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Repeated measures of extremely high levels of high-density lipoprotein cholesterol and subsequent all-cause mortality and cardiovascular events: A longitudinal study

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HIGHLIGHTS

- Extremely high levels of HDL cholesterol had been cautioned as risk factor for all-cause mortality and cardiovascular disease.
- Previous studies did not take into account changes of HDL cholesterol and other risk factors over time.
- An extremely high HDL had lower risks of outcomes compared to low HDL, but higher risks compared to very high HDL.

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ABSTRACT

Background and aims: Extremely high level high-density lipoprotein (HDL) cholesterol had been cautioned as risk factor for all-cause mortality and cardiovascular disease. However, both the physician and the patient may underestimate the risk due to the emphasis on “good cholesterol”, resulting in passive treatment or adoption of a less healthy lifestyle. The aim of this study is to re-evaluate the association with longitudinal data to account for fluctuations in HDL cholesterol and covariates.

Methods: We conducted a retrospective longitudinal study at a large teaching hospital in Tokyo, Japan, from 2005 to 2016. We included all adults who participated in health check-ups. Outcomes were all-cause mortality and cardiovascular events. HDL cholesterol was repeatedly measured at each visit and categorized into five groups. The time-varying Cox model was applied to longitudinal analyses.

Results: We included a total of 83,100 participants; the mean age was 45.5 (standard deviation:12.4) years; 41,013 (49.4%) were male, and 4475 participants belonged to the extremely high level HDL cholesterol group (> 90 mg/dl). During a median follow-up of 1746 (interquartile range:740–3112.5) days, 382 (0.5%) participants died, and 2023 (2.4%) experienced cardiovascular events. Although the extremely high level HDL cholesterol group had significantly lower hazard ratios (HRs) for all-cause mortality (HR:0.49, 95%confidence interval(CI):0.26–0.90) and cardiovascular events (HR:0.71, 95%CI:0.54–0.94) compared to the low group (< 40 mg/dl), HRs were higher than in the very high level HDL cholesterol group.

Conclusions: Our study demonstrated that extremely high level HDL cholesterol has significantly lower risks of all-cause mortality and cardiovascular events compared to low level, but higher risks compared to very high level, as previously reported.

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1. Introduction

Although the impact of a high level of high-density lipoprotein (HDL) cholesterol has been well studied, and a conclusion has been reached regarding prediction of future cardiovascular disease [1–4], but may not its preventive effects on cardiovascular diseases, as shown in some randomized controlled trials and genetic studies [5–8], some have cautioned that an extremely high level of HDL cholesterol (usually defined as > 90 or > 80 mg/dl) is paradoxically associated with an increased risk of cardiovascular disease [7,9,10]. However, evidence is mixed because others have suggested that an extremely high level of HDL cholesterol does not increase the risk of cardiovascular disease but rather gives a risk similar to that associated with a normal level of HDL cholesterol [11].

Studies that supported the hypothesis of an increased risk for all-cause mortality and cardiovascular disease suggested that this was potentially due to genetic variation [12]. A mutation in the cholesteryl ester transfer protein gene (*CETP*) [13] and single nucleotide polymorphisms (SNPs) in the hepatic lipase promoter [14] and in the ATP-binding-cassette transporter A1 *(ABCA1)* [15] may play a role in the association because they both cause a high incidence of cardiovascular disease and an increase in HDL cholesterol. Studies that opposed the hypothesis of an increased risk have pointed to the small number of patients with extremely high levels of HDL cholesterol and suggested that there was an insufficient number of covariates for adjustment in multivariate analysis [11].

Additional concerns about changes in risk factors during follow-up periods have been raised. We thought that it was important to consider fluctuations in HDL cholesterol during the follow-up period, and changes over time in social histories related to cardiovascular disease, such as alcohol consumption, smoking and exercise, and medical histories, such as hypertension and diabetes, to evaluate more a precise association between HDL cholesterol and outcomes. Moreover, medication for dyslipidemia during the follow-up period, which is usually indicated for the treatment of high levels of low-density lipoprotein (LDL) cholesterol and not for low levels of HDL cholesterol, could be associated with the development of future cardiovascular disease. Because both the physician and the patient may underestimate the risk of cardiovascular disease linked to high levels of HDL cholesterol due to the emphasis on “high levels of good cholesterol” [16], the physician may provide passive treatment, such as only physical or dietary therapies, and the patient may prefer a less healthy lifestyle, even though they may have risk factors for developing cardiovascular disease other than their level of HDL cholesterol. All these conditions during follow-up should be considered to estimate the actual association between an extremely high level of HDL cholesterol and cardiovascular disease.

The aim of this study is to re-evaluate this association with longitudinal data to account for fluctuations in HDL cholesterol and changes in treatment status and lifestyle.

2. Materials and methods

We conducted a retrospective longitudinal study at St. Luke's International Hospital, a large teaching hospital in Tokyo, Japan, from 2005 to 2016. We included all adults who participated in voluntary health check-ups at the center for preventive medicine in the hospital. We excluded participants who had a prior history of cardiovascular disease before their first visit. Our primary outcomes were all-cause mortality and cardiovascular events. Secondary outcomes were acute coronary syndrome and stroke. All participants' information both at baseline and follow-up visits were obtained, including HDL cholesterol, categorized into five groups. Outcomes among the HDL cholesterol groups were compared by longitudinal analyses, and all variables were treated as time-dependent variables.

The Ethics Committee Institutional Review Board at St Luke's International Hospital approved this study (18-R011).

