Online-only Supplementary Data

Association between low-density lipoprotein cholesterol and cardiovascular mortality in statin non-users: a prospective cohort study in 14.9 million Korean adults

Sang-Wook Yi, MD, PhD, Department of Preventive Medicine and Public Health, Catholic Kwandong University College of Medicine, Republic of Korea; **Sang Joon An**, MD, Department of Neurology, Catholic Kwandong University College of Medicine, International St. Mary's Hospital, Repuclic of Korea; **Hyung Bok Park**, MD, Department of Cardiology, Catholic Kwandong University College of Medicine, International St. Mary's Hospital; **Jee-Jeon Yi**, PhD, Institute for Occupational and Environmental Health, Catholic Kwandong University, Republic of Korea; **Heechoul Ohrr**, MD, PhD, Department of Preventive Medicine, Yonsei University College of Medicine, Republic of Korea;

Correspondence: Sang-Wook Yi, MD, PhD, Department of Preventive Medicine and Public Health, Catholic Kwandong University College of Medicine, Bumil-ro 579-beongil 24, Gangneung, Gangwon-do, 25601, Republic of Korea; Tel: +82-33-649-7468; Fax +82-33-641-1074. e-mail: flyhigh@cku.ac.kr

Supplementary material. Statistical analysis

LDL-C levels were categorized into 17 groups (mg/dL; <50, 50-59 to 190-199 by 10, and ≥200 mg/dL 100-109 mg/dL as reference) for overall CVD mortality, and into 11 groups for subtypes of CVD (mg/dL; <55, 55-69 to 175-189 by 15, and ≥190 mg/dL 100-114 mg/dL as reference), and into 6 groups for age-specific analyses (<70, 70-99, 100-129 [reference], 130-159, 160-189, and ≥190 mg/dL). The LDL-C category with the lowest overall CVD mortality was used as the reference. Log risk was regressed on LDL-C as a continuous variable within the ranges of <100 mg/dL (termed "lower range"), 100-300 mg/dL ("upper range"), or ≤300 mg/dL, yielding HRs per 39 mg/dL (1 mmol/L) increase in LDL-C in each range. An analysis using a restricted cubic spline transformation of LDL-C with 5 (or 4) predefined knots (5th, 27.5th, 50th, 72.5th, and 95th percentile; or [5th, 35th, 65th, and 95th percentile]) was also performed to examine non-linear associations. P-values for non-linearity were assessed with the likelihood ratio test, in which the model with only the linear term was compared with the model with the cubic spline terms.

The hazard ratios (HRs) for mortality were calculated using Cox proportional hazard models stratified by baseline age (years: 18-24, 25-34, 35-44, 45-54, 55-64, 65-74, or 75-84, 85-99) using the STRATA statement [1-3]. In the multivariable model, the following variables were adjusted for: age (continuous variable within each age stratum), sex, income status (quartile: 1st [low income], 2nd, 3rd, and 4th), smoking status (current smoker, former smoker, never smoker, or missing information), alcohol use frequency (days/week; <1, 1-2, 3-4, 5-7, or missing information), physical activity (moderate activity for ≥30 minutes per week; none, once, ≥2 times), SBP (continuous variable), fasting glucose (continuous variable), BMI (<18.5, 18.5-24.9, 25-29.9, or ≥30 kg/m^2), log transformation of triglyceride levels (continuous variable), and HDL-C levels (<40, 40-59, or ≥60 mg/dL). Based on qualitative observations of the curvilinear association, the intervals of 44 mg/dL (roughly 1.5 mmol/L) with the lowest risk (the lowest unweighted geometric mean of HRs in 3 consecutive LDL-C categories in the 11-group analysis) were identified as the optimal range. An analysis excluding the first 3 years of follow-up was performed. In the Cox model for CVD mortality, the cause-specific hazard method was used to handle competing risks; individuals who experienced other causes of death or reached the end of the follow-up were treated

as censored. Schoenfeld residuals were used to test the proportional hazard assumption. Subgroup analyses by age and sex, as well as various categorical, spline, and linear analyses, served as sensitivity analyses. Cochran's Q statistic was calculated as the interaction test to examine the difference in the effect size of each 1-mmol/L increment of LDL-C between age and sex groups. All p-values were 2-sided. All analyses used SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Reference

1. Yi SW, Ohrr H, Shin SA, Yi JJ. Sex-age-specific association of body mass index with all-cause mortality among 12.8 million Korean adults: a prospective cohort study. *Int J Epidemiol*. 2015;44(5):1696-1705.
2. Yi SW, Yi JJ, Ohrr H. Total cholesterol and all-cause mortality by sex and age: a prospective cohort study among 12.8 million adults. *Sci Rep*. 2019;9(1):1596.
3. Yi SW, Park SJ, Yi JJ, Ohrr H, Kim H. High-density lipoprotein cholesterol and all-cause mortality by sex and age: a prospective cohort study among 15.8 million adults. Int J Epidemiol. 2020.

- The National Health Insurance Service (NHIS) provides mandatory health insurance for 97% of the Korean population and nationwide biennial health screening.
- Clinical chemistry and anthropometric and blood pressure measurement were performed, and Information on smoking status, alcohol use, physical activity, and history of various diseases was collected via a questionnaire, during each biennial health screenings.
- The health examinations and data collection followed a standard protocol documented by the Ministry of Health and Welfare.

