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Non-High-Density Lipoprotein Cholesterol and Risk of Cardiovascular Disease: The Japan Epidemiology Collaboration on Occupational Health Study

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Aims: We aimed to investigate the association between non-high-density lipoprotein cholesterol (non-HDL-C) levels and the risk of cardiovascular disease (CVD) and its subtypes.

Methods: In this contemporary cohort study, we analyzed the data of 63,814 Japanese employees aged ≥ 30 years, without known CVD in 2012 and who were followed up for up to 8 years. The non-HDL-C level was divided into 5 groups: <110, 110-129, 130-149, 150-169, and ≥ 170 mg/dL. The Cox proportional hazards model was used to calculate the hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) for CVD and its subtypes associated with each non-HDL-C group, considering 130-149 mg/dL as the reference group.

Results: During the study period, 271 participants developed CVD, including 78 myocardial infarctions and 193 strokes (102 ischemic strokes, 89 hemorrhagic strokes, and 2 unknowns). A U-shaped association between non-HDL-C and stroke was observed. In the analysis of stroke subtypes, the multivariable-adjusted HR (95% CI) for hemorrhagic stroke was 2.61 (1.19–5.72), 2.02 (0.95–4.29), 2.10 (1.01–4.36), and 1.98 (0.96-4.08), while that for ischemic stroke was 1.54 (0.77-3.07), 0.91 (0.46-1.80), 0.73 (0.38-1.41), and 1.50 (0.87-2.56) in the <110, 110-129, 150-169, and ≥ 170 mg/dL groups, respectively. Individuals with elevated non-HDL-C levels had a higher risk of myocardial infarction.

Conclusions: High non-HDL-C levels were associated with an increased risk of myocardial infarction. Moreover, high and low non-HDL-C levels were associated with a high risk of stroke and its subtypes among Japanese workers.

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Key words: Non-high-density lipoprotein cholesterol, Stroke, Myocardial infarction

Introduction

Cardiovascular disease (CVD) is a leading cause of mortality, accounting for 31% of all global deaths in 2016 [1]. In Japan, CVD accounted for approximately 23% of all deaths in 2019 [2]. Stroke is the most prevalent CVD in Japanese, accounting for >60% of all CVD cases[3]. To reduce the burden of CVD, especially stroke, it is necessary to identify the modifiable risk factors.

Non-high-density lipoprotein cholesterol (non-HDL-C) is the sum of atherogenic lipoproteins (e.g., very low-density lipoprotein, intermediate-density lipoprotein, and low-density lipoprotein cholesterol (LDL-C)). High levels of non-HDL-C are assumed to carry a high risk of atherosclerotic diseases. Further, high non-HDL-C levels have been consistently associated with an increased risk of coronary heart disease (CHD) and CVD[4-7].

However, the association between non-HDL-C levels and the risk of stroke is less clear. Studies on the risk of total stroke associated with non-HDL-C levels are mainly from Asian countries, and reported mixed findings. Cohort studies from China and Korea have reported that high non-HDL-C levels are associated with an increased risk of total stroke[8-10]. However, a pooled analysis of 10 Japanese cohort studies did not find such an association[11]. Further, a recent study has reported a U-shaped association in Japanese men[12]. With regard to stroke subtypes, a meta-analysis of 68 prospective studies (mainly conducted in Europe and North America) reported that higher non-HDL-C levels were associated with higher risk of ischemic stroke, but not hemorrhagic stroke[4]. However, the pooled analysis of Japanese cohort studies did not find significant associations between non-HDL-C levels and ischemic stroke or hemorrhagic stroke[11]. A Japanese study has reported an increased risk of intracerebral hemorrhage among men with low non-HDL-C levels (<110 mg/dL), suggesting a need for additional research on the association between low non-HDL-C levels and the risk of stroke[12].

Previous studies on the association between non-HDL-C levels and stroke in Japan were based on cohorts established in the 1980s and the 1990s, and the participants were mainly middle-aged and older community dwelling adults[11, 12]. Population characteristics including circulating lipids (e.g., an increasing trend in high-density lipoprotein cholesterol (HDL-C))[13, 14] and morbidity (e.g., a decline in the incidence of stroke)[15, 16] have changed markedly over the past decades. In addition, the productivity losses and economic burden due to CVD in the Japanese working population are substantial, accounting for more than one in five premature deaths in 2015 [17]. Thus, evidence from a working population based on recent measurements of lipids is warranted to prevent premature CVD deaths in workers.

