1.** Incidence rates of CHD, stroke, and stroke subtypes according to non-HDL cholesterol quintile and sex

**Table 2.** Sex-specific multivariable adjusted hazard ratios and 95% confidence intervals of non-HDL cholesterol (non-HDL-C) quintiles in relation to the incidence of coronary heart disease and stroke

Sex		Non-HDL-C quintile					P for trend		
		Q1	Q2	Q3	Q4	Q5	Linear	Non-linear	
Men	Range of non-HDL-C, mmol/L (mg/dL)	< 2.87 (111)	2.87-3.34 (111-129)	3.37-3.81 (130-147)	3.83-4.38 (148-169)	≥ 4.40 (170)			
	Stroke	Cases, <i>n</i>	182	167	165	138	168		
	Person-years	30,889	31,776	32,455	32,269	32,501			
	Model 1	1.00	0.92 (0.75-1.14)	0.90 (0.73-1.11)	0.79 (0.63-0.99)	0.99 (0.80-1.22)	> 0.2	< 0.001	
	Model 2	1.00	0.90 (0.73-1.11)	0.87 (0.70-1.08)	0.76 (0.61-0.96)	0.92 (0.73-1.15)	> 0.2	< 0.001	
	CHD	Cases, <i>n</i>	11	23	33	44	67		
	Person-years	31,724	32,536	33,237	32,744	33,009			
	Model 1	1.00	2.13 (1.04-4.37)	3.06 (1.54-6.05)	4.25 (2.19-8.23)	6.55 (3.45-12.4)	< 0.001	N/A	
	Model 2	1.00	1.86 (0.90-3.85)	2.62 (1.32-5.23)	3.42 (1.74-6.71)	4.64 (2.39-8.98)	< 0.001	N/A	
	Women	Range of non-HDL-C, mmol/L (mg/dL)	< 3.16 (122)	3.16-3.63 (122-140)	3.65-4.12 (141-159)	4.14-4.69 (160-181)	≥ 4.71 (182)		
Stroke		Cases, <i>n</i>	156	175	180	177	197		
Person-years		65,792	65,478	68,115	65,347	64,538			
Model 1		1.00	0.95 (0.77-1.18)	0.87 (0.70-1.08)	0.86 (0.69-1.07)	0.96 (0.78-1.19)	> 0.2	N/A	
Model 2		1.00	0.91 (0.73-1.14)	0.81 (0.65-1.02)	0.79 (0.63-0.99)	0.86 (0.68-1.07)	> 0.2	N/A	
CHD		Cases, <i>n</i>	10	17	25	28	38		
Person-years		66,528	66,198	68,829	66,158	65,286			
Model 1		1.00	1.47 (0.67-3.22)	1.93 (0.93-4.04)	2.14 (1.04-4.43)	2.88 (1.43-5.80)	< 0.001	N/A	
Model 2		1.00	1.29 (0.59-2.84)	1.60 (0.76-3.37)	1.63 (0.78-3.42)	2.02 (0.97-4.19)	0.014	N/A	

Model 1 was adjusted for age stratified by community.

Model 2 was further adjusted for smoking status (never, ex-, < 20, or ≥ 20 cigarettes/day in men; or current smoker or not in women), alcohol intake (0, 1-150, 151-300, or ≥ 301 g/week in men; or ≥ 1 day/week alcohol drinker or not in women), sports during leisure time (rarely, 1-2, 3-4 times/week, or almost every day), body mass index, menopause (women only), systolic blood pressure, use of antihypertensive agents, diabetes, HDL-C, and use of antilipemic agents.

Linear trends were tested by using continuous values of non-HDL-C, and non-linear trends were further tested if the fractional polynomial models were fitted at a significance level of *p* < 0.05. N/A, not applicable.