2.1. Outcomes

Our primary outcomes were all-cause mortality and cardiovascular events. Mortality information was extracted from electronic medical records at the hospital. We defined cardiovascular events as composite events of acute coronary syndrome and stroke. Information on cardiovascular events, either fatal or nonfatal, was obtained from either electronic medical records or participants' self-reports. Our secondary outcomes were the development of acute coronary syndrome and stroke. If patients developed outcomes multiple times during the follow-up period, we only used the participant's data prior to and at the first outcome.

2.2. HDL cholesterol measures

HDL cholesterol was measured as a part of the health check-ups at baseline and at each follow-up visit. Each HDL cholesterol measurement at baseline and follow-up visit was categorized into five groups based on previous studies [9–11,17]; low (< 40 mg/dl (1.03 mmol/L)), normal (40–59 mg/dl (1.03–1.53 mmol/L)), high (60–79 mg/dl (1.53–2.04 mmol/L)), very high (80–89 mg/dl (2.04–2.30 mmol/L)), and extremely high (≥90 mg/dl (2.30 mmol/L)). For each participant, each HDL cholesterol category at follow-up visit was treated as a time-dependent variable to evaluate the changes in HDL cholesterol over time. All HDL cholesterol levels were assessed by a direct measurement method [18]. Because the health check-ups were completely voluntary-based, number of re-visits and its timing depended on participants. However, approximately 70% of participants underwent the health check-ups twice or more, at one-year intervals.

2.3. Covariates

We obtained participants' information about demographics, social history, medical history, physical examinations and laboratory measures as part of the health check-ups at baseline and follow-up visits. Participants' demographic information included age and sex. Social history included alcohol consumption (abstainer, occasional drinker, or regular drinker), smoking status (never smoker, former smoker, or current smoker), and exercise habits (almost none, 1–2 times a week, 3–5 times a week, or almost every day) and was based on participants' self-report. We collected information that focused on medical histories related to cardiovascular disease, such as hypertension, diabetes and dyslipidemia. In terms of medical history of dyslipidemia, information about medication use was also obtained. Systolic/diastolic blood pressure, weight and height were measured by trained staff. Body mass index (BMI) was calculated and classified into three groups: underweight (< 18.5 kg/m^2), normal (18.5–24.9 kg/m^2), and obese/overweight (25.0 kg/m^2 or more) based on the World Health Organization criteria for the Asian population [19]. Laboratory measures related to cardiovascular diseases were also obtained. Because fasting blood sugar depends heavily on fasting status, all participants were asked not to eat anything after 8:00 p.m. prior the check-up day. LDL cholesterol was also assessed by a direct measurement method [20]. All the above information was obtained at each follow-up visit and was treated as time-dependent variables to account for the change in condition, life-style and treatment status.

2.4. Statistical methods

For the baseline comparison of characteristics, we compared participants' demographic, social history, medical history, physical examinations and laboratory measures by the HDL cholesterol category using analysis of variance (ANOVA) and Chi-squared test. Then, we performed longitudinal analyses with follow-up data for primary and

secondary outcomes by using time-varying Cox proportional hazard model. Adjusted hazard ratios (HRs) were calculated, considering low level of HDL cholesterol group low (< 40 mg/dl (1.03 mmol/L)) as the reference group. We applied different models with different covariates as adjustments to confirm the findings; model 1 included the HDL cholesterol category as the interest variable with participant's age, sex and time variable as adjustments; model 2 adjusted for the variables in model 1 plus social histories and body mass index; model 3 adjusted for the variables in model 2 plus a history of hypertension and diabetes; model 4 adjusted for all variables in model 3 plus LDL cholesterol, triglycerides, and medications for dyslipidemia. By using the generalized estimating equation (GEE) from the binominal family with logit link function and unstructured working correlation, we conducted sensitivity analyses in a similar manner to confirm the results. GEE can be used to estimate the parameters for repeated measurements [21,22]. It can consider correlation within subjects' data. In this study, we can deal with interest variable (HDL cholesterol category) and all covariates as time-dependent variables by using GEE. To visualize risks by HDL cholesterol category, we draw curves of adjusted cumulative hazards for cardiovascular events stratified by HDL cholesterol, after adjustment with model 4. We also performed Cox proportional hazard model with baseline covariates, without time-dependent covariates, which was mainly used previous studies to help readers compare findings in this study to those in previous studies. Moreover, we analysed the data with a similar approach, but stratified by another HDL cholesterol category divided into quintile. As a subanalysis, we performed a time-varying Cox proportional hazard model in a similar manner, stratifying by sex. We performed sensitivity analyses with different cutoff values of HDL cholesterol categories in females (each cutoff value was 10 mg/dl higher: low (< 50 mg/dl), normal (50–69 mg/dl), high (70–89 mg/dl), very high (90–99 mg/dl), and extremely high (≥100 mg/dl)) based on a report from experts stating that HDL cholesterol among females is approximately 10 mg/dl higher than that among males [23]. Furthermore, to investigate whether the association between HDL cholesterol and outcomes was U-shape as previously reported or linear, we compared the model dealing HDL cholesterol with a categorical variable to that with a continuous variable by using Akaike's information criteria (AIC) and Bayesian's information criteria (BIC). We also conducted restrict cubic spline analyses with knots at HDL cholesterol levels of 40, 60, 80 and 90 mg/dl as same to defined cut-off values [24].

All analyses were performed in 2019 using STATA 14 (STATA Corp., College Station, TX, USA).