Aim

In this study, we examined the association between non-HDL-C levels and the risk of CVD and its subtypes using data from an ongoing large-scale cohort study of Japanese workers.

Methods

Setting

This cohort study used data from the Japan Epidemiology Collaboration on Occupational Health (J-ECOH) Study, which is an ongoing multi-company study of workers in Japan. To date, annual health checkup data between January 2008 and March 2020 have been collected. In the J-ECOH Study, the CVD registry was established in participating companies in April 2012. Details of the J-ECOH Study and CVD registration have been described elsewhere[18, 19]. The study protocol, including the consent procedure, was approved by the Ethics Committee of the National Center for Global Health and Medicine, Japan.

Participants

The baseline population of the present study is comprised of workers in 8 participating companies which provided data on serum lipids including total cholesterol. A total of 79,039 participants aged ≥ 30 years attended either the 2010 or 2011 health checkup. We excluded participants who reported a history of CVD at baseline (n=835); those with missing data on total cholesterol, HDL-C, body mass index (BMI), and smoking status or those with missing data necessary for diagnosis of diabetes and hypertension at baseline (n=7,307). We further excluded participants who neither attended any subsequent health checkups nor had information on CVD, mortality, and long-term sick leave (n=7,083). Finally, 63,814 participants, comprising 53,550 men

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and 10,264 women, were included

Annual Health Checkup

The body height and weight were measured using a scale while the participant wore light clothes and no shoes. BMI was calculated as weight in kilograms divided by the square of height in meters. Smoking status was assessed by using a self-administered questionnaire. Blood pressure (BP) was measured using an automatic BP monitor, with the participants in a sitting position. Total cholesterol, LDL-C, and HDL-C levels were measured using the enzymatic method. Plasma glucose levels were measured using either the enzymatic or glucose oxidase peroxidative electrode method. HbA1c levels were measured using a latex agglutination immunoassay, high-performance liquid chromatography, or the enzymatic method. All the laboratories involved in the health checkups of the participating companies received satisfactory scores (rank A or a score >95 out of 100) from external quality control agencies.

Exposure

We used the 2011 health checkup data for exposure assessment. When 2011 data were not available, we used the 2010 checkup data. Non-HDL-C levels were calculated by subtracting HDL-C levels from total cholesterol levels. Non-HDL-C levels were classified into 5 groups according to the previous study among Japanese general population[12] and the Japan Atherosclerosis Society guideline[20]: <110, 110-129, 130-149, 150-169, and ≥ 170 mg/dL.

Outcome

Incident CVD events, including fatal and non-fatal myocardial infarction (MI) and stroke, were ascertained from April 2012 to March 2020. For fatal cases, the cause of death was determined based on available information, including data from death certificates (51%), information obtained from the bereaved family or colleagues (21%), and other sources/missing (13%, source not specified; 15%, missing). For non-fatal cases, the diagnosis of each CVD event was based on data from medical certificates written by a treating physician and submitted to the company through the worker (85%), confirmation with the treating physician (2%), self-report (7%), or missing (6%).

Covariates

The covariates included age, sex, smoking status, BMI, hypertension, diabetes, the HDL-C level, and lipid-lowering treatment. Hypertension was defined as systolic BP ≥ 140 mmHg, diastolic BP ≥ 90 mmHg, or receiving medical treatment for hypertension[21]. Diabetes was defined as HbA1c level ≥ 6.5%, fasting plasma glucose level ≥ 126 mg/dL, random plasma glucose level ≥ 200 mg/dL, or receiving medical treatment for diabetes[22].

Statistical Analysis

We calculated age-and sex-adjusted baseline characteristics of the subjects using the analysis of covariance for continuous variables and the marginal structural binomial regression model for categorical variables[23]. Person-time was calculated from March 31, 2012 (one day before the beginning of the follow-up period) to the date of first occurrence of a CVD event; date of censoring, which was determined individually based on the available information, including data on annual health checkups, sick leave, retirement, and death; or the end of follow-up (for most companies, this was March 31, 2020). Cox proportional hazards regression models were performed to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for CVD and its subtypes associated with each non–HDL-C group using the 130-149 mg/dL group as the reference group, considering that a U-shaped association may exist between non-HDL-C levels and the risk of total stroke[12]. We first adjusted for age (years, continuous) and sex in model 1, and then further adjusted for current smoker (yes or no), BMI (kg/m^2, continuous), hypertension (yes or no), and diabetes (yes or no) in model 2. We additionally adjusted for the HDL-C level and lipid-lowering treatment in model 3. Worksite was treated as strata. We tested the linear trend by treating non-HDL-C as a continuous variable and tested the non-linear trend using the fractional polynomials analysis. To further facilitate comparability with previous studies[5, 11], we also calculated the HRs for the development of MI associated with a one standard deviation (SD) unit change in the non-HDL-C level.