**Table 3.** Multivariable adjusted hazard ratios and 95% confidence intervals of non-HDL cholesterol (non-HDL-C) quintiles in relation to stroke subtypes in men

Subtypes of stroke		Non-HDL-C quintile					P for linear trend
		Q1	Q2	Q3	Q4	Q5	
Subarachnoid hemorrhage	Cases, n	13	9	6	4	8	
	Model 1	1	0.68 (0.29-1.58)	0.44 (0.17-1.16)	0.30 (0.10-0.92)	0.61 (0.25-1.49)	0.06
	Model 2	1	0.79 (0.33-1.89)	0.55 (0.20-1.49)	0.40 (0.12-1.31)	0.86 (0.32-2.30)	>0.2
Intracerebral hemorrhage	Cases, n	59	49	46	45	32	
	Model 1	1	0.81 (0.56-1.19)	0.75 (0.51-1.10)	0.78 (0.53-1.15)	0.57 (0.37-0.87)	0.008
	Model 2	1	0.82 (0.56-1.20)	0.74 (0.50-1.10)	0.79 (0.53-1.19)	0.55 (0.35-0.87)	0.010
Ischemic stroke	Cases, n	107	109	112	89	126	
	Model 1	1	1.03 (0.79-1.35)	1.05 (0.81-1.37)	0.88 (0.66-1.16)	1.28 (0.99-1.66)	0.10
	Model 2	1	0.99 (0.76-1.30)	0.99 (0.75-1.30)	0.81 (0.60-1.09)	1.13 (0.86-1.49)	>0.2
Lacunar infarction	Cases, n	40	49	43	38	53	
	Model 1	1	1.23 (0.81-1.87)	1.08 (0.70-1.66)	1.00 (0.64-1.55)	1.41 (0.93-2.13)	0.13
	Model 2	1	1.19 (0.78-1.81)	1.01 (0.65-1.57)	0.92 (0.58-1.46)	1.25 (0.80-1.94)	>0.2
Large-artery occlusive infarction	Cases, n	15	25	20	25	32	
	Model 1	1	1.68 (0.89-3.19)	1.33 (0.68-2.59)	1.75 (0.92-3.33)	2.34 (1.26-4.33)	0.005
	Model 2	1	1.63 (0.86-3.11)	1.18 (0.59-2.34)	1.60 (0.82-3.09)	2.05 (1.07-3.93)	0.033
Embolic infarction	Cases, n	43	30	41	24	37	
	Model 1	1	0.71 (0.45-1.13)	0.95 (0.62-1.46)	0.59 (0.36-0.97)	0.94 (0.60-1.46)	>0.2
	Model 2	1	0.68 (0.42-1.09)	0.94 (0.61-1.47)	0.55 (0.33-0.93)	0.84 (0.52-1.35)	>0.2

Model 1 was adjusted for age and community. Model 2 was further adjusted for smoking status (never, ex-, <20, or  $\geq 20$  cigarettes/day), alcohol intake (0, 1-150, 151-300, or  $\geq 301$  g/week), sports at leisure time (rarely, 1-2, 3-4 times/week, or almost every day), body mass index, systolic blood pressure, use of antihypertensive agents, diabetes, HDL-C, and use of antilipemic agents. Linear trends were tested by using continuous values of non-HDL-C.

decreased by 0.40 (95% CI, 0.17–0.98) in the fourth non-HDL-C quintile. Likewise, the HR for deep ICH in the highest non-HDL-C quintile was 0.56 (95% CI, 0.32–0.98), but the linear trend was not significant ( $p$  for trend=0.14).

Multivariable-adjusted HRs of CHD, ICH, and large-artery occlusive infarction for each standard deviation (SD) increase in non-HDL-C in men were stratified by overweight, hypertension, hypertriglyceridemia, and drinking alcohol (Table 5). The HRs for CHD and large-artery occlusive infarction increased, while the HRs for ICH decreased for each SD increase in non-HDL-C, independent of overweight, hypertension, and hypertriglyceridemia status. The association between drinking alcohol and non-HDL-C for CHD was significant ( $p=0.008$ ), with the HR being greater in patients who did not drink alcohol compared to those who did.

Finally, a sensitivity analysis was performed on the association between non-HDL-C and ICH, excluding the first 3-yr follow-up period; patients using antilipemic agents; and those who exhibited a

HDL-C of  $\geq 90$  mg/dl. However, the inverse association remained unchanged (Supplemental Table 1).