3. Results

A total of 126,373 participants underwent health check-ups at least once during the study period. Among them, 3847 were excluded due to prior history of outcomes at baseline. Among the remaining 122,526 participants, 83,100 (67.8%) had follow-up health check-ups. Missing covariates were found in 7 participants. The mean age was 45.5 (standard deviation 12.4) years, and 41,013 (49.4%) were male. Table 1 shows the participants' characteristics by HDL cholesterol category; 4475 participants belonged to the extremely high level HDL cholesterol group at baseline. More participants in the higher level HDL cholesterol groups tended to be female and were more underweight, and fewer were obese/overweight than participants in the lower level HDL cholesterol groups. In terms of social histories, the higher level HDL cholesterol groups tended to drink alcohol more regularly, engage in more exercise, and smoke less than lower level HDL cholesterol groups. With regard to medical histories, lower level HDL cholesterol groups tended to have less hypertension, diabetes and dyslipidemia. Among dyslipidemic participants, those in the extremely high level HDL cholesterol group had a lower rate of medication use for dyslipidemia (76.9%) compared to those in the very high (78.3%) and high HDL cholesterol groups (82.3%). Participants in the higher level HDL cholesterol groups tended to have a lower systolic/diastolic blood pressure, diabetes-related measures, LDL cholesterol and triglycerides but had higher levels of total cholesterol than participants in the lower level HDL cholesterol groups.

During a median follow-up of 1746 (interquartile range (IQR): 740–3112.5) days and a median follow-up of 5 visits (IQR: 3–8), 382 participants (0.5%) died, and 2023 (2.4%) experienced cardiovascular events, of whom 1237 (1.5%) had acute coronary syndrome, and 786 (1.0%) had stroke. The number of fatal cardiovascular events was 20 (0.02%). Table 2 shows adjusted HRs for primary and secondary outcomes according to the HDL cholesterol category with different models. Although the extremely high level HDL cholesterol group had significantly lower HRs in some outcomes (all-cause mortality, HR 0.49, 95% confidence interval (CI): 0.26–0.90; cardiovascular events, HR 0.71, 95%CI: 0.54–0.94; acute coronary syndrome, HR 0.60, 95%CI: 0.42–0.86; stroke, HR 0.90, 95%CI: 0.58–1.41 in model 4) compared to the low level HDL group through models, the extremely high level HDL cholesterol group had higher HRs for all outcomes compared to the very high level HDL cholesterol group. Dose-dependent reduction in HRs for all outcomes in the HDL cholesterol group were observed, except only for the extremely high level HDL cholesterol group. The normal level HDL cholesterol group had significantly lower HRs for cardiovascular events (HR 0.82, 95%CI: 0.69–0.99) including acute coronary syndrome (HR 0.78, 95%CI: 0.63–0.98), but not statistically significant HR for all-cause mortality (HR 0.70, 95%CI: 0.47–1.06) and stroke (HR 0.89, 95%CI: 0.64–1.23) in model 4 compared to the low level HDL group. High and very high level HDL groups had significantly lower HRs for mortality, cardiovascular events and acute coronary syndrome, but not statistically significant HRs for stroke compared to the low level HDL cholesterol group. When we used GEE to estimate hazard ratios of outcomes by the HDL cholesterol category, the findings were similar to those observed using time-varying Cox proportional hazard model (Supplementary Data 1). Fig. 1 shows curves of adjusted cumulative hazards for cardiovascular events stratified by HDL cholesterol category. The higher HDL cholesterol group tended to have lower adjusted cumulative hazards in a dose-dependent manner, expect for the extremely high level HDL cholesterol group. In the analyses using the Cox proportional hazard model with baseline covariates, without time-dependent covariates, the findings observed in the main analyses were still significant in terms of cardiovascular events, including acute coronary syndrome, whereas all HRs for all-cause mortality and stroke by HDL cholesterol groups were not significant through models (Supplementary Data 2). When we divided HDL cholesterol measurements into quintile (1st quintile, < 51 mg/dl; 2nd quintile, 51–58 mg/dl; 3rd quintile, 59–66 mg/dl; 4th quintile, 67–76 mg/dl; 5th quintile, ≥ 77 mg/dl), the HRs for all outcomes decreased dose-dependently as HDL cholesterol category stepped up. In contrast to the results from HDL cholesterol groups divided by defined cut-off values, the fifth quintile group had lower or similar HRs for outcomes compared to the fourth quintile group (Supplementary Data 3).

When we compared HDL cholesterol by sex, females had higher HDL cholesterol levels compared to males at baseline (mean HDL cholesterol (SD), 69.6 (14.5) mg/dl for females, 55.5 (13.1) mg/dl for males, $p < 0.01$). The results of the subanalysis stratified by sex are shown in Table 3. The findings of the subanalysis were roughly similar to the main results but were more pronounced in the all-cause mortality outcome among females and in cardiovascular events and acute coronary syndrome outcomes among males. These findings were the same when we used GEE instead of the time-varying Cox proportional hazard model (Supplementary Data 4).

Supplementary Data 5 and 6 show the results of the sensitivity analyses with different cutoff values of HDL cholesterol among females. Most adjusted HRs that had statistical significance in the main/sub analysis were no longer statistically significant in sensitivity analyses.

In terms of comparing the goodness of fit, AICs and BICs of the model dealing with HLD cholesterol with a categorical variable, and that with a continuous variable were very close through outcomes

Table 1
Baseline patient characteristics by high-density lipoprotein cholesterol category.