Multiple sensitivity analyses were performed by excluding participants who were receiving lipid-lowering treatment, fatal CVD cases occurred during the first three years of follow-up, and CVD cases without death/medical certificates. Fractional polynomial analysis was conducted using STATA version 15.0 (StataCorp, College Station, TX, USA). All other statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA). A two-sided P value of <0.05 was considered statistically significant.

Table 1. Age- and sex-adjusted means or frequencies of risk factors for CVD according to non-HDL-C levels at baseline

	Non-HDL-C (mg/dL)				
	< 110	110-129	130-149	150-169	≥ 170
N	9,839	12,823	14,721	12,530	13,901
Male, %[a]	75.0	80.4	85.9	88.1	90.6
Age (years)[b]	44.0 (0.09)	45.7 (0.08)	46.8 (0.07)	47.6 (0.08)	47.5 (0.07)
Body mass index (kg/m^2)	21.9 (0.03)	22.9 (0.03)	23.6 (0.03)	24.2 (0.03)	24.8 (0.03)
Current smoker, %	35.7	32.7	33.5	34.0	36.0
Total cholesterol (mg/dL)	160.5 (0.18)	181.4 (0.16)	197.7 (0.14)	214.8 (0.16)	245.1 (0.15)
High-density lipoprotein cholesterol (mg/dL)	64.9 (0.14)	61.3 (0.12)	58.3 (0.11)	55.9 (0.12)	53.3 (0.12)
Lipid-lowering treatment, %	5.1	6.4	6.9	7.3	9.7
Systolic blood pressure (mmHg)	119.5 (0.15)	120.9 (0.13)	121.7 (0.12)	122.9 (0.13)	124.4 (0.12)
Diastolic blood pressure (mmHg)	74.8 (0.10)	75.8 (0.09)	76.5 (0.08)	77.5 (0.09)	78.5 (0.09)
Hypertension, %	20.3	21.3	22.4	23.3	24.5
HbA1c (%)	5.50 (0.01)	5.56 (0.01)	5.61 (0.01)	5.66 (0.01)	5.76 (0.01)
Blood glucose (mg/dL)	98.1 (0.20)	99.2 (0.18)	100.2 (0.16)	101.1 (0.18)	103.1 (0.17)
Diabetes, %	7.8	8.1	8.5	8.8	10.0

a, age adjusted; b, sex adjusted

Table 2. Hazard ratio and 95% confidence interval for CVD according to non-HDL-C levels

	No. of events	Person-years	Model 1	Model 2	Model 3
Non-HDL-C (mg/dL)					
< 110	34	61,439	1.37 (0.88-2.15)	1.53 (0.97-2.40)	1.67 (1.06-2.63)
110-< 130	38	79,235	1.04 (0.68-1.60)	1.10 (0.71-1.69)	1.14 (0.74-1.76)
130-< 150	45	89,704	Reference	Reference	Reference
150-< 170	59	76,073	1.45 (0.99-2.14)	1.38 (0.94-2.04)	1.35 (0.91-1.99)
≥ 170	95	84,655	2.06 (1.44-2.93)	1.85 (1.30-2.64)	1.75 (1.23-2.50)
P for linear trend			< 0.001	0.008	0.06
P for non-linear trend			Not applicable	Not applicable	< 0.001

Model 1: adjusted for age and ex
Model 2: adjusted for covariates in model 1, smoking, BMI, hypertension, and diabetes
Model 3: adjusted for covariates in model 2, HDL-C, and lipid-lowering treatment

Results

Table 1 shows the age-and sex-adjusted baseline characteristics of the study participants according to their non-HDL-C levels. Participants with higher non-HDL-C levels were more likely to be men and current smokers, and had higher BMI, BP, HbA1c levels, and blood glucose levels. Accordingly, they had a higher prevalence of hypertension and diabetes.