## Discussion

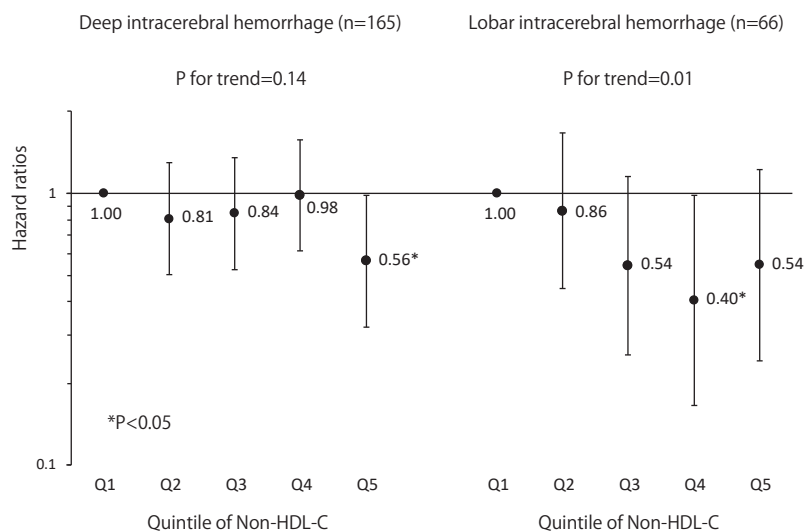
This long-term prospective study found a U-shaped association between total stroke incidence and non-HDL-C in men but not in women. This is in contrast to the previously identified linear association between non-HDL-C and CHD. Furthermore, high non-HDL-C strongly increased the risk of large-artery occlusive infarction and decreased the risk of ICH, particularly lobar ICH, independent of other established CVD risk factors in men. The lowest risk of embolic infarction was in the third and fourth non-HDL-C quintiles in men and women, respectively.

As expected, our study supports the association between non-HDL-C and CHD risk as reported in the Emerging Risk Factors Collaboration<sup>1</sup> and epidemiological studies in Japan<sup>4-6, 24-26</sup>. In addition, our findings provide a new understanding of stroke risk. Non-HDL-C was eliminated as a risk factor for stroke

**Table 4.** Multivariable adjusted hazard ratios and 95% confidence intervals of non-HDL cholesterol (non-HDL-C) quintiles in relation to stroke subtypes in women

Subtypes of stroke		Non-HDL-C quintile					P for linear trend
		Q1	Q2	Q3	Q4	Q5	
Subarachnoid hemorrhage	Cases, n	25	34	29	25	19	
	Model 1	1	1.21 (0.72-2.04)	0.93 (0.54-1.60)	0.82 (0.47-1.43)	0.61 (0.34-1.12)	0.07
	Model 2	1	1.22 (0.72-2.08)	0.93 (0.54-1.63)	0.79 (0.44-1.42)	0.59 (0.31-1.11)	0.06
Intracerebral hemorrhage	Cases, n	53	45	45	41	57	
	Model 1	1	0.71 (0.47-1.05)	0.64 (0.43-0.95)	0.58 (0.38-0.87)	0.82 (0.56-1.19)	>0.2
	Model 2	1	0.75 (0.50-1.12)	0.68 (0.45-1.02)	0.62 (0.41-0.95)	0.88 (0.59-1.32)	>0.2
Ischemic stroke	Cases, n	77	94	105	111	120	
	Model 1	1	1.04 (0.77-1.40)	1.02 (0.76-1.37)	1.08 (0.81-1.45)	1.17 (0.88-1.56)	0.15
	Model 2	1	0.92 (0.68-1.26)	0.87 (0.65-1.18)	0.90 (0.66-1.21)	0.93 (0.68-1.26)	>0.2
Lacunar infarction	Cases, n	26	36	57	45	57	
	Model 1	1	1.18 (0.71-1.96)	1.66 (1.04-2.64)	1.30 (0.80-2.12)	1.64 (1.03-2.62)	0.04
	Model 2	1	1.01 (0.60-1.68)	1.38 (0.86-2.22)	1.04 (0.63-1.71)	1.23 (0.75-2.00)	>0.2
Large-artery occlusive infarction	Cases, n	15	18	19	30	19	
	Model 1	1	1.02 (0.51-2.02)	0.96 (0.49-1.89)	1.52 (0.81-2.84)	0.98 (0.49-1.94)	>0.2
	Model 2	1	0.86 (0.43-1.73)	0.77 (0.38-1.55)	1.20 (0.63-2.29)	0.74 (0.36-1.51)	>0.2
Embolic infarction	Cases, n	31	35	23	28	37	
	Model 1	1	0.97 (0.60-1.58)	0.55 (0.32-0.95)	0.68 (0.41-1.15)	0.90 (0.56-1.46)	>0.2
	Model 2	1	0.93 (0.57-1.52)	0.50 (0.29-0.88)	0.60 (0.35-1.02)	0.76 (0.46-1.28)	0.18