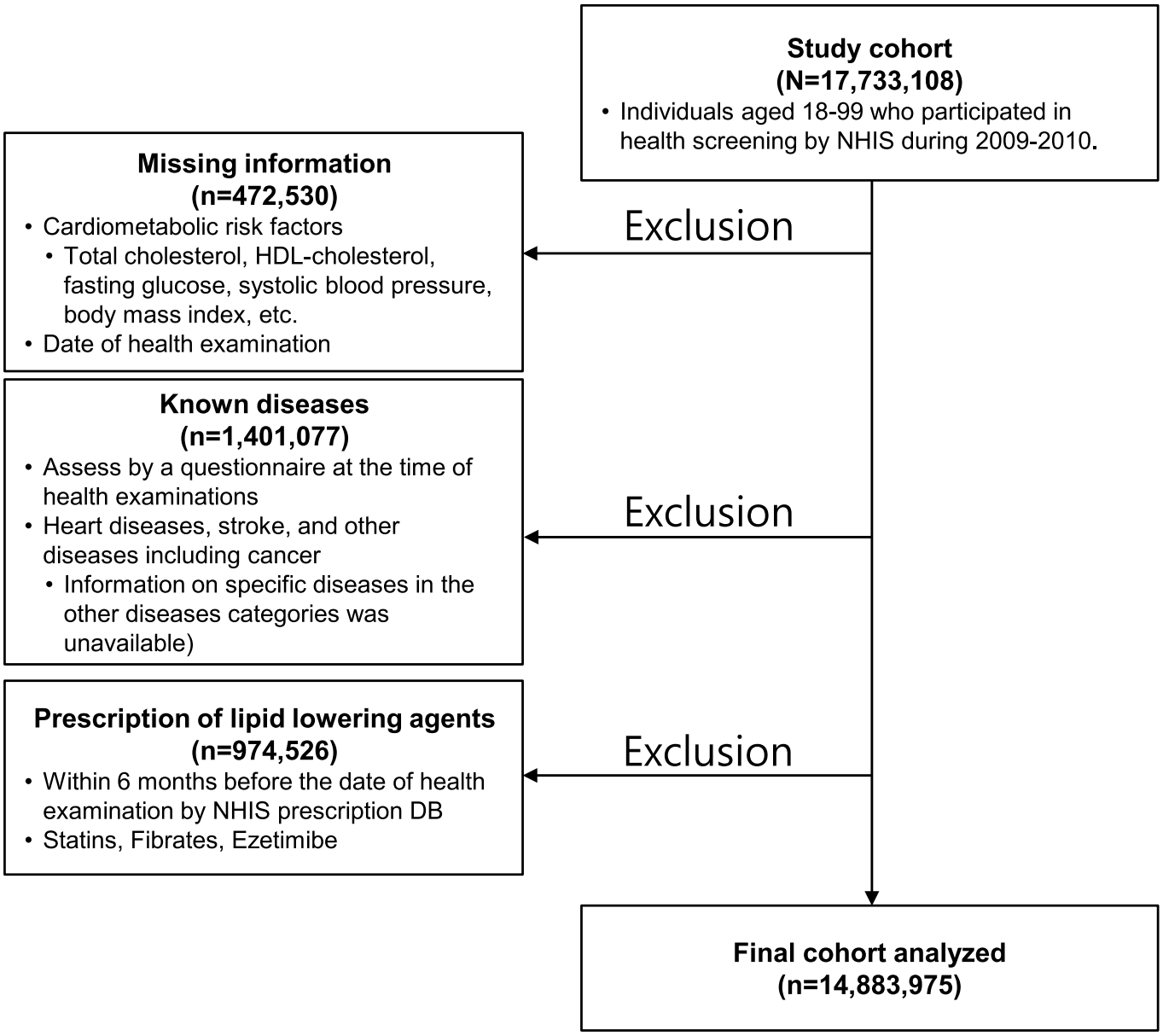

Figure S1. Study flow chart

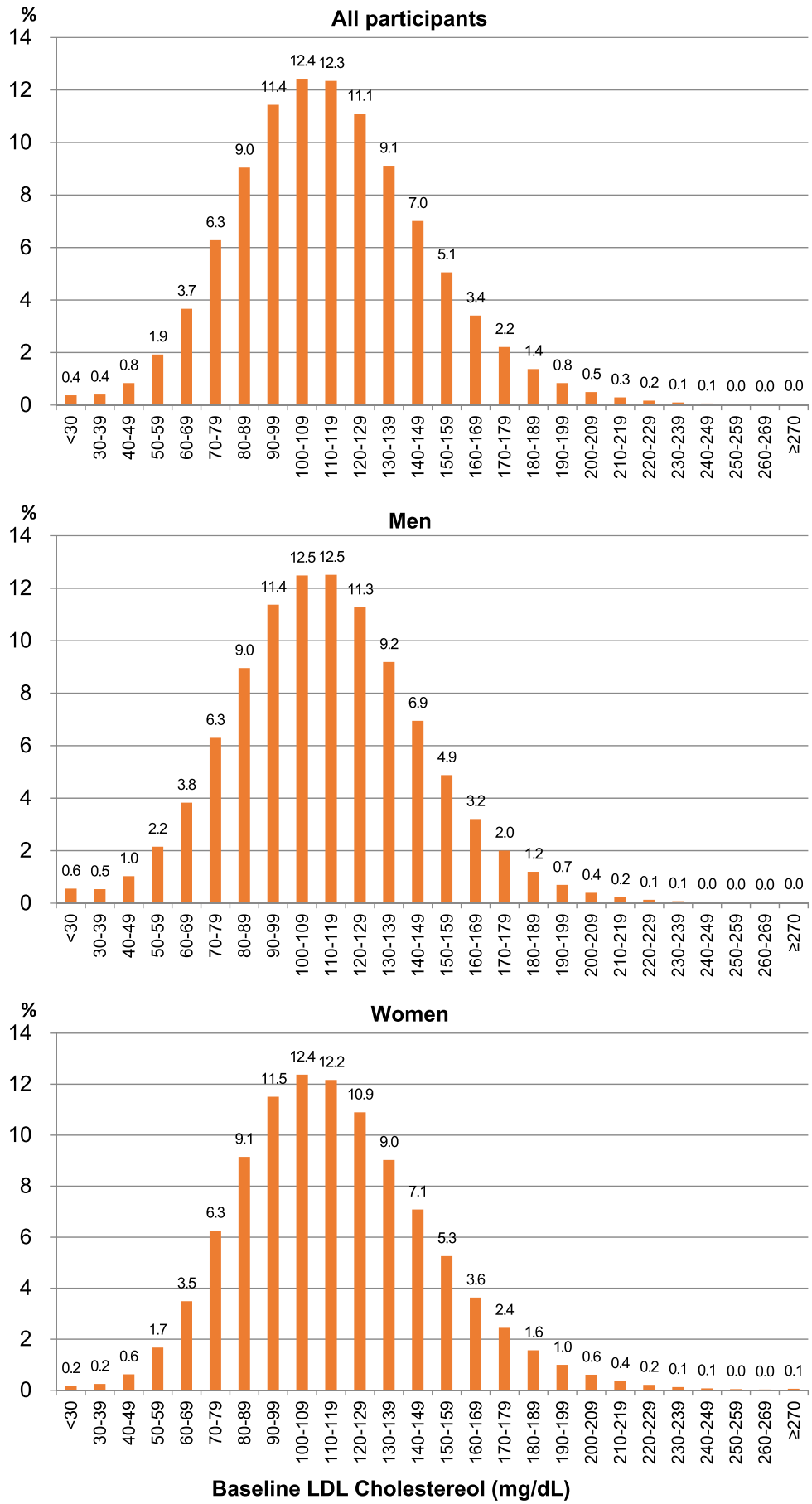

Figure S2. Distribution of low density lipoprotein-cholesterol (LDL-C) concentration.
To convert cholesterol from mg/dL to mmol/L, multiply by 0.02586

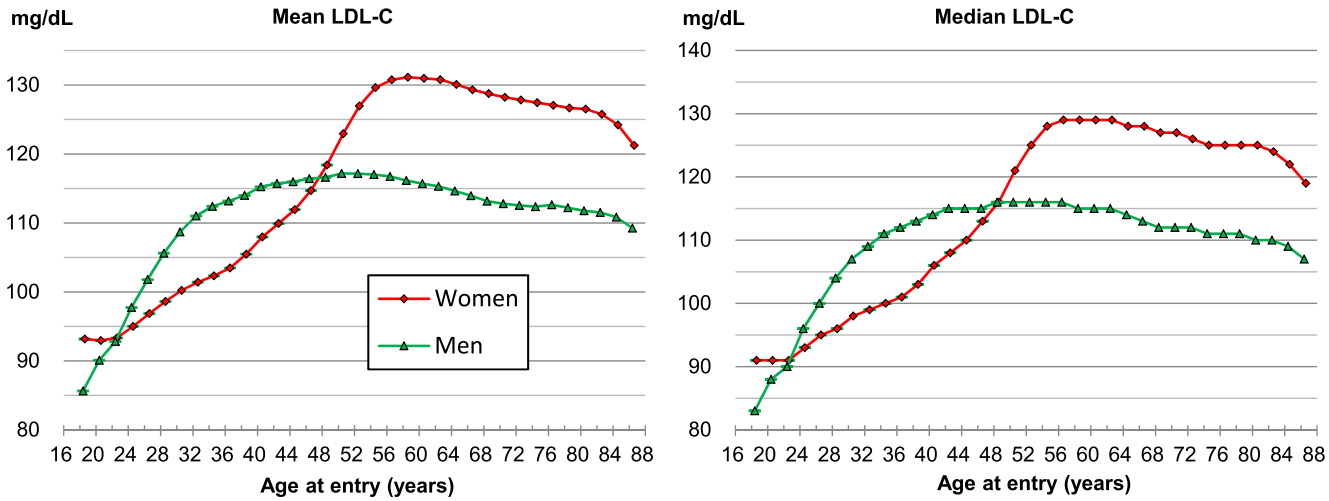

Figure S3. Mean and median concentrations of low-density lipoprotein cholesterol (LDL-C).
To convert LDL-C from mg/dL to mmol/L, multiply by 0.02586.

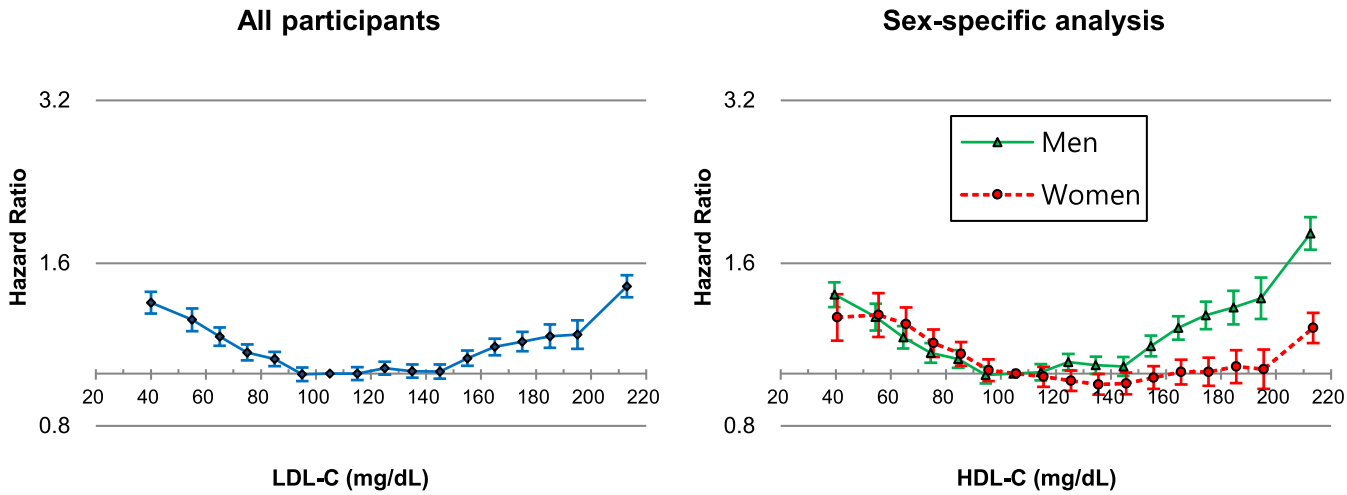

Figure S4. HRs* across 17 categories of LDL-C for CVD mortality.

LDL-C categories (mg/dL: <50, 50-59 to 190-199 by 10, ≥200, 100-109 as reference). The midpoint was used as a representative value of each LDL-C category, except both ends (40 and 213) for which the median was used. *Hazard ratios and 95% confidence intervals were calculated using Cox proportional hazard models with adjustment for sex (for all participants only), age at baseline, smoking status, alcohol consumption frequency, physical activity, household income, systolic blood pressure, fasting glucose, body mass index, triglyceride and high-density lipoprotein cholesterol. CVD cardiovascular disease; LDL-C, low density lipoprotein cholesterol. To convert LDL-C from mg/dL to mmol/L, multiply by 0.02586.