During 391,106 person-years of follow-up, there were 271 incident CVD cases, including 78 MI cases and 193 stroke cases (102 ischemic stroke cases, 89 hemorrhagic stroke cases, and 2 unknown cases). Table 2 shows that low and high non-HDL-C levels were associated with an increased risk of total CVD, with a multivariable-adjusted HR (95% CI) of 1.67 (1.06-2.63), 1.14 (0.74-1.76), 1.35 (0.91-1.99) and 1.75 (1.23-2.50) in the < 110, 110-129, 150-169, and ≥ 170 mg/dL groups, respectively, compared to the 130-159 mg/d group.

Table 3 and Supplementary Fig. 1 show a U-shaped association between non-HDL-C levels and the risk of total stroke (*P* for nonlinear trend = 0.001). In the analysis of stroke subtypes, the multivariable-adjusted HR for hemorrhagic stroke was 2.61 (1.19–5.72), 2.02 (0.95–4.29), 2.10 (1.01–4.36), and 1.98 (0.96-4.08), while that for ischemic stroke was 1.54 (0.77-3.07), 0.91 (0.46-1.80), 0.73 (0.38-1.41), and 1.50 (0.87-2.56) in the < 110, 110-129, 150-169, and ≥ 170 mg/dL groups, respectively.

The association between non-HDL-C levels and the risk of MI was linear (Table 4). The multivariable-adjusted HR for MI was 0.85 (0.27-2.63), 0.69 (0.26-1.82), 1.58 (0.79-3.15), and 1.90 (1.00-3.61) in the

Table 3. Hazard ratio and 95% confidence interval for stroke

	No. of events	Person-years	Model 1	Model 2	Model 3
Total stroke					
Non-HDL-C (mg/dL)					
<110	30	61,439	1.69 (1.03-2.79)	1.80 (1.09-2.98)	1.92 (1.16-3.20)
110-<130	32	79,235	1.23 (0.75-2.00)	1.27 (0.78-2.08)	1.31 (0.80-2.14)
130-<150	32	89,704	Reference	Reference	Reference
150-<170	38	76,073	1.32 (0.83-2.12)	1.28 (0.80-2.04)	1.25 (0.78-2.04)
≥ 170	61	84,655	1.87 (1.22-2.87)	1.74 (1.13-2.67)	1.67 (1.09-2.58)
P for linear trend			0.13	0.44	0.72
P for non-linear trend			0.001	0.001	0.001
Hemorrhagic stroke					
Non-HDL-C (mg/dL)					
<110	16	61,439	2.53 (1.17-5.48)	2.58 (1.18-5.63)	2.61 (1.19-5.72)
110-<130	18	79,235	1.97 (0.93-4.18)	2.02 (0.95-4.28)	2.02 (0.95-4.29)
130-<150	11	89,704	Reference	Reference	Reference
150-<170	21	76,073	2.15 (1.04-4.47)	2.10 (1.01-4.37)	2.10 (1.01-4.36)
≥ 170	23	84,655	2.07 (1.01-4.26)	1.96 (0.95-4.04)	1.98 (0.96-4.08)
P for linear trend			0.97	0.82	0.85
P for non-linear trend			0.97	0.98	0.98
Ischemic stroke					
Non-HDL-C (mg/dL)					
<110	14	61,439	1.25 (0.63-2.46)	1.37 (0.69-2.73)	1.54 (0.77-3.07)
110-<130	14	79,235	0.83 (0.42-1.63)	0.87 (0.44-1.71)	0.91 (0.46-1.80)
130-<150	21	89,704	Reference	Reference	Reference
150-<170	15	76,073	0.78 (0.40-1.52)	0.75 (0.39-1.46)	0.73 (0.38-1.41)
≥ 170	38	84,655	1.76 (1.03-3.00)	1.61 (0.94-2.75)	1.50 (0.87-2.56)
P for linear trend			0.05	0.22	0.52
P for non-linear trend			0.001	0.001	0.001

Model 1: adjusted for age and sex
Model 2: adjusted for covariates in model 1, smoking, BMI, hypertension, and diabetes
Model 3: adjusted for covariates in model 2, HDL-C, and lipid-lowering treatment

Table 4. Hazard ratio and 95% confidence interval for myocardial infarction

	No. of events	Person-years	Model 1	Model 2	Model 3
Non-HDL-C (mg/dL)					
<110	4	61,439	0.58 (0.19-1.77)	0.71 (0.23-2.19)	0.85 (0.27-2.63)
110-<130	6	79,235	0.58 (0.22-1.52)	0.64 (0.24-1.68)	0.69 (0.26-1.82)
130-<150	13	89,704	Reference	Reference	Reference
150-<170	21	76,073	1.77 (0.89-3.53)	1.64 (0.82-3.28)	1.58 (0.79-3.15)
≥ 170	34	84,655	2.47 (1.30-4.69)	2.10 (1.11-3.99)	1.90 (1.00-3.61)
P for linear trend			<0.001	<0.001	0.004
1-SD increase			1.55 (1.33-1.80)	1.35 (1.16-1.57)	1.26 (1.08-1.48)