Model 1 was adjusted for age and community. Model 2 was further adjusted for smoking status (current smoker or not), alcohol intake ( $\geq 1$  day/week alcohol drinker or not), sports during leisure time (rarely, 1-2, 3-4 times/week, or almost every day), body mass index, menopause, systolic blood pressure, use of antihypertensive agents, diabetes, HDL-C, and use of antilipemic agents. Linear trends were tested by using continuous values of non-HDL-C.



**Fig. 2.** Multivariable adjusted HRs for deep and lobar ICH, grouped by non-HDL cholesterol quintile in men

HRs were adjusted for variables in Model 2 of Table 3.

**Table 5.** Multivariable adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of one standard deviation (SD) increase in non-HDL cholesterol related to the incidence of coronary heart disease (CHD) and stroke subtypes according to the presence/absence of overweight, hypertension, and hypertriglyceridemia in men

	Cardiovascular disease outcomes								
	CHD			Intracerebral hemorrhage			Large-artery occlusive infarction		
	Cases, <i>n</i>	HR (95% CI)*	<i>P</i> for interaction	Cases, <i>n</i>	HR (95% CI)*	<i>P</i> for interaction	Cases, <i>n</i>	HR (95% CI)*	<i>P</i> for interaction
Overweight									
No	111	1.71 (1.49-1.97)	0.91	164	0.79 (0.66-0.94)	0.22	71	1.22 (0.96-1.56)	0.72
Yes	66	1.55 (1.21-1.98)		67	0.96 (0.74-1.24)		46	1.28 (0.94-1.74)	
Hypertension									
No	57	1.87 (1.56-2.23)	0.32	81	0.90 (0.70-1.15)	0.45	47	1.34 (1.03-1.75)	0.34
Yes	120	1.55 (1.30-1.85)		150	0.81 (0.68-0.96)		70	1.15 (0.90-1.47)	
Hypertriglyceridemia									
No	143	1.62 (1.37-1.91)	0.97	202	0.85 (0.73-1.00)	0.49	103	1.16 (0.94-1.43)	0.19
Yes	34	1.60 (1.22-2.09)		29	0.64 (0.42-0.98)		14	1.83 (1.20-2.79)	
Alcohol drinking									
No	91	1.95 (1.60-2.36)	0.008	77	0.86 (0.68-1.10)	0.34	48	1.19 (0.89-1.58)	0.93
Yes	86	1.49 (1.24-1.78)		154	0.83 (0.69-1.00)		69	1.28 (1.00-1.62)	

\*Adjusted for age, smoking status (never, ex-, <20, or ≥ 20 cigarettes/day), alcohol intake (0, 1-150, 151-300, or ≥ 301 g/week), sports at leisure time (rarely, 1-2, 3-4 times/week, or almost every day), and body mass index stratified by community. When stratified by alcohol drinking status, it was excluded from the model. HRs are expressed according to SD increase in non-HDL-C.

by previous Japanese investigations<sup>4-7, 24, 27</sup>). Data from our study suggest that this finding can be explained by characteristics of the different types of ischemic stroke. A large proportion of ischemic strokes in Japan are lacunar infarctions<sup>9, 21</sup>). This fact may have weakened the measured association between non-HDL-C and ischemic stroke because the pathogenesis of lacunar infarction is quite different from that of large-artery occlusive infarction and atherothrombotic infarction<sup>11</sup>).

Consistent with this, a previous study suggested that the development of lacunar infarction was very close to that of ICH in combination with hypertension and a low cholesterol level<sup>28</sup>). Furthermore, the risk of cardioembolic infarction decreased with increased non-HDL-C<sup>4</sup>). This phenomenon was due to increased risk of atrial fibrillation among individuals with low cholesterol levels<sup>12, 13</sup>).