	High-density lipoprotein cholesterol category				
	Low (< 40 mg/dl)(n = 3,750, 4.5%)	Normal (40–59 mg/dl)(n = 34,102, 41.0%)	High (60–79 mg/dl)(n = 33,595, 40.4%)	Very high (80–89 mg/dl)(n = 7,171, n = 8.6%)	Extremely high (≥90 mg/dl)(n = 4,475, 5.4%)
Demographics					
Age, years (SD)	46.5 (12.1)	45.7 (12.4)	44.9 (12.5)	45.4 (12.1)	47.2 (12.1)
Male, n (%)	3426 (91.4)	23,994 (70.4)	11,615 (34.6)	1310 (18.3)	666 (14.9)
Body mass index, n (%)					
Underweight (< 18.5 kg/m^2)	23 (0.6)	1282 (3.8)	4256 (12.7)	1449 (20.2)	1176 (26.3)
Normal (18.5–24.9 kg/m^2)	1814 (48.4)	22,793 (66.8)	25,813 (76.8)	5415 (75.5)	3153 (70.5)
Obesity/overweight (25.0 kg/m^2 <)	1913 (51.0)	10,027 (29.4)	3526 (10.5)	306 (4.3)	145 (3.2)
Outcomes					
Death, n (%)	28 (0.8)	157 (0.5)	145 (0.4)	28 (0.4)	24 (0.5)
Cardiovascular event, n (%)	159 (4.2)	956 (2.8)	681 (2.0)	129 (1.8)	98 (2.2)
Acute coronary syndrome, n (%)	118 (3.2)	609 (1.8)	390 (1.2)	64 (0.9)	56 (1.3)
Stroke, n (%)	41 (1.1)	350 (1.0)	293 (0.9)	66 (0.9)	42 (0.9)
Duration of follow-up, n (%)					
More than 1000 days	2426 (64.7)	23,015 (67.5)	23,086 (68.7)	5057 (70.5)	3147 (70.3)
More than 2000 days	1548 (41.3)	14,680 (43.1)	15,106 (45.0)	3421 (47.7)	2115 (47.3)
More than 3000 days	874 (23.3)	8594 (25.2)	8923 (26.6)	2133 (29.7)	1323 (29.6)
Social history					
Alcohol, n (%)					
Abstainer	1570 (41.9)	12,804 (37.6)	14,007 (41.7)	2881 (40.2)	1602 (35.8)
Occasional	786 (21.0)	6114 (17.9)	5660 (16.9)	1244 (17.4)	663 (14.8)
Regular	1394 (37.2)	15,184 (44.5)	13,928 (41.5)	3046 (42.5)	2210 (49.4)
Smoking, n (%)					
Never	1389 (37.0)	17,669 (51.8)	23,160 (68.9)	5387 (75.1)	3340 (74.6)
Former	969 (25.8)	8753 (25.7)	6481 (19.3)	1215 (16.9)	761 (17.0)
Current	1392 (37.1)	7680 (22.5)	3954 (11.8)	569 (7.9)	374 (8.4)
Exercise, n (%)					
Almost none	1637 (43.7)	13,221 (38.8)	12,873 (38.3)	2587 (36.1)	1478 (33.0)
1–2 times per week	1351 (36.0)	12,964 (38.0)	12,359 (36.8)	2563 (35.7)	1587 (35.3)
3–5 times per week	466 (12.4)	4910 (14.4)	5158 (15.4)	1288 (18.0)	852 (19.0)
Almost all days	296 (7.9)	3007 (8.8)	3205 (9.5)	733 (10.2)	558 (12.5)
Medical history					
Hypertension, n (%)	463 (12.4)	3135 (9.2)	2032 (6.1)	313 (4.4)	219 (4.9)
Diabetes, n (%)	152 (4.1)	893 (2.6)	429 (1.3)	54 (0.8)	37 (0.8)
Dyslipidemia, n (%)	199 (5.3)	1585 (4.7)	1235 (3.7)	230 (3.2)	156 (3.5)
Treatment for dyslipidemia	131 (65.8)	1235 (77.9)	1017 (82.3)	180 (78.3)	120 (76.9)
Physical examination and laboratory measures					
Systolic blood pressure, mmHg (SD)	123.2 (16.2)	120.3 (16.7)	115.2 (16.7)	113.7 (16.6)	114.3 (16.6)
Diastolic blood pressure, mmHg (SD)	76.1 (11.0)	74.1 (11.3)	70.6 (11.2)	69.9 (11.1)	70.5 (11.0)
Fasting blood glucose, mg/dl (SD)	105.7 (22.4)	101.5 (16.7)	96.8 (12.0)	95.3 (11.0)	95.3 (10.8)
Hemoglobin A1c, % (SD)	5.7 (0.9)	5.6 (0.6)	5.5 (0.4)	5.4 (0.4)	5.4 (0.4)
Total cholesterol, mg/dl (SD)	191.3 (36.4)	197.3 (35.2)	198.7 (32.8)	208.7 (30.5)	222.2 (31.7)
Low-density lipoprotein cholesterol, mg/dl (SD)	117.4 (30.5)	122.5 (30.2)	111.7 (29.6)	105.5 (28.1)	102.2 (29.0)
Triglyceride, mg/dl (SD)	207.5 (168.5)	119.9 (78.9)	74.4 (40.7)	62.0 (29.3)	59.0 (27.6)

All variables had a p value less than 0.01.

Table 2
Adjusted hazard ratios for outcomes by HDL cholesterol category with time-varying Cox proportional hazard model.