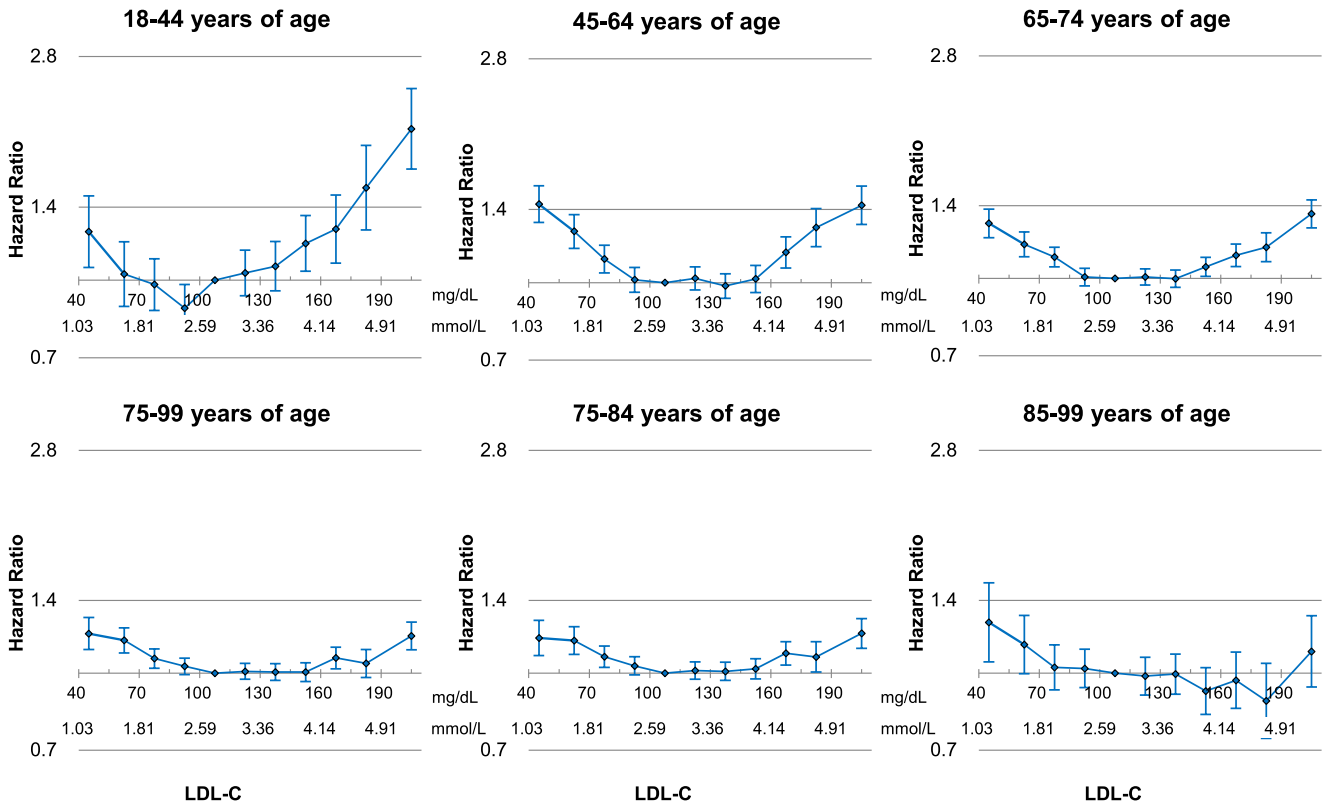

Figure S5. HRs* across 11 categories of LDL-C for CVD mortality according to age.
LDL-C categories (mg/dL: <55, 55-69 to 175-189 by 15, ≥190, 100-114 as reference). The midpoint was used as a representative value of each LDL-C category, except both ends (45 and 205) for which the median was used. *Hazard ratios and 95% confidence intervals were calculated using the same method as in Figure S4. CVD cardiovascular disease; LDL-C, low density lipoprotein cholesterol. To convert LDL-C from mg/dL to mmol/L, multiply by 0.02586.
.

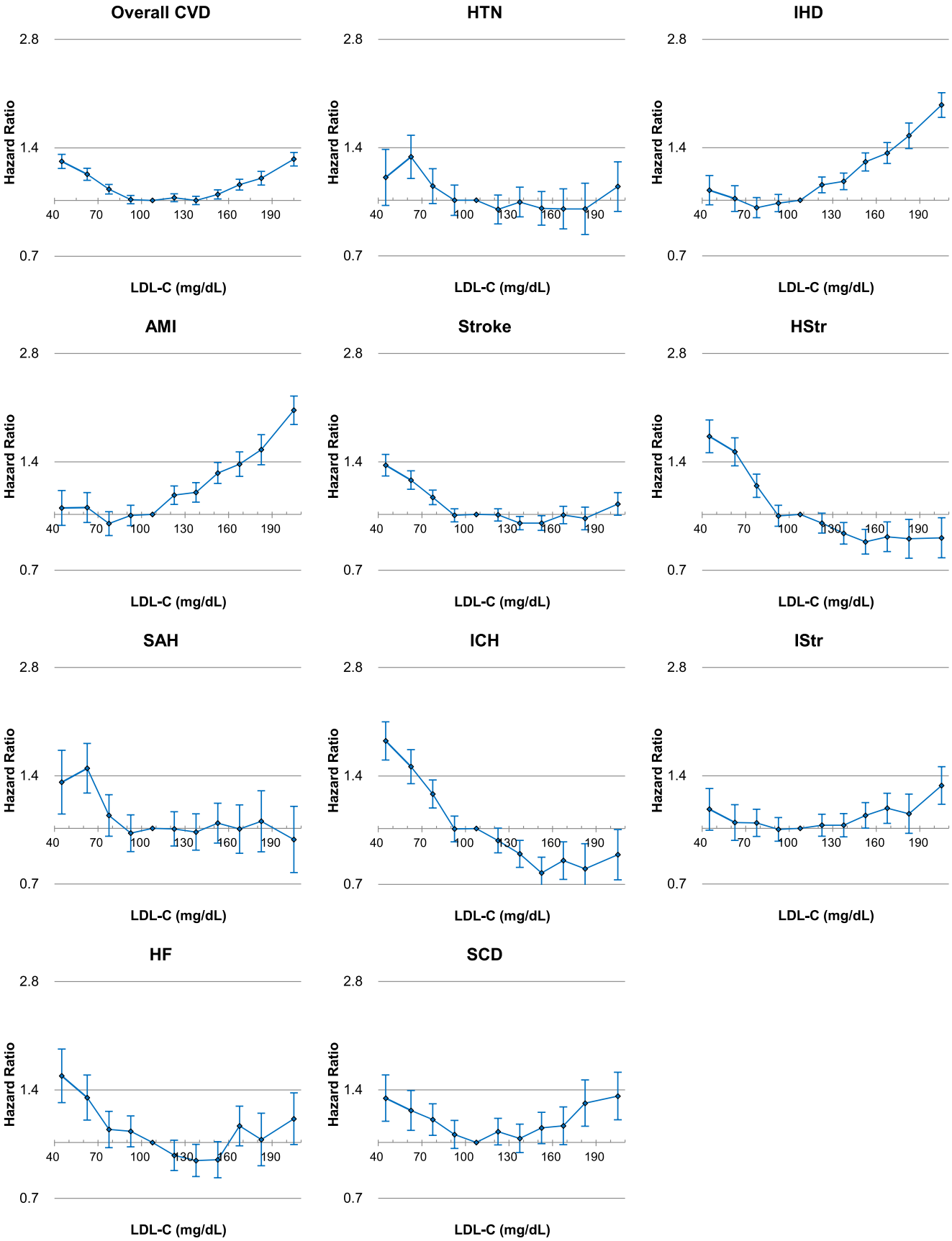

Figure S6. HRs* for mortality from CVD and its subtypes after exclusion of first 3 years of deaths.

LDL-C categories (mg/dL: <55, 55-69 to 175-189 by 15, ≥190, 100-114 as reference). The midpoint was used as a representative value of each LDL-C category, except both ends (45 and 205) for which the median was used. *Hazard ratios (HRs) and 95% confidence intervals were calculated using the same method as in Figure S4. AMI, acute myocardial infarction; CVD cardiovascular disease; HF, heart failure; HStr, hemorrhagic stroke; HTN, hypertensive disease; ICH, intracerebral hemorrhage; IHD, ischemic heart disease; IStr, ischemic stroke; LDL-C, low density lipoprotein cholesterol; SAH, subarachnoid hemorrhage; SCD, sudden cardiac death. To convert LDL-C from mg/dL to mmol/L, multiply by 0.02586.