Low non-HDL-C, as well as low total cholesterol, was associated with an increased risk of ICH in previous studies<sup>29-31</sup>), although some studies could not identify non-HDL-C as a risk factor for ICH<sup>4, 6, 32</sup>). Two negative studies in Japan appeared to demonstrate insufficient power to detect this association<sup>4, 6</sup>). Another study in China used a large cohort in an urban area<sup>32</sup>). Our data were obtained only in local communities in Japan. It is possible these inverse asso-

ciations are a characteristic of individuals living in rural areas. When ICH was classified by location (deep or lobar), the present study found that low non-HDL-C was associated with an increased risk of lobar ICH but not with deep ICH. Regarding deep ICH, the highest quintile of non-HDL-C exhibited a decreased risk of developing this condition, although a linear trend was not observed. The JPHC study demonstrated that lower intake of saturated fatty acids elevated the risk of lacunar infarction and deep ICH<sup>33</sup>). Conversely, non-HDL-C concentrations exhibited a great impact on large vessels in the brain, leading to large-artery occlusive infarction and lobar ICH events. Our findings support a previous report on the association of low cholesterol with lobar cerebral microbleeds<sup>34</sup>).

Non-HDL-C concentration is considered to reflect apolipoprotein B and triglyceride-rich lipoprotein levels, as well as levels of other atherogenic lipids<sup>35</sup>). The ability of non-HDL-C levels to predict CHD occurrence was comparable to apolipoprotein B and LDL-C measurements<sup>5, 36</sup>). Though elevated non-HDL-C increased the risk of CHD regardless of triglycerides levels, it was more predictive of large-artery occlusive infarction among individuals with hypertriglyceridemia. This stratification analysis implied that, similar to CHD, large-artery occlusive infarction is an



atherogenic disease.

Drinking alcohol exhibited an impact on the association between non-HDL-C concentration and occurrence of CHD. Our JPHC study showed previously that consumption of alcohol was inversely associated with CHD in men and exhibited a protective effect against CHD<sup>37</sup>). Consistent with this finding, we observed a marked association between non-HDL-C concentration and CHD in non-alcohol drinkers, with alcohol exhibiting no beneficial effect on atherosclerosis.

In the present study, the obvious relationship between non-HDL-C and stroke subtype was limited to men. Although we examined the association of sex, there was no significant interaction between them. Thereby, whether there was a sex difference in non-HDL-C levels related to the occurrence of stroke subtypes remains unclear. Furthermore, we did not observe different results according to menopausal status in women.

The strengths of our study were that it recruited a large number of participants across Japan who were followed for 15 years and used a power of analysis that allowed for estimation of stroke subtype and CHD risk by sex. Moreover, we found a novel association between non-HDL-C and ICH in men, primarily lobar ICH rather than deep ICH. Nevertheless, several limitations must be considered. First, the study participants were limited to those who received total and HDL cholesterol values assessment during annual health checkups. This might have caused a “healthy voluntary effect” as mentioned elsewhere and thus an underestimation of CVD HR<sup>38</sup>). Second, since our populations consisted of patients living in rural areas, the results may not be representative of Japan. Third, we only used baseline non-HDL-C values in the analysis and did not evaluate changes in non-HDL-C during follow-up. Fourth, we did not gather information on electrocardiograph findings. Therefore, we were unable to adjust for atrial fibrillation as a stroke risk factor in the final analysis. Low non-HDL-C may be caused by poor nutritional status, which can increase ICH events. However, as we did not assess nutritional status, further investigations are needed to confirm our hypothesis.

In conclusion, unlike its association with CHD, the association between non-HDL-C concentration and the risk of stroke varied by stroke subtype. Lower non-HDL-C concentrations were associated with a lower risk of large-artery occlusion infarction but a higher risk of ICH, particularly lobar ICH.