	Adjusted hazard ratio (95% confidence interval)			
	Model 1	Model 2	Model 3	Model 4
All-cause mortality				
Low HDL (< 40 mg/dl)	Reference			
Normal HDL (40–59 mg/dl)	**0.62(0.42–0.91)**	**0.66(0.44–0.97)**	**0.67(0.45–0.99)**	0.70(0.47–1.06)
High HDL (60–79 mg/dl)	**0.48(0.32–0.72)**	**0.50(0.33–0.75)**	**0.51(0.34–0.78)**	**0.52(0.33–0.81)**
Very high HDL (80–89 mg/dl)	**0.45(0.26–0.77)**	**0.42(0.24–0.73)**	**0.44(0.25–0.77)**	**0.43(0.24–0.76)**
Extremely high HDL (≥90 mg/dl)	**0.55(0.31–0.96)**	**0.50(0.28–0.90)**	**0.52(0.29–0.94)**	**0.49(0.26–0.90)**
Cardiovascular events				
Low HDL (< 40 mg/dl)	Reference			
Normal HDL (40–59 mg/dl)	**0.77(0.65–0.92)**	**0.82(0.69–0.98)**	0.84(0.71–1.01)	**0.82(0.69–0.99)**
High HDL (60–79 mg/dl)	**0.61 (0.51–0.73)**	**0.69 (0.57–0.83)**	**0.72 (0.60–0.87)**	**0.67 (0.55–0.83)**
Very high HDL (80–89 mg/dl)	**0.51 (0.40–0.65)**	**0.59 (0.46–0.76)**	**0.63 (0.49–0.82)**	**0.58 (0.44–0.75)**
Extremely high HDL (≥90 mg/dl)	**0.62 (0.48–0.80)**	**0.76 (0.58–0.99)**	0.80 (0.61–1.05)	**0.71 (0.54–0.94)**
Acute coronary syndrome				
Low HDL (< 40 mg/dl)	Reference			
Normal HDL (40–59 mg/dl)	**0.71 (0.58–0.88)**	**0.76 (0.62–0.95)**	**0.78 (0.63–0.97)**	**0.78 (0.63–0.98)**
High HDL (60–79 mg/dl)	**0.52 (0.41–0.65)**	**0.59 (0.47–0.75)**	**0.62 (0.49–0.78)**	**0.59 (0.46–0.76)**
Very high HDL (80–89 mg/dl)	**0.44 (0.32–0.60)**	**0.53 (0.39–0.74)**	**0.57 (0.41–0.79)**	**0.53 (0.38–0.74)**
Extremely high HDL (≥90 mg/dl)	**0.50 (0.36–0.70)**	**0.63 (0.49–0.90)**	**0.67 (0.47–0.95)**	**0.60 (0.42–0.86)**
Stroke				
Low HDL (< 40 mg/dl)	Reference			
Normal HDL (40–59 mg/dl)	0.88 (0.64–1.20)	0.92 (0.67–1.26)	0.94 (0.69–1.29)	0.89 (0.64–1.23)
High HDL (60–79 mg/dl)	0.79 (0.57–1.09)	0.86 (0.62–1.20)	0.91 (0.66–1.26)	0.82 (0.58–1.16)
Very high HDL (80–89 mg/dl)	**0.64 (0.43–0.96)**	0.71 (0.47–1.08)	0.76 (0.50–1.15)	0.67 (0.44–1.04)
Extremely high HDL (≥90 mg/dl)	0.85 (0.56–1.28)	0.97 (0.63–1.49)	1.03 (0.67–1.58)	0.90 (0.58–1.41)

Model 1 included the participant's age and sex as well as time variable as adjustments. Model 2 adjusted for variables in model 1 plus social histories and body mass index. Model 3 adjusted for variables in model 2 plus history of hypertension and diabetes. Model 4 adjusted for all variables in model 3 plus LDL cholesterol, triglycerides, and medications for dyslipidemia.
The numbers in bold represent $p < 0.05$.

(categorical model *vs*. continuous model; AIC 6715.2 *vs.* 6712.2, BIC 6932.3 *vs*. 6896.7 in all-cause mortality; AIC 39,618.3 *vs*.39,619.2, BIC 39,835.4 *vs.* 39,803.7 in cardiovascular events; AIC 23,867.7 *vs*. 23,869.0, BIC 24,084.7 *vs.* 24,053.5 in acute coronary syndrome; AIC 15,873.8 *vs*. 15,869.3, BIC 16,090.9 *vs*. 16,053.8 in stroke). However, estimated restricted cubic splines of the association between HDL cholesterol and outcomes showed roughly U-shapes (Fig. 2).

4. Discussion

Based on a longitudinal analysis and consideration of changes in social history, comorbidities and treatment status, our study revealed that an extremely high level of HDL cholesterol was associated with significantly lower risk of all-cause mortality and cardiovascular events compared to that associated with a low level of HDL cholesterol, but increased risk of outcomes compared to very high level HDL of cholesterol. Dose-dependent reduction in HRs for all outcomes in the HDL cholesterol group were observed, except only for the extremely high level HDL cholesterol group. Although females had higher HDL cholesterol levels than males, the association between the level of HDL cholesterol and outcomes was similar between sexes.