Model 1: adjusted for age and sex
Model 2: adjusted for covariates in model 1, smoking, BMI, hypertension, and diabetes
Model 3: adjusted for covariates in model 2, HDL-C, and lipid-lowering treatment

<110, 110-129, 150-169, and ≥ 170 mg/dL groups, respectively (*P* for linear trend=0.004).

The study results were generally supported by the sensitivity analyses. The associations between non-HDL-C levels and risk of CVD and its subtypes did not change after excluding participants who were

receiving lipid-lowering treatment, fatal CVD cases occurred within the first three years, and CVD cases without death/medical certificates **(Supplementary Table 1, 2, 3)**.

Discussion

In this large-scale prospective study of a working population in Japan, we found that low and high non-HDL-C levels were associated with an increased risk of CVD. Regarding the CVD subtypes, we found a U-shaped association between non-HDL-C levels and total stroke. For MI, a positive linear relationship was observed. To our knowledge, this is the first study to investigate the association between non-HDL-C levels and CVD using data from a contemporary cohort in Japan.

Our finding that low and high non-HDL-C levels were associated with an increased risk of CVD was partly in line with a previous study, which showed a U-shaped association between non-fasting triglycerides and CVD mortality in Japanese general population[24]. To our knowledge, no previous study has reported a U-shaped association between non-HDL-C levels and the risk of total stroke, except one recent Japanese study, which suggested a U-shaped association in men[12]. However, several studies conducted in China and Korea reported a positive association between non-HDL-C levels and the risk of total stroke[8-10]. Our study showed that high and very low non-HDL-C levels were associated with a high risk of hemorrhagic stroke, although the nonlinear association was not statistically significant, due in part to the small number of hemorrhagic strokes. A meta-analysis of mainly Western studies and a pooled analysis of 10 Japanese cohort studies have not shown any increase in the risk of hemorrhagic stroke associated with either low or high non-HDL-C levels[4, 11]. The Japan Public Health Center-based Prospective Study and the Rotterdam Study reported an inverse association between non-HDL-C and risk of hemorrhagic stroke[12, 25]. We have no plausible reasons for these inconsistent data. One potential explanation may be that low non-HDL-C levels (e.g., <110 mg/dL) were included in the reference group in prior studies[4, 8-12, 25], which may have limited their ability to detect the risk of hemorrhagic stroke associated with high and low non-HDL-C levels. Our findings on hemorrhagic stroke are partially supported by those of the Women's Health Study, which reported an increased risk of hemorrhagic stroke among those with low levels of LDL-C (<70 mg/dL), a major component of non-HDL-C, and among those with high levels of LDL-C (≥ 160 mg/dL)[26].

The mechanism underlying the observed association between non-HDL-C levels and the risk of hemorrhagic stroke is unclear. The possible explanation for the association between the risk of hemorrhagic stroke and low non-HDL-C levels is that low serum cholesterol levels can cause medial layer smooth muscle cell necrosis in intracerebral arteries and that the impaired endothelium may be more prone to microaneursyms that may subsequently rupture[27]. The association between an increased risk of hemorrhagic stroke and high non-HDL-C levels may due to the atherosclerotic effects of lipoproteins such as LDL-C. Some studies have shown that cerebral microbleeds are associated with arterial and aortic stiffness[28-30]. Given the conflicting evidence, further studies are needed to confirm the association between non-HDL-C levels, especially its low levels, and the risk of hemorrhagic stroke.

We also observed a higher risk of ischemic stroke in people with high (≥ 170 mg/dL) and low (≤ 110 mg/dL) non-HDL-C levels, but this increase in risk was not statistically significant. Our analysis could be underpowered due to small number of ischemic stroke cases included in our study. Studies from both Western and Asian countries, except Japan, have reported a positive association between non-HDL-C and ischemic stroke[4, 9]. In contrast, previous studies in Japan have consistently reported no association[11, 12, 31]. For example, a pooled analysis of 10 Japanese cohort studies did not show an association between non-HDL-C levels and the risk of ischemic stroke[11]. Lacunar infarctions account for a larger proportion (> 50%) of ischemic stroke in the Japanese population than in Western or other Asian populations (10-30%)[32]. Previous studies have shown non-HDL-C levels are associated with atherothrombotic infarction (another subtype of ischemic stroke) but not with lacunar infarction[12, 31]. The difference in the subtype distribution of ischemic stroke may account for the lack of association between non-HDL-C and ischemic stroke in Japanese studies, including our study.