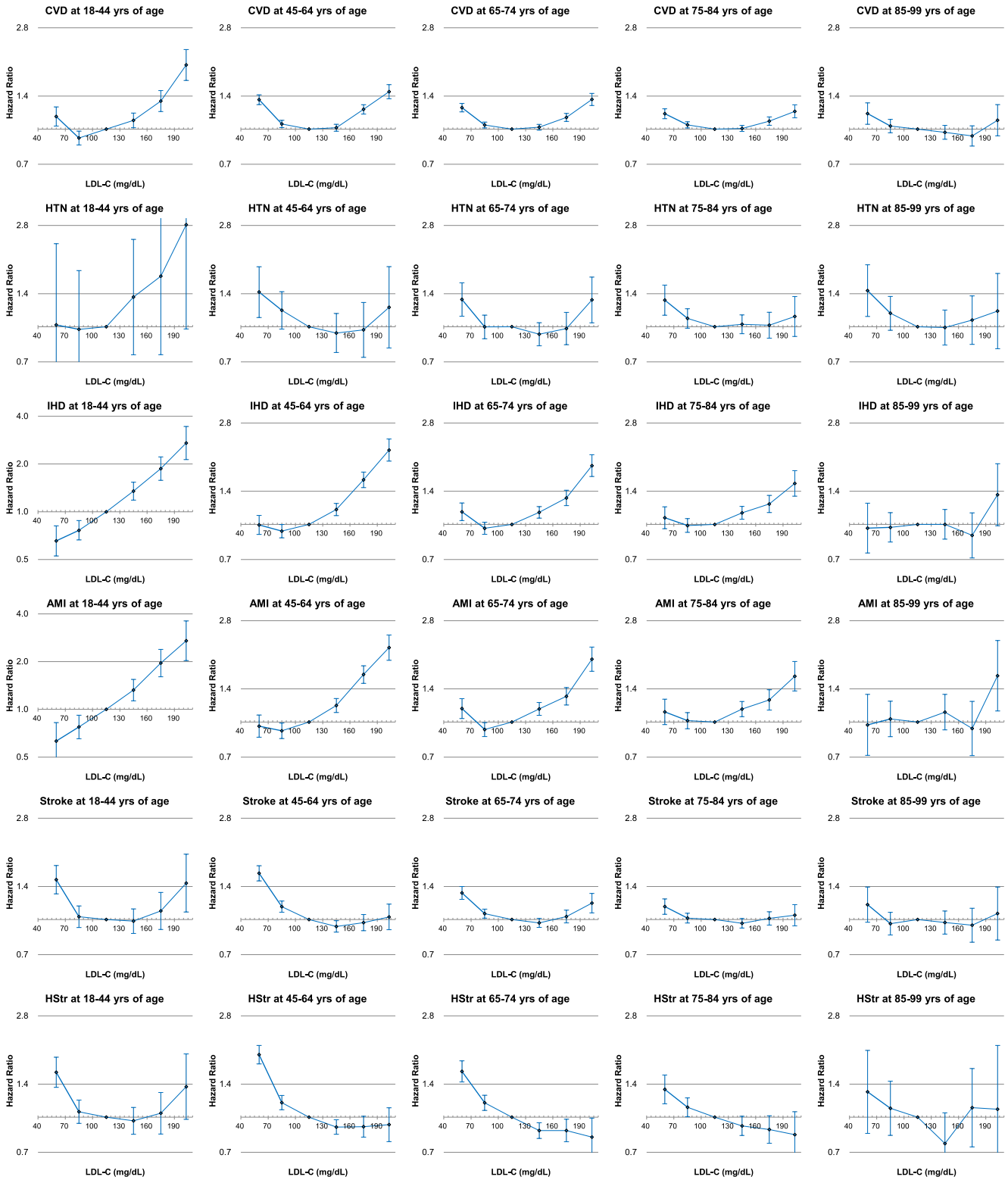

Figure S7. HRs* for mortality from CVD and its subtypes according to age

LDL-C categories (mg/dL: <70, 70-99, 100-129 [reference], 130-159, 160-189, ≥190). The midpoint was used as a representative value of each LDL-C category, except both ends (45 and 205) for which the median was used. *Hazard ratios and 95% confidence intervals were calculated using the same method as in Figure S4. Same abbreviation was used as in Figure S6. To convert LDL-C from mg/dL to mmol/L, multiply by 0.02586.

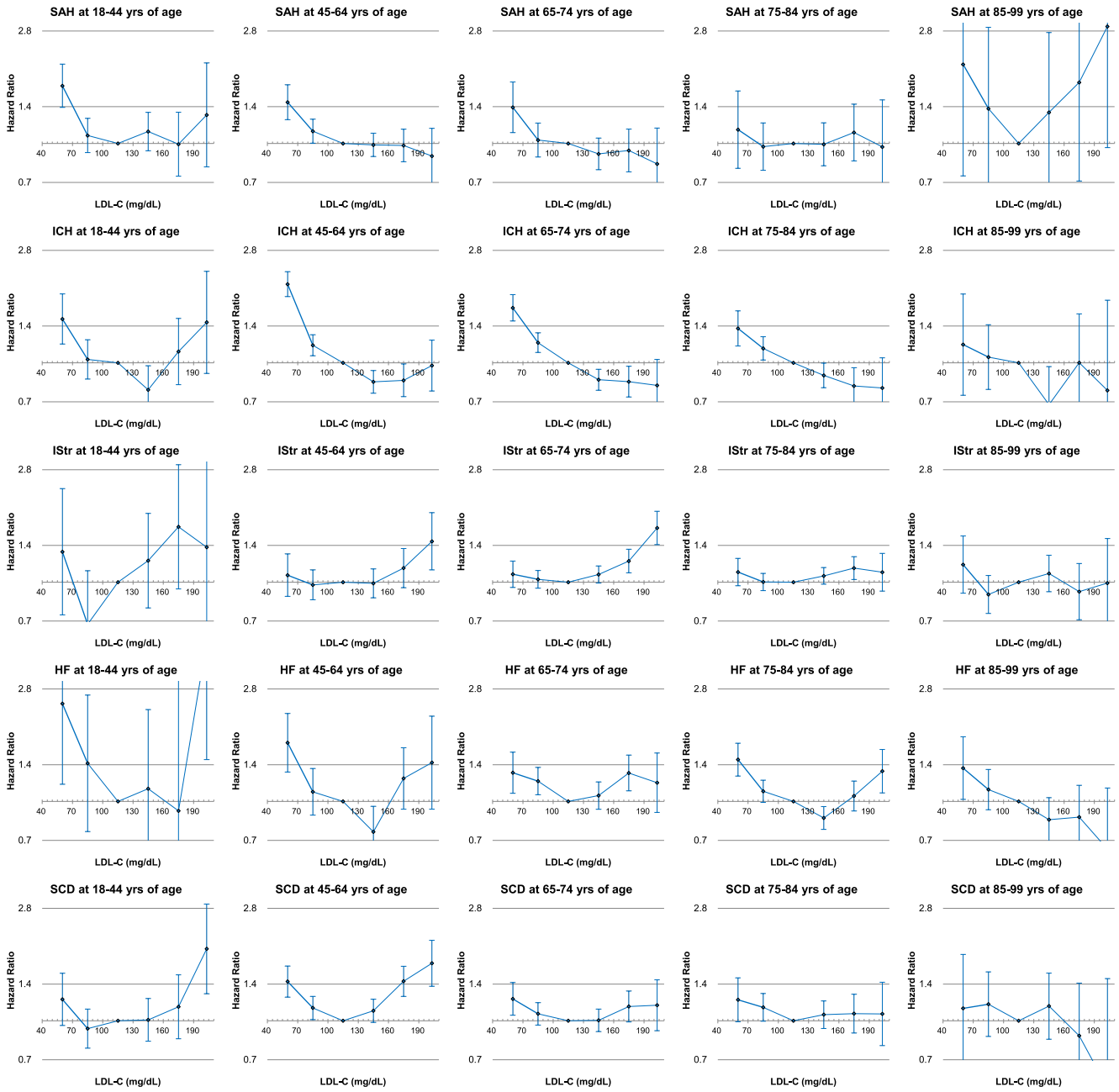

Figure S7. Continued.