Our study had three strengths: a longitudinal study design, a large sample size, and sufficient covariates. Our longitudinal study design considered not only fluctuations in HDL cholesterol itself over time but

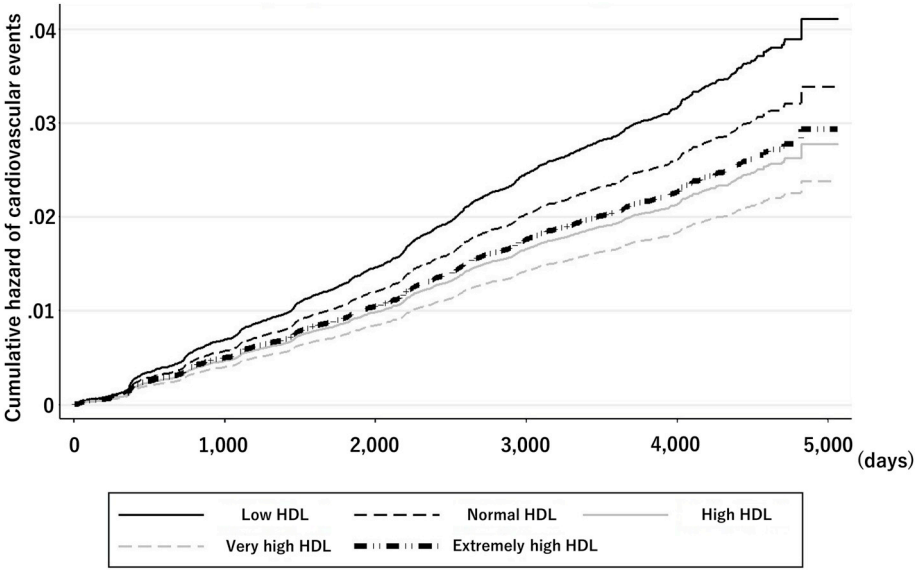

Fig. 1. Cumulative hazard of cardiovascular events by HDL cholesterol category.

Table 3
Adjusted hazard ratios for outcomes by HDL cholesterol category with time-varying Cox proportional hazard model, stratified by sex.

	Adjusted hazard ratio (95% confidence interval)							
	Female				Male			
	Model 1	Model 2	Model 3	Model 4	Model 1	Model 2	Model 3	Model 4
All-cause mortality								
Low HDL (< 40 mg/dl)	Reference				Reference			
Normal HDL (40–59 mg/dl)	**0.38 (0.17–0.84)**	**0.38 (0.17–0.83)**	**0.38 (0.17–0.85)**	**0.33 (0.15–0.76)**	0.68 (0.43–1.06)	0.72 (0.46–1.13)	0.73 (0.46–1.15)	0.81 (0.50–1.30)
High HDL (60–79 mg/dl)	**0.21 (0.09–0.45)**	**0.19 (0.09–0.43)**	**0.20 (0.09–0.44)**	**0.16 (0.07–0.38)**	0.66 (0.41–1.06)	0.70 (0.43–1.14)	0.72 (0.44–1.17)	0.76 (0.45–1.29)
Very high HDL (80–89 mg/dl)	**0.22 (0.09–0.53)**	**0.19 (0.08–0.47)**	**0.20 (0.08–0.49)**	**0.16 (0.06–0.41)**	0.60 (0.29–1.27)	0.57 (0.27–1.24)	0.61 (0.28–1.31)	0.59 (0.27–1.31)
Extremely high HDL (≥90 mg/dl)	**0.27 (0.11–0.66)**	**0.22 (0.09–0.56)**	**0.23 (0.09–0.58)**	**0.18 (0.07–0.49)**	0.61 (0.25 – 1.51)	0.61 (0.24 – 1.56)	0.64 (0.25 – 1.62)	0.56 (0.21 – 1.45)
Cardiovascular events								
Low HDL (< 40 mg/dl)	Reference				Reference			
Normal HDL (40–59 mg/dl)	1,01 (0.54–1.91)	1.06 (0.56–1.99)	1.10 (0.58–2.07)	1.15 (0.60–2.20)	**0.75 (0.62–0.90)**	**0.80 (0.66–0.96)**	**0.82 (0.68–0.99)**	**0.79 (0.65–0.96)**
High HDL (60–79 mg/dl)	0.79 (0.42–1.48)	0.86 (0.46–1.63)	0.91 (0.48–1.72)	0.98 (0.51–1.90)	**0.61 (0.50–0.74)**	**0.69 (0.56–0.84)**	**0.73 (0.59–0.89)**	**0.64 (0.51–0.80)**
Very high HDL (80–89 mg/dl)	0.66 (0.34–1.27)	0.74 (0.38–1.43)	0.79 (0.41–1.54)	0.86 (0.43–1.72)	**0.51 (0.36–0.71)**	**0.61 (0.43–0.87)**	**0.66 (0.46–0.93)**	**0.54 (0.38–0.78)**
Extremely high HDL (≥90 mg/dl)	0.86 (0.44–1.66)	0.99 (0.51–1.94)	1.05 (0.54–2.05)	1.15 (0.57–2.31)	**0.55 (0.36–0.82)**	0.68 (0.45–1.03)	0.72 (0.48–1.10)	**0.55 (0.36–0.85)**
Acute coronary syndrome								
Low HDL (< 40 mg/dl)	Reference				Reference			
Normal HDL (40–59 mg/dl)	1.49 (0.55–4.04)	1.54 (0.57–4.17)	1.60 (0.59–4.32)	1.71 (0.62–4.70)	**0.68 (0.55–0.85)**	**0.73 (0.58–0.91)**	**0.75 (0.60–0.94)**	**0.74 (0.58–0.93)**
High HDL (60–79 mg/dl)	1.15 (0.43–3.10)	1.25 (0.46–3.37)	1.31 (0.49–3.55)	1.44 (0.52–4.02)	**0.48 (0.38–0.62)**	**0.56 (0.43–0.72)**	**0.59 (0.46–0.76)**	**0.53 (0.40–0.69)**
Very high HDL (80–89 mg/dl)	0.95 (0.34–2.64)	1.08 (0.38–3.01)	1.15 (0.41–3.23)	1.28 (0.44–3.72)	**0.42 (0.28–0.65)**	**0.52 (0.34–0.81)**	**0.56 (0.36–0.87)**	**0.47 (0.30–0.73)**
Extremely high HDL (≥90 mg/dl)	1.09 (0.39–3.05)	1.28 (0.45–3.61)	1.35 (0.48–3.82)	1.50 (0.51–4.40)	**0.49 (0.30–0.81)**	0.62 (0.37–1.05)	0.67 (0.40–1.12)	**0.50 (0.30–0.86)**
Stroke								
Low HDL (< 40 mg/dl)	Reference				Reference			
Normal HDL (40–59 mg/dl)	0.70 (0.30–1.59)	0.74 (0.32–1.68)	0.77 (0.33–1.75)	0.79 (0.34–1.84)	0.88 (0.63–1.24)	0.92 (0.65–1.29)	0.95 (0.68–1.34)	0.88 (0.62–1.25)
High HDL (60–79 mg/dl)	0.55 (0.24–1.25)	0.61 (0.27–1.39)	0.65 (0.28–1.47)	0.68 (0.29–1.62)	0.88 (0.62–1.26)	0.96 (0.67–1.38)	1.02 (0.71–1.47)	0.87 (0.59–1.28)
Very high HDL (80–89 mg/dl)	0.48 (0.20–1.14)	0.53 (0.22–1.27)	0.57 (0.24–1.37)	0.61 (0.24–1.53)	0.69 (0.39–1.20)	0.78 (0.44–1.38)	0.84 (0.47–1.49)	0.68 (0.38–1.23)
Extremely high HDL (≥90 mg/dl)	0.70 (0.30–1.11)	0.80 (0.33–1.91)	0.85 (0.35–2.03)	0.92 (0.36–2.31)	0.66 (0.33–1.31)	0.76 (0.37–1.54)	0.82 (0.40–1.67)	0.62 (0.30–1.29)