In our study, the risk of MI increased with the increasing non-HDL-C levels, with an adjusted HR (95% CI) of 1.26 (1.08–1.48) for a one SD unit change in the non-HDL-C level. Concordant with our findings, two meta-analyses that were mainly based on studies on Western populations showed that non-HDL-C was positively associated with CHD[4, 5], with one reporting an adjusted HR of 1.50 (1.39-1.61) for a one SD unit change in the non-HDL-C level[4]. Similarly, the pooled analysis of 10 Japanese cohort studies showed that the incidence rate ratio of acute MI was 1.62 (1.35-1.95) for a one SD unit change in the non-HDL-C level[11]. Our study was

conducted in a working population, including young- and middle- aged people, and used the most recent data on lipids and CVD (study period 2011-2019). The findings from our study and previous studies[4, 5, 11] provide strong evidence that non-HDL-C levels can be used to identify individuals at a high risk of MI.

Strengths and Limitations

The strength of our study is that we included young-and middle-aged people and used data from a large working population. However, our study has some limitations. First, the lack of data on the subtypes of hemorrhagic stroke and ischemic stroke did not allow us to analyze their associations with non-HDL-C levels. Second, the CVD registry data are mainly based on data from medical certificates written by a physician and submitted to the company by the worker. This registry primarily covers relatively severe cases because the submission of a medical certificate is required when taking long-term (≥ 2 weeks) sick leave. On the other hand, patients with milder forms of CVD were not well covered by this registration system because they were not required to submit a medical certificate if they took sick leave for <2 weeks. We also noticed that about 20% did not provide medical certificates (self-reported or missing data). However, the results did not change obviously after excluding cases without death/medical certificates. Third, due to the lack of data on socioeconomic status, family history of CVD, and lifestyle factors other than smoking status (e.g., alcohol consumption, diet, and physical activity), we were unable to control for potential effects of these factors. Fourth, our study is a Japanese occupational cohort. Therefore, our findings may not be generalizable to the general population or other racial/ethnic groups.

Conclusion

Using data from a recent cohort study including Japanese workers, our study showed that high non-HDL-C levels were associated with a high risk of MI. Moreover, high and low non-HDL-C levels were associated with a high risk of total stroke, especially hemorrhagic stroke. Further studies are needed to confirm the present finding of a U-shaped association between non-HDL-C levels and the risk of total stroke and its subtypes.

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Conflict of Interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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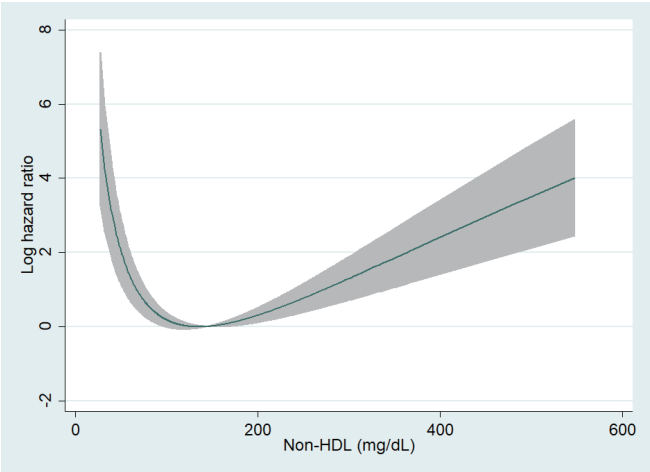

Supplementary Fig. 1. Non-linear relationship between non-high-density lipoprotein cholesterol and total stroke

Supplementary Table 1. Hazard ratio and 95% confidence interval for CVD according to non-HDL-C levels (excluded people who were taking lipid-lowering medications)