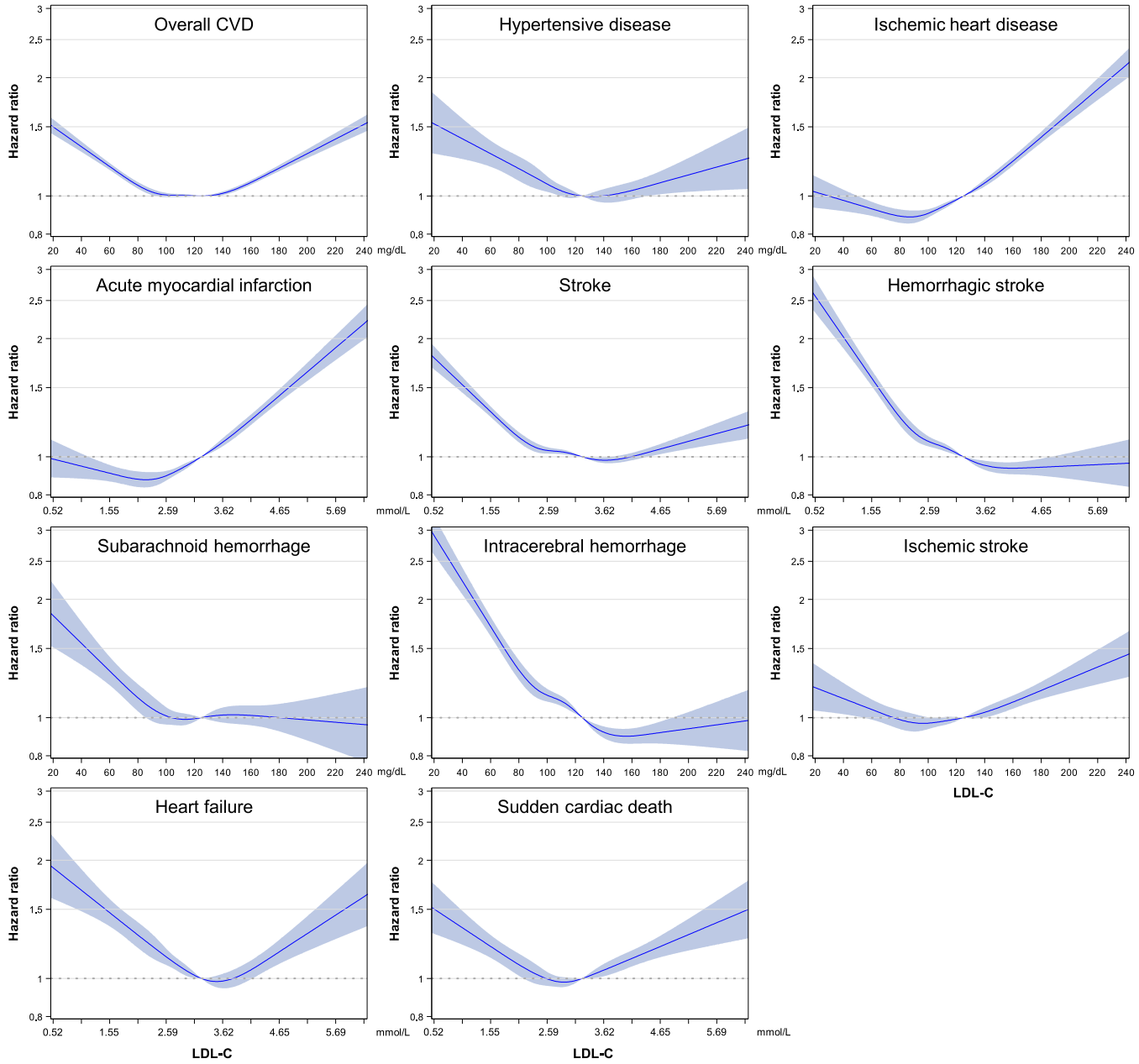

Figure S8. HRs* for mortality from cardiovascular disease (CVD) and its subtypes using spline analysis.
Restricted cubic splines of low-density lipoprotein cholesterol (LDL-C) with 5 knots (5th, 27.5th, 50th, 72.5th, and 95th percentile) and 125 mg/dL as a reference were used. *Hazard ratios and 95% CIs were calculated using Cox proportional hazards models after adjustment for the same variables as in Figure S4. To convert cholesterol from mg/dL to mmol/L, multiply by 0.02586.

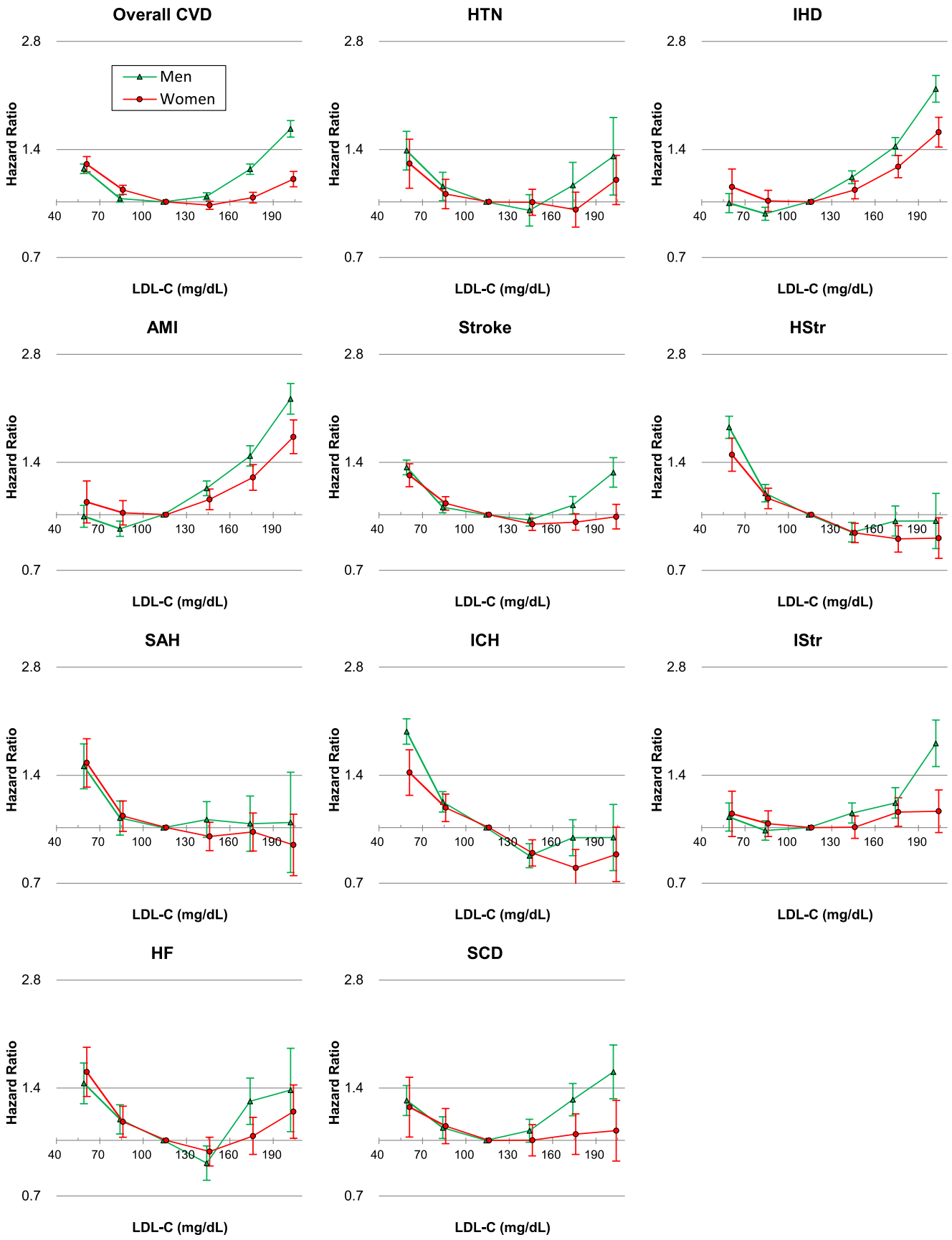

Figure S9. HRs* across 6 categories of LDL-C for mortality from CVD and its subtypes according to sex. LDL-C categories (mg/dL: <70, 70-99, 100-129 [reference], 130-159, 160-189, ≥190). The midpoint was used as a representative value of each LDL-C category, except both ends (45 and 205) for which the median was used. *Hazard ratios and 95% confidence intervals were calculated using the same method as in Figure S4. Same abbreviation was used as in Figure S6. To convert LDL-C from mg/dL to mmol/L, multiply by 0.02586.