Model 1 included the participant's age and sex as well as time variables as adjustments. Model 2 adjusted for variables in model 1 plus social histories and body mass index. Model 3 adjusted for variables in model 2 plus history of hypertension and diabetes. Model 4 adjusted for all variables in model 3 plus LDL cholesterol, triglycerides, and medications for dyslipidemia.
The numbers in bold represent $p < 0.05$.

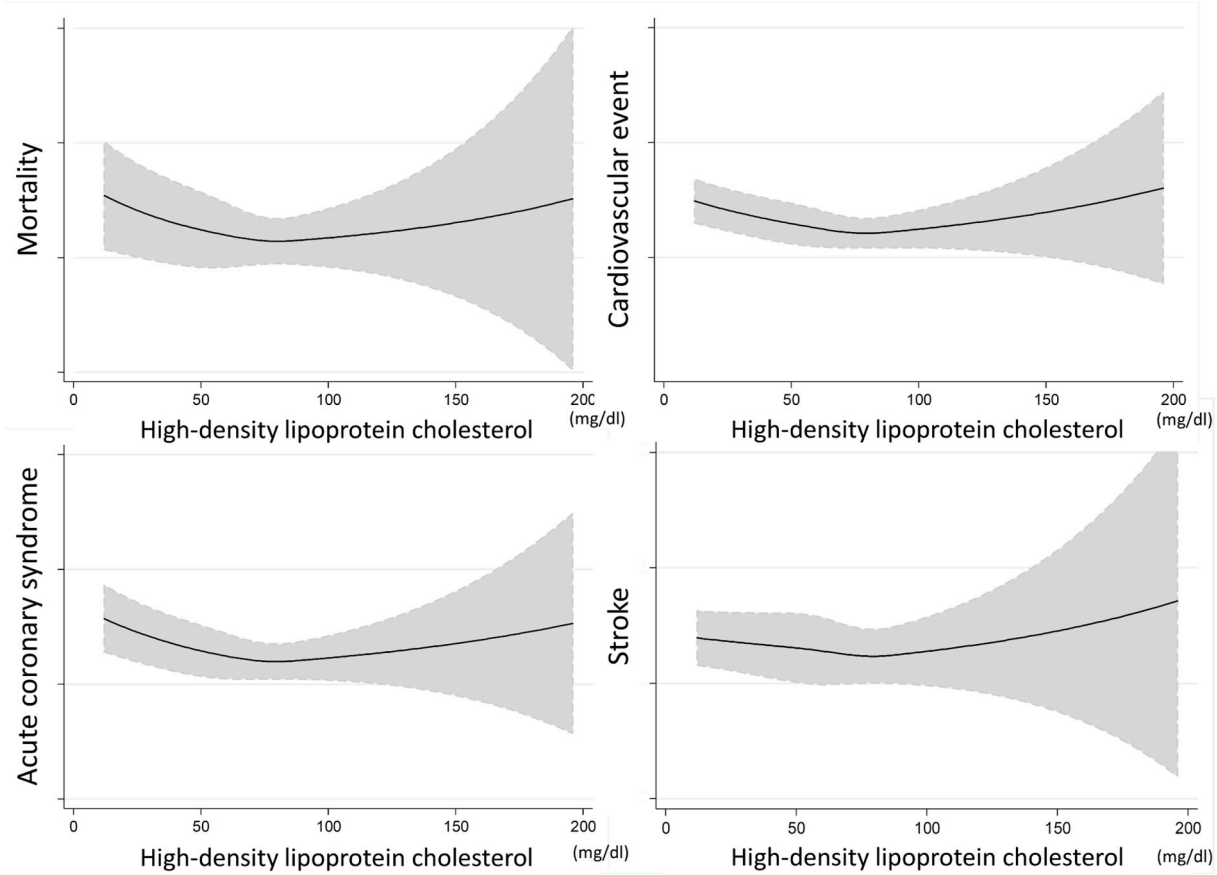

Fig. 2. Estimated restricted cubic splines of the associations between HDL cholesterol and outcomes.

also changes in cardiovascular risk factors over time to estimate the risk of outcomes. In addition, the very large sample size of more than 80,000 participants, especially more than 4000 participants with > 90 mg/dl of HDL cholesterol, is helpful for the analysis. Finally, sufficient covariates, not only cardiovascular risk factors but also the treatment status for dyslipidemia, enhance our findings. Although some other recent studies had these strengths [9,25], our study can add evidence to the association.