	No. of events	Person-years	Model 1	Model 2	Model 3
Total CVD					
Non-HDL-C (mg/dL)					
<110	32	59,263	1.51 (0.94-2.42)	1.70 (1.06-2.74)	1.86 (1.15-3.01)
110-<130	36	75,154	1.16 (0.74-1.83)	1.22 (0.78-1.93)	1.27 (0.80-2.01)
130-<150	38	83820	Reference	Reference	Reference
150-<170	52	70,479	1.52 (1.00-2.31)	1.44 (0.95-2.19)	1.40 (0.92-2.13)
≥ 170	84	75,918	2.20 (1.50-3.23)	1.97 (1.34-2.90)	1.86 (1.26-2.74)
Myocardial Infarction					
Non-HDL-C (mg/dL)					
<110	3	59,263	0.55 (0.15-2.00)	0.68 (0.19-2.49)	0.83 (0.23-3.05)
110-<130	5	75,154	0.62 (0.21-1.82)	0.67 (0.23-1.95)	0.72 (0.25-2.12)
130-<150	10	83820	Reference	Reference	Reference
150-<170	17	70,479	1.87 (0.85-4.08)	1.69 (0.77-3.70)	1.61 (0.74-3.52)
≥ 170	31	75,918	2.98 (1.46-6.08)	2.46 (1.20-5.04)	2.22 (1.08-4.56)
1-SD increase			1.66 (1.39-1.97)	1.48 (1.23-1.79)	1.38 (1.13-1.67)
Hemorrhagic stroke					
Non-HDL-C (mg/dL)					
<110	16	59,263	2.53 (1.17-5.47)	2.64 (1.21-5.77)	2.64 (1.20-5.79)
110-<130	18	75,154	1.97 (0.93-4.17)	2.03 (0.96-4.31)	2.03 (0.96-4.31)
130-<150	11	83820	Reference	Reference	Reference
150-<170	19	70,479	1.95 (0.93-4.10)	1.90 (0.90-3.99)	1.90 (0.90-3.99)
≥ 170	20	75,918	1.85 (0.89-3.86)	1.74 (0.83-3.64)	1.74 (0.83-3.65)
Ischemic stroke					
Non-HDL-C (mg/dL)					
<110	13	59,263	1.42 (0.69-2.93)	1.57 (0.75-3.26)	1.79 (0.85-3.74)
110-<130	13	75,154	0.95 (0.46-1.95)	0.99 (0.48-2.04)	1.05 (0.51-2.15)
130-<150	17	83820	Reference	Reference	Reference
150-<170	14	70,479	0.91 (0.45-1.84)	0.86 (0.43-1.75)	0.83 (0.41-1.69)
≥ 170	33	75,918	1.92 (1.07-3.45)	1.76 (0.98-3.17)	1.62 (0.90-2.93)

Model 1: adjusted for age and sex
Model 2: further adjusted for smoking, BMI, hypertension, and diabetes
Model 3: further adjusted for HDL-C

Supplementary Table 2. Hazard ratio and 95% confidence interval for CVD according to non-HDL-C levels (excluded fatal CVD cases in the first 3 years)

	No. of events	Person-years	Model 1	Model 2	Model 3
Total CVD					
Non-HDL-C (mg/dL)					
<110	29	61,433	1.27 (0.79-2.05)	1.44 (0.89-2.33)	1.56 (0.96-2.54)
110-<130	34	79,230	1.02 (0.65-1.61)	1.08 (0.69-1.71)	1.12 (0.71-1.77)
130-<150	41	89,698	Reference	Reference	Reference
150-<170	55	70,670	1.49 (0.99-2.23)	1.41 (0.94-2.11)	1.38 (0.92-2.06)
≥ 170	85	84,637	2.02 (1.39-2.93)	1.81 (1.24-2.63)	1.72 (1.18-2.51)
Myocardial Infarction					
Non-HDL-C (mg/dL)					
<110	2	61,433	0.37 (0.08-1.68)	0.46 (0.10-2.10)	0.54 (0.12-2.49)
110-<130	4	79,230	0.50 (0.16-1.59)	0.55 (0.17-1.77)	0.60 (0.19-1.91)
130-<150	10	89,698	Reference	Reference	Reference
150-<170	20	70,670	2.20 (1.03-4.69)	2.01 (0.94-4.31)	1.94 (0.91-4.15)
≥ 170	29	84,637	2.73 (1.33-5.60)	2.30 (1.16-4.73)	2.09 (1.02-4.31)
1-SD increase			1.60 (1.38-1.86)	1.39 (1.20-1.61)	1.31 (1.12-1.53)
Hemorrhagic stroke					
Non-HDL-C (mg/dL)					
<110	13	61,433	2.24 (0.98-5.14)	2.39 (1.03-5.52)	2.37 (1.02-5.51)
110-<130	16	79,230	1.92 (0.87-4.24)	1.99 (0.90-4.40)	1.98 (0.90-4.38)
130-<150	10	89,698	Reference	Reference	Reference
150-<170	18	70,670	2.03 (0.94-4.41)	1.96 (0.91-4.25)	1.97 (0.91-4.28)
≥ 170	18	84,637	1.79 (0.83-3.89)	1.66 (0.77-3.62)	1.71 (0.78-3.73)
Ischemic stroke					
Non-HDL-C (mg/dL)					
<110	14	61,433	1.25 (0.63-2.46)	1.37 (0.69-2.72)	1.54 (0.77-3.07)
110-<130	14	79,230	0.83 (0.42-1.63)	0.87 (0.44-1.71)	0.91 (0.46-1.80)
130-<150	21	89,698	Reference	Reference	Reference
150-<170	15	70,670	0.78 (0.40-1.52)	0.75 (0.39-1.46)	0.73 (0.38-1.41)
≥ 170	38	84,637	1.76 (1.03-3.00)	1.61 (0.94-2.75)	1.50 (0.87-2.56)