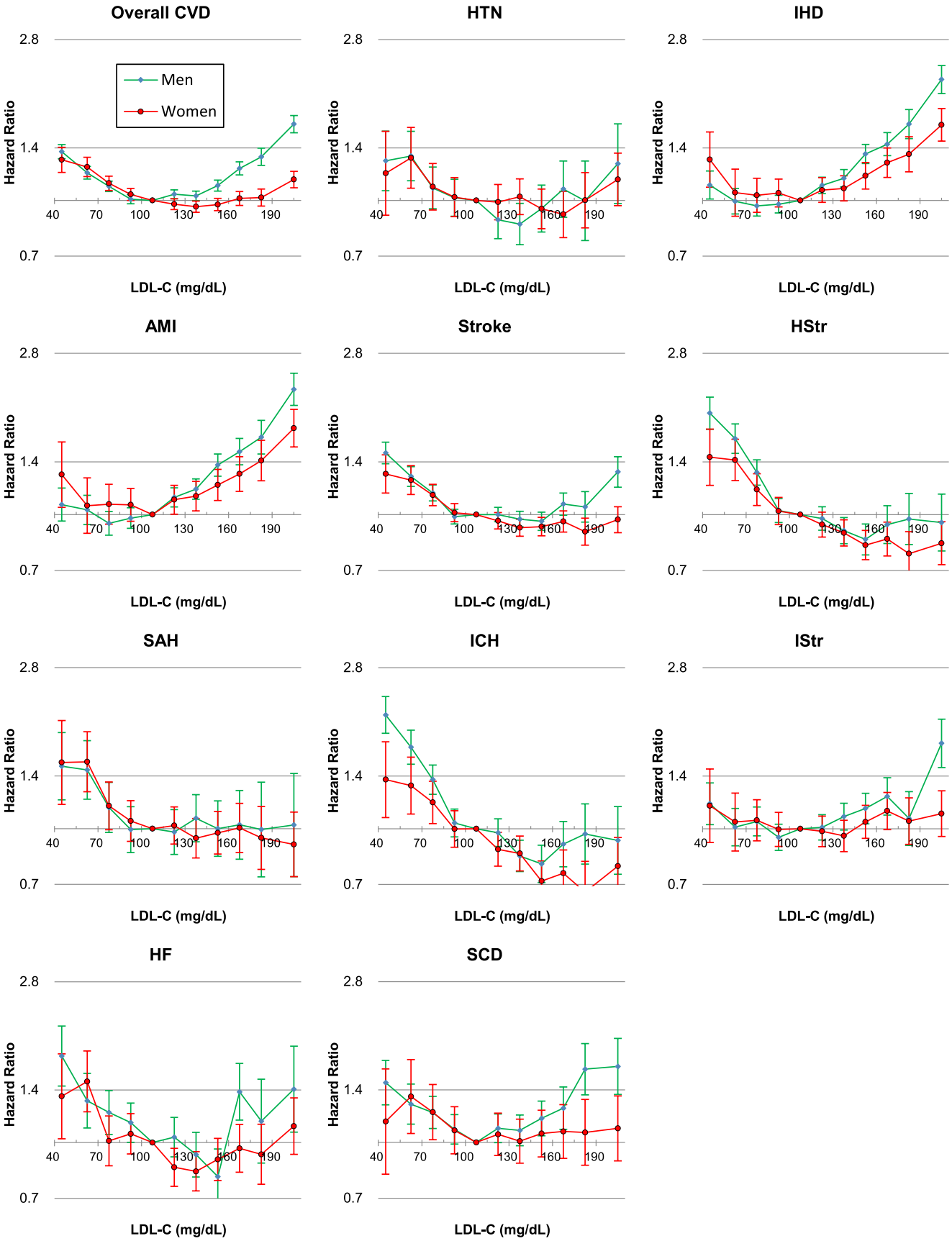

Figure S10. HRs* across 11 categories of LDL-C for mortality from CVD and its subtypes according to sex.
LDL-C categories (mg/dL: <55, 55-69 to 175-189 by 15, ≥190, 100-114 as reference). The midpoint was used as a representative value of each LDL-C category, except both ends (45 and 205) for which the median was used. *Hazard ratios and 95% confidence intervals were calculated using the same method as in Figure S4. Same abbreviation was used as in Figure S6. To convert LDL-C from mg/dL to mmol/L, multiply by 0.02586.

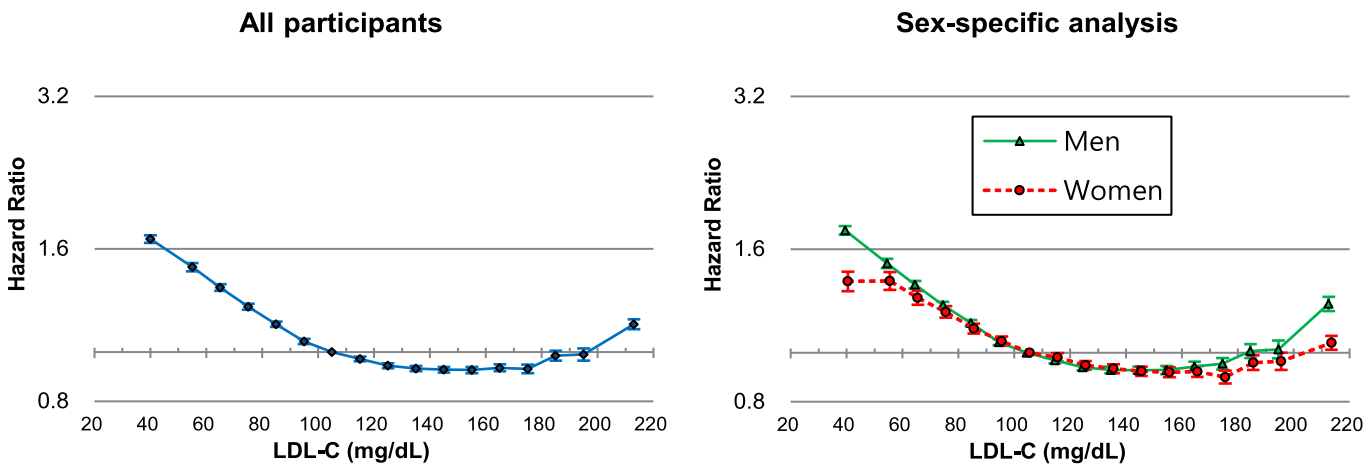

Figure S11. HRs* across 17 categories of LDL-C for all-cause mortality (no. of death=536,975).
LDL-C categories (mg/dL: <50, 50-59 to 190-199 by 10, ≥200, 100-109 as reference). The midpoint was used as a representative value of each LDL-C category, except both ends (40 and 213) for which the median was used. *Hazard ratios and 95% confidence intervals were calculated using Cox proportional hazard models with adjustment for sex (for all participants only), age at baseline, smoking status, alcohol consumption frequency, physical activity, household income, systolic blood pressure, fasting glucose, body mass index, triglyceride and high-density lipoprotein cholesterol. LDL-C, low density lipoprotein cholesterol. To convert LDL-C from mg/dL to mmol/L, multiply by 0.02586.

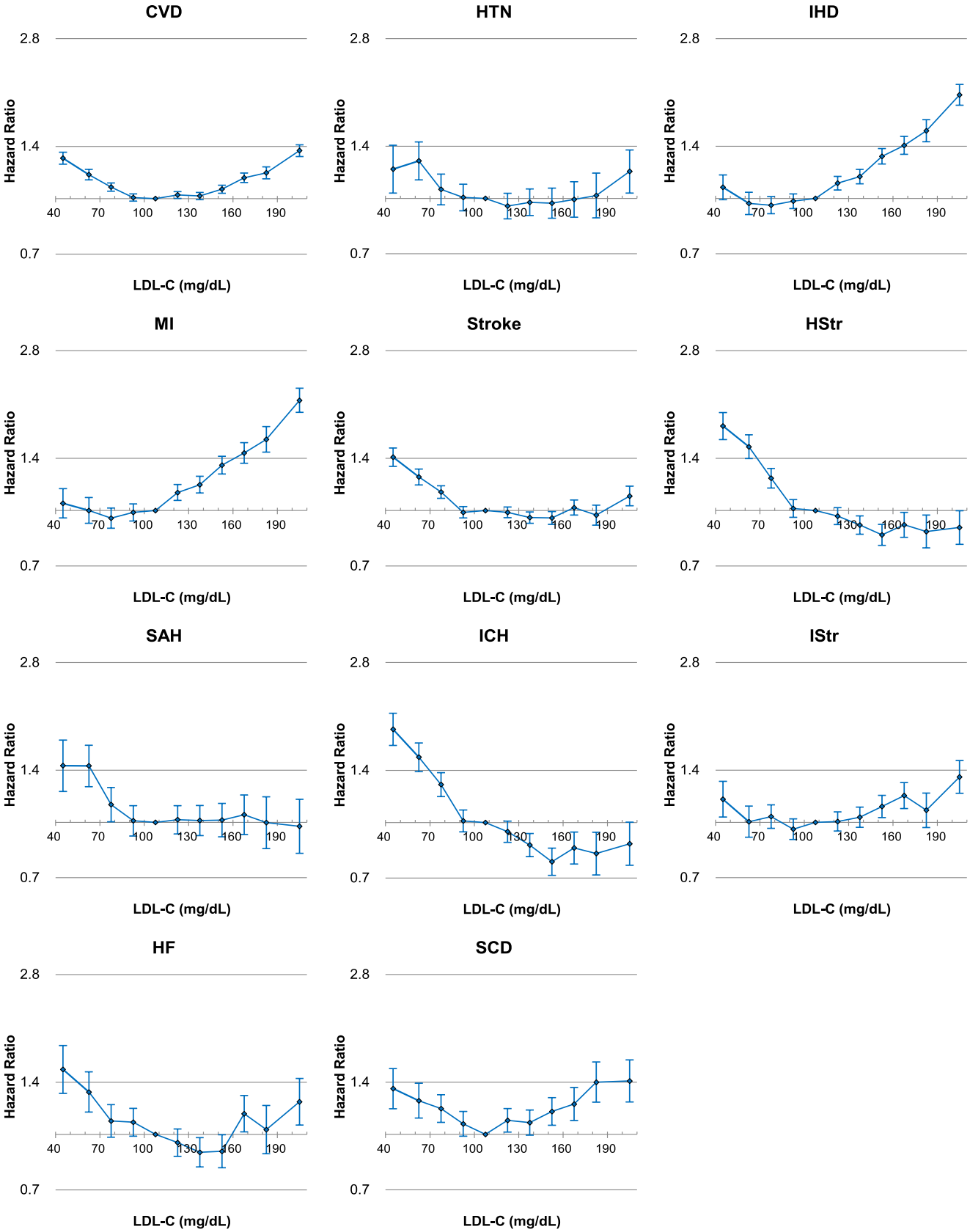

Figure S12. HRs* for mortality from CVD and its subtypes after further adjustment for anemia (sensitivity analysis)

LDL-C categories (mg/dL: <55, 55-69 to 175-189 by 15, ≥190, 100-114 as reference). The midpoint was used as a representative value of each LDL-C category, except both ends (45 and 205) for which the median was used. *Hazard ratios and 95% confidence intervals were calculated using the same method as in Figure S4 after further adjustment for anemia (defined by baseline hemoglobin <12 [women], <13 g/L [men]). Same abbreviation was used as in Figure S6. To convert LDL-C from mg/dL to mmol/L, multiply by 0.02586.