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**Supplemental Table 1.** Multivariable adjusted hazard ratio of non-HDL-C related to CHD and stroke subtypes in men

		Quintile of non-HDL cholesterol concentrations					<i>P</i> for trend
		Q1	Q2	Q3	Q4	Q5	
Excluding the first 3-yr follow-up period ( <i>n</i> = 515 for CHD and <i>n</i> = 613 for stroke)							
Men	CHD	1	1.58 (0.72-3.46)	2.81 (1.37-5.77)	3.11 (1.52-6.36)	4.38 (2.18-8.80)	<0.001
	Intracerebral hemorrhage	1	0.82 (0.55-1.24)	0.71 (0.46-1.09)	0.83 (0.54-1.27)	0.55 (0.34-0.89)	0.016
	Large-artery occlusive infarction	1	1.63 (0.85-3.10)	1.11 (0.55-2.23)	1.48 (0.75-2.89)	2.00 (1.04-3.84)	0.045
Women	CHD	1	1.26 (0.55-2.89)	1.62 (0.74-3.53)	1.79 (0.83-3.87)	2.04 (0.95-4.38)	0.013
	Intracerebral hemorrhage	1	0.76 (0.49-1.18)	0.81 (0.52-1.24)	0.64 (0.41-1.02)	0.98 (0.64-1.52)	0.72
	Large-artery occlusive infarction	1	0.87 (0.42-1.78)	0.77 (0.38-1.59)	1.23 (0.63-2.38)	0.78 (0.38-1.61)	0.83
Excluding those who used antilipemic agents ( <i>n</i> = 939)							
Men	CHD	1	2.05 (0.97-4.34)	2.81 (1.37-5.75)	3.66 (1.81-7.40)	5.14 (2.58-10.2)	<0.001
	Intracerebral hemorrhage	1	0.82 (0.56-1.20)	0.74 (0.50-1.11)	0.78 (0.52-1.18)	0.52 (0.33-0.83)	0.005
	Large-artery occlusive infarction	1	1.62 (0.85-3.10)	1.17 (0.59-2.32)	1.47 (0.75-2.88)	2.02 (1.06-3.88)	0.05
Women	CHD	1	1.25 (0.57-2.78)	1.53 (0.72-3.25)	1.61 (0.76-3.41)	2.07 (0.99-4.32)	0.018
	Intracerebral hemorrhage	1	0.75 (0.50-1.13)	0.70 (0.46-1.06)	0.64 (0.42-0.99)	0.89 (0.59-1.34)	0.92
	Large-artery occlusive infarction	1	0.82 (0.41-1.68)	0.80 (0.40-1.61)	1.19 (0.62-2.28)	0.77 (0.37-1.58)	0.83
Excluding those with HDL-C ≥ 90 mg/dl ( <i>n</i> = 847)							
Men	CHD	1	1.72 (0.83-3.57)	2.51 (1.26-5.01)	3.10 (1.58-6.09)	4.42 (2.29-8.55)	<0.001
	Intracerebral hemorrhage	1	0.88 (0.59-1.31)	0.78 (0.52-1.17)	0.85 (0.56-1.29)	0.59 (0.37-0.94)	0.022
	Large-artery occlusive infarction	1	1.93 (0.96-3.87)	1.41 (0.68-2.93)	1.90 (0.94-3.85)	2.44 (1.22-4.89)	0.008
Women	CHD	1	1.42 (0.63-3.20)	1.74 (0.80-3.76)	1.77 (0.82-3.81)	2.12 (0.99-4.53)	0.015
	Intracerebral hemorrhage	1	0.67 (0.45-1.02)	0.63 (0.42-0.96)	0.60 (0.39-0.91)	0.82 (0.55-1.23)	0.66
	Large-artery occlusive infarction	1	0.90 (0.44-1.84)	0.76 (0.37-1.55)	1.25 (0.65-2.41)	0.76 (0.37-1.57)	0.91

Sex-specified hazard ratios were adjusted for age, smoking status (never, ex-, <20, or ≥ 20 cigarettes/day in men; or current smoker or not in women), alcohol intake (0, 1-150, 151-300, or ≥ 301 g/week in men; or ≥ 1 day/week alcohol drinker or not in women), sports during leisure time (rarely, 1-2, 3-4 times/week, or almost every day), body mass index, menopause (women only), systolic blood pressure, use of antihypertensive agents, diabetes, HDL-C, and use of antilipemic agents stratified by community.