Our study supported the results from previous studies that showed additional risk of mortality or cardiovascular events among the extremely high HDL cholesterol population compared to that among the very high HDL cholesterol population [9,10]. Our findings support those of previous studies that showed an increased risk of mortality or cardiovascular events among patients with extremely high levels of HDL cholesterol, although we adjusted for covariates over time. Because people with extremely high levels of HDL cholesterol may underestimate their risk of cardiovascular events, they may adopt less healthy lifestyles or hesitate to take medicine for dyslipidemia diagnosed based on criteria other than the level of HDL cholesterol. In fact, people in our sample with extremely high levels of HDL cholesterol were more likely to be regular alcohol drinkers and less likely to be treated for dyslipidemia than people with lower levels of HDL cholesterol. However, considering these situations, the findings were still observed. HDL cholesterol efflux capacity, which is the function of HDL cholesterol in reversing cholesterol transport from macrophages to the liver [26], may contribute to the result that the extremely high HDL cholesterol group had increased risk of outcomes compared to the very high level HDL cholesterol group. Impaired HDL cholesterol function has been reported in some patients [27] and has been identified as causing a high number of cardiovascular events. People with an extremely high level of HDL cholesterol may actually have a large amount of dysfunctional HDL cholesterol, resulting in an increased risk compared to that observed in people with a very high level of HDL cholesterol.

In terms of the association between low levels of HDL cholesterol and mortality/cardiovascular events, our study showed a significantly higher risk than that associated with normal levels or higher levels of HDL cholesterol. Although the results of many studies from Western countries are consistent with our findings [28–30], a previous study from Japan demonstrated that low isolated HDL cholesterol was not associated with an increased risk of cardiovascular diseases [31]. This discrepancy may also be explained by changes in HDL cholesterol itself and other risk factors, such as the treatment status for dyslipidemia and a sufficient number of covariates as stated above. Therefore, our study may support the universal findings even in the Japanese population.

Interestingly, the 10 mg/dl higher HDL cholesterol cutoff values among females than among men diminished the association found in our main analyses and in previous studies, although the HDL cholesterol level in females was 14.2 mg/dl higher than in males. Previous studies have reported sex differences in HDL cholesterol levels [23,32–34], and a few studies have recommended that different cutoff values of HDL cholesterol for males and females should be used to estimate cardiovascular risk (5 mg/dl higher in females than in males) [35]. Our study may support that cutoff values of HDL cholesterol used to predict cardiovascular events should be the same or similar between sexes.

Our study had some limitations. First, the treatment status for dyslipidemia included only information about whether patients had taken their medication. The type and dosages of medication were not obtained in this study. Treatment with medications other than statins, such as ezetimibe or a PCSK9 inhibitor, alone or in combination, may differentially influence the risk of outcomes [36,37]. However, because

only 2–4% of dyslipidemic patients were treated with medications other than statins in Japan [38], the bias due to the use of these medications would be minimized. Another limitation was that our population was likely to be more health conscious than the general population because they participated in the health check-ups voluntarily. This may underestimate our results. Because our data did not overlap with that from the national database, some participants might have had a fatal event that occurred away from the hospital. However, such missing information can occur randomly, regardless of the participants' HDL cholesterol levels, and would not have a large impact on the results. In addition, we do not have any genetic information related to both high levels of HDL cholesterol and cardiovascular disease, such as *CETP* deficiency [39,40]. Although *CETP* deficiency is relatively more common in Japan than in Western countries [39], the prevalence of homozygous *CETP* deficiency is one per several tens of thousands [41]. Therefore, the effect of genetic abnormality on the results may be negligible. Next, a median follow-up of approximately 5 years may be short to evaluate cardiovascular mortality. In fact, the limited number of fatal cardiovascular events precluded this type of analysis. Finally, a longitudinal study design cannot mention causality that increased HDL cholesterol prevented unfavorable outcomes. Because previous randomized controlled trials with Niacin [5,42] or CETP inhibitors [6,7,43] and a genetic study [8] failed to show the preventive effect on cardiovascular diseases through increased HDL cholesterol, we only concluded that high HDL cholesterol could be a predictive factor, not a preventive factor for all-cause mortality and cardiovascular events.

Based on a longitudinal analysis and a consideration of changes in social history, comorbidities and treatment status, our study demonstrated that an extremely high level HDL cholesterol (> 90 mg/dl) had lower risks of all-cause mortality and cardiovascular events compared to low level HDL cholesterol (< 40 mg/dl), but higher risk of outcomes compared to very high level HDL cholesterol (80–89 mg/dl) with longitudinal analysis, considering change of social history, comorbidities and treatment status, as previously reported.

Conflicts of interest

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

Author contributions

All authors contributed to the design and conduct of the study, data collection and management, analysis interpretation of the data; and preparation, review, or approval of the manuscript. TS, HN and KA supervised the study and DK is the guarantor.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2019.06.918.

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