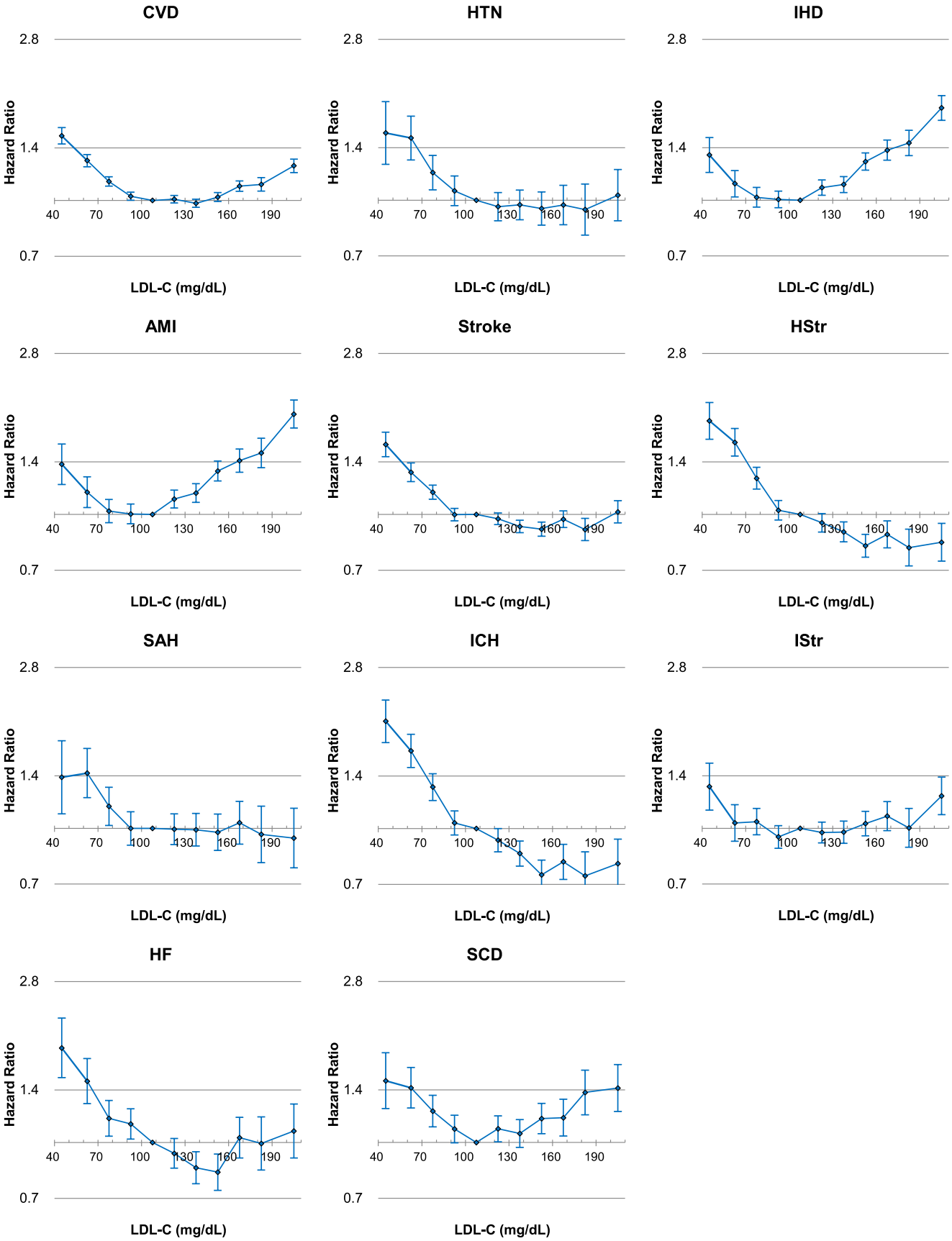

Figure S13. HRs* for mortality from CVD and its subtypes in individuals with triglyceride <200 mg/dL in which Friedewald measurements have a higher validity (sensitivity analysis)
LDL-C categories (mg/dL: <55, 55-69 to 175-189 by 15, ≥190, 100-114 as reference). The midpoint was used as a representative value of each LDL-C category, except both ends (45 and 205) for which the median was used. *Hazard ratios and 95% confidence intervals were calculated using the same method as in Figure S4. Same abbreviation was used as in Figure S6. To convert LDL-C from mg/dL to mmol/L, multiply by 0.02586.

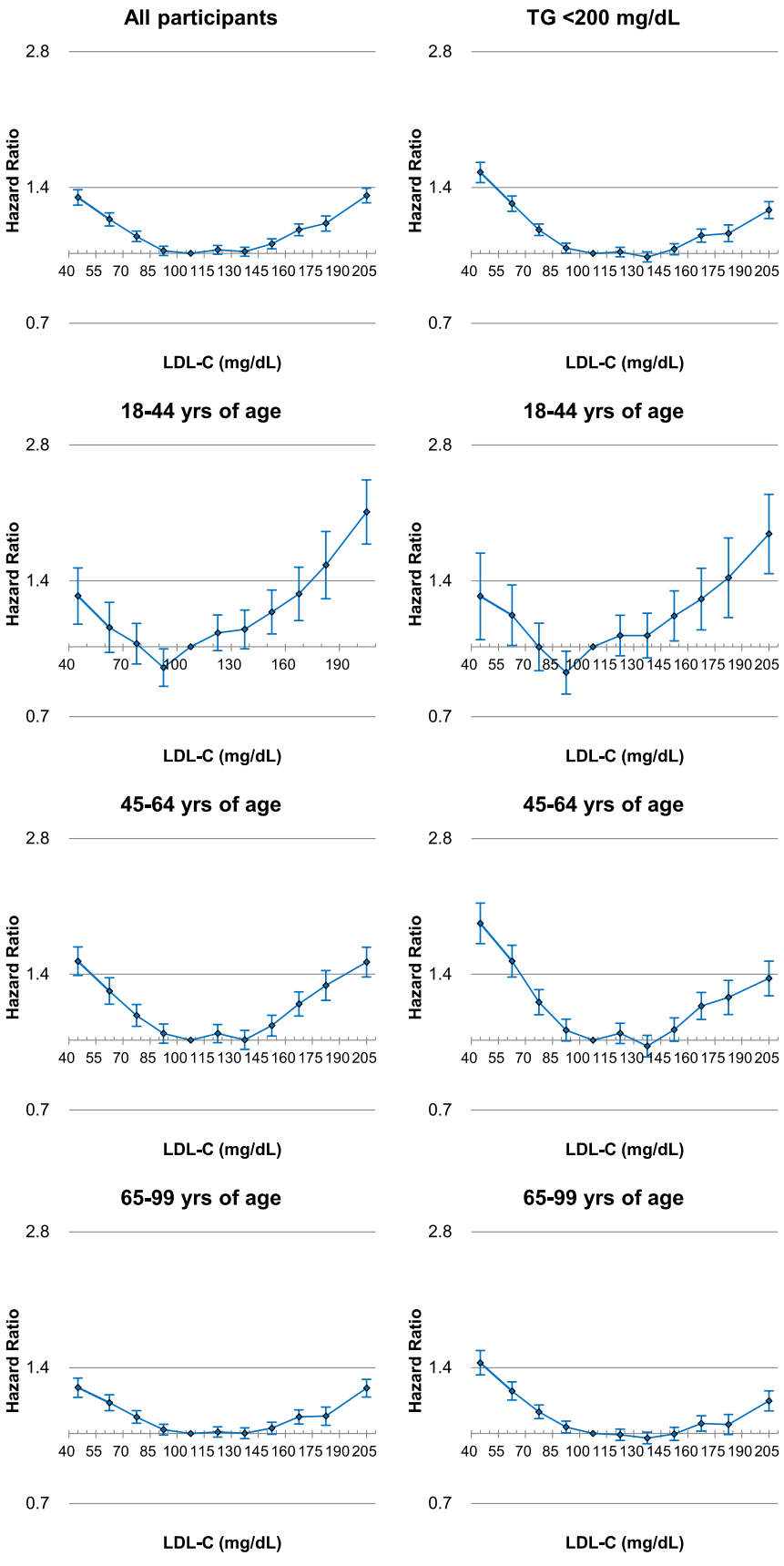

Figure S14. HRs* for CVD mortality by age in all participants and individuals with triglyceride <200 mg/dL in which Friedewald measurements have a higher validity (sensitivity analysis)
*Hazard ratios and 95% confidence intervals were calculated using the same method as in Figure S4. CVD cardiovascular disease; LDL-C, low density lipoprotein cholesterol. To convert LDL-C from mg/dL to mmol/L, multiply by 0.02586.