Model 1: adjusted for age and sex
Model 2: further adjusted for smoking, BMI, hypertension, and diabetes
Model 3: further adjusted for HDL-C

Supplementary Table 3. Hazard ratio and 95% confidence interval for CVD according to non-HDL-C levels (excluded CVD cases without death/medical certificate)

	No. of events	Person-years	Model 1	Model 2	Model 3
Total CVD					
Non-HDL-C (mg/dL)					
<110	26	61,428	1.29 (0.78-2.14)	1.46 (0.87-2.43)	1.55 (0.93-2.59)
110-<130	34	79,225	1.16 (0.72-1.85)	1.23 (0.77-1.97)	1.26 (0.79-2.02)
130-<150	36	89,685	Reference	Reference	Reference
150-<170	47	76,044	1.45 (0.94-2.24)	1.38 (0.89-2.13)	1.35 (0.88-2.09)
≥ 170	79	84,608	2.15 (1.45-3.19)	1.92 (1.30-2.86)	1.86 (1.25-2.76)
Myocardial Infarction					
Non-HDL-C (mg/dL)					
<110	3	61,428	0.52 (0.14-1.84)	0.63 (0.17-2.27)	0.73 (0.20-2.66)
110-<130	4	79,225	0.46 (0.15-1.43)	0.50 (0.16-1.56)	0.54 (0.17-1.69)
130-<150	11	89,685	Reference	Reference	Reference
150-<170	17	76,044	1.69 (0.79-3.61)	1.57 (0.73-3.35)	1.52 (0.71-3.24)
≥ 170	25	84,608	2.18 (1.07-4.44)	1.86 (0.91-3.79)	1.70 (0.83-3.47)
1-SD increase			1.58(1.33-1.88)	1.38 (1.16-1.63)	1.29 (1.08-1.55)
Hemorrhagic stroke					
Non-HDL-C (mg/dL)					
<110	12	61,428	2.19 (0.92-5.24)	2.35 (1.00-5.67)	2.29 (0.95-5.55)
110-<130	17	79,225	2.23 (0.99-5.00)	2.32 (1.03-5.22)	2.29 (1.02-5.16)
130-<150	9	89,685	Reference	Reference	Reference
150-<170	15	76,044	1.90 (0.83-4.35)	1.83 (0.80-4.19)	1.85 (0.81-4.23)
≥ 170	19	84,608	2.13 (0.96-4.70)	1.95 (0.88-4.33)	1.99 (0.89-4.43)
Ischemic stroke					
Non-HDL-C (mg/dL)					
<110	11	61,428	1.28 (0.59-2.76)	1.42 (0.65-3.08)	1.54 (0.71-3.36)
110-<130	13	79,225	1.01 (0.49-2.10)	1.06 (0.51-2.22)	1.10 (0.53-2.30)
130-<150	16	89,685	Reference	Reference	Reference
150-<170	14	76,044	0.96 (0.47-1.97)	0.92 (0.45-1.89)	0.90 (0.44-1.85)
≥ 170	35	84,608	2.12 (1.17-3.83)	1.94 (1.07-3.52)	1.84 (1.01-3.34)

Model 1: adjusted for age and sex
Model 2: further adjusted for smoking, BMI, hypertension, and diabetes
Model 3: further adjusted for HDL-C