Table S1. Number of deaths from cardiovascular causes by sex

		Total		Men		Women	
Cardiovascular causes of death	ICD-10	n	(%)	n	(%)	n	(%)
Cardiovascular diseases	I00-I99	94,344	(100.0)	56,057	(100.0)	38,287	(100.0)
Rheumatic heart diseases	I00-I09	174	(0.2)	80	(0.1)	94	(0.2)
Hypertensive diseases	I10-I15	6,792	(7.2)	3,141	(5.6)	3,651	(9.5)
Ischemic heart diseases	I20-I25	24,496	(26.0)	16,530	(29.5)	7,966	(20.8)
AMI	I21	18,307	(19.4)	12,371	(22.1)	5,936	(15.5)
Pulmonary heart diseases	I26-I28	932	(1.0)	404	(0.7)	528	(1.4)
Other heart diseases	I30-I52	20,917	(22.2)	12,542	(22.4)	8,375	(21.9)
Heart failure	I50	5,978	(6.3)	2,820	(5.0)	3,158	(8.2)
Sudden cardiac death	I46	8,177	(8.7)	5,610	(10.0)	2,567	(6.7)
Stroke	I60-I69	38,085	(40.4)	21,505	(38.4)	16,580	(43.3)
Hemorrhagic stroke	I60-I62	15,178	(16.1)	8,234	(14.7)	6,944	(18.1)
Subarachnoid hemorrhage	I60	5,461	(5.8)	2,266	(4.0)	3,195	(8.3)
Intracerebral hemorrhage	I61-I62	9,717	(10.3)	5,968	(10.6)	3,749	(9.8)
Ischemic stroke	I63	11,845	(12.6)	6,901	(12.3)	4,944	(12.9)
Diseases of arteries	I70-I79	2,669	(2.8)	1,704	(3.0)	965	(2.5)
Other diseases	I80-I99	279	(0.3)	151	(0.3)	128	(0.3)

Table S2. Mean and median of LDL-C (mg/dL) (Including numerical version of Figure 1).

Age,	Men and women				Men				Women				Sex difference[a]	
years	n	Median	Mean	(SD)	n	Median	Mean	(SD)	n	Median	Mean	(SD)	Median	Mean
18-99	14,884,975	112	114.5	(33.4)	7,839,191	112	113.1	(14.2)	7,045,784	113	116.1	(33.6)	-1	-3.0
18-19	28,495	88	90.3	(24.4)	10,885	83	85.6	(24.0)	17,610	91	93.2	(24.3)	-8	-7.5
20-21	78,304	90	92.0	(25.2)	26,458	88	90.1	(25.2)	51,846	91	93.0	(25.2)	-3	-2.9
22-23	193,128	91	93.1	(25.7)	71,525	90	92.8	(26.1)	121,603	91	93.3	(25.4)	-1	-0.5
24-25	348,494	94	96.1	(26.5)	144,828	96	97.7	(27.6)	203,666	93	95.0	(25.5)	3	2.7
26-27	546,642	97	99.4	(27.7)	281,707	100	101.8	(29.0)	264,935	95	96.9	(26.1)	5	4.9
28-29	650,862	100	102.8	(29.0)	389,735	104	105.6	(29.9)	261,127	96	98.6	(26.9)	8	7.0
30-31	599,261	103	105.7	(30.0)	384,486	107	108.7	(30.8)	214,775	98	100.2	(27.5)	9	8.5
32-33	548,637	106	107.9	(30.8)	370,791	109	111.0	(31.7)	177,846	99	101.4	(27.8)	10	9.6
34-35	544,394	107	109.3	(31.2)	376,774	111	112.4	(32.2)	167,620	100	102.3	(27.7)	11	10.1
36-37	570,437	108	110.2	(31.6)	394,670	112	113.2	(32.7)	175,767	101	103.5	(27.8)	11	9.7
38-39	581,369	109	111.3	(31.7)	397,242	113	114.0	(32.9)	184,127	103	105.5	(28.1)	10	8.5
40-41	937,267	109	111.5	(31.4)	450,709	114	115.2	(33.4)	486,558	106	108.0	(28.9)	8	7.3
42-43	851,086	111	112.9	(31.7)	433,357	115	115.7	(33.5)	417,729	108	109.9	(29.3)	7	5.8
44-45	757,921	112	114.0	(32.0)	385,578	115	116.0	(33.7)	372,343	110	111.9	(30.0)	5	4.0
46-47	746,117	114	115.6	(32.3)	373,973	115	116.4	(33.8)	372,144	113	114.7	(30.7)	2	1.7
48-49	829,996	116	117.5	(32.9)	406,439	116	116.6	(33.9)	423,557	116	118.4	(31.9)	0	-1.8
50-51	811,891	119	120.2	(33.5)	388,572	116	117.2	(33.9)	423,319	121	123.0	(33.0)	-5	-5.8
52-53	724,917	121	122.2	(34.2)	352,502	116	117.1	(34.0)	372,415	125	127.0	(33.7)	-9	-9.8
54-55	678,462	122	123.6	(34.7)	325,196	116	117.0	(34.0)	353,266	128	129.6	(34.2)	-12	-12.6
56-57	548,884	123	123.9	(34.8)	268,104	116	116.7	(33.9)	280,780	129	130.8	(34.2)	-13	-14.0
58-59	469,870	122	123.9	(34.8)	227,833	115	116.1	(33.8)	242,037	129	131.1	(34.2)	-14	-15.0
60-61	436,364	122	123.4	(34.9)	217,463	115	115.7	(33.7)	218,901	129	131.0	(34.4)	-14	-15.3
62-63	417,442	122	123.1	(34.8)	207,571	115	115.3	(33.4)	209,871	129	130.8	(34.4)	-14	-15.5
64-65	315,933	121	122.3	(34.7)	158,935	114	114.6	(33.3)	156,998	128	130.1	(34.3)	-14	-15.4
66-67	325,424	120	121.7	(34.8)	160,023	113	113.9	(33.3)	165,401	128	129.3	(34.5)	-15	-15.4
68-69	341,410	120	121.1	(34.7)	168,480	112	113.2	(33.1)	172,930	127	128.8	(34.6)	-15	-15.6
70-71	257,877	119	120.7	(34.9)	126,184	112	112.8	(33.3)	131,693	127	128.2	(34.7)	-15	-15.4
72-73	211,973	119	120.4	(34.8)	102,586	112	112.5	(32.9)	109,387	126	127.8	(34.9)	-14	-15.3
74-75	173,801	119	120.3	(34.9)	82,089	111	112.4	(33.0)	91,712	125	127.4	(35.1)	-14	-15.1
76-77	126,103	119	120.5	(34.8)	57,223	111	112.6	(32.9)	68,880	125	127.0	(35.0)	-14	-14.4
78-79	86,305	119	120.5	(34.9)	36,736	111	112.2	(32.7)	49,569	125	126.7	(35.2)	-14	-14.5
80-81	56,623	118	120.4	(34.8)	23,429	110	111.8	(32.1)	33,194	125	126.5	(35.3)	-15	-14.7
82-83	38,161	118	119.9	(34.5)	15,744	110	111.5	(32.1)	22,417	124	125.8	(34.8)	-14	-14.2
84-85	21,901	116	118.6	(35.0)	9,230	109	110.8	(32.3)	12,671	122	124.2	(35.9)	-13	-13.4
86-99	29,224	114	116.3	(34.2)	12,134	107	109.2	(31.7)	17,090	119	121.2	(35.0)	-12	-12.0

LDL-C, low density lipoprotein cholesterol; SD, standard deviation.

[a] Concentration in women minus concentration in men.

Confidence interval of mean LDL-cholesterol levels in each sex and age group can be calculated by $1.96 \times SD/\sqrt{n}$

The *p* values which were calculated by T-test between sexes, were <0.001 for each age group including those aged 22-23 years.

To convert cholesterol from mg/dL to mmol/L, multiply by 0.02586.

Table S3. HRs[a] for mortality from CVD and its subtypes across 11 LDL-C categories (Including numerical version of Figure 4).

CVD subtypes	LDL -C		No. of Deaths	Crude rate per 10^6	Sex, and age adjusted[b]		Multivariable adjusted[c]	
	mmol/L	mg/dL			p-value	HR (95% CI)	p-value	HR (95% CI)
CVD	<1.42	<55	3,217	1,023	<0.001	1.61 (1.55-1.68)	<0.001	1.33 (1.28-1.38)
	1.42-1.80	55-69	4,365	696	<0.001	1.29 (1.25-1.33)	<0.001	1.19 (1.15-1.23)
	1.81-2.19	70-84	8,309	603	<0.001	1.13 (1.11-1.17)	<0.001	1.09 (1.06-1.12)
	2.20-2.58	85-99	12,748	594	0.037	1.03 (1.00-1.05)	0.265	1.01 (0.99-1.04)
	2.59-2.96	100-114	15,770	641		1.00 (Reference)		1.00 (Reference)
	2.97-3.35	115-129	15,922	704	0.170	1.02 (0.99-1.04)	0.103	1.02 (1.00-1.04)
	3.36-3.74	130-144	12,763	753	0.487	1.01 (0.99-1.03)	0.476	1.01 (0.99-1.03)
	3.75-4.13	145-159	9,072	830	<0.001	1.05 (1.03-1.08)	<0.001	1.05 (1.02-1.08)
	4.14-4.52	160-174	5,737	940	<0.001	1.15 (1.11-1.18)	<0.001	1.13 (1.09-1.16)
	4.53-4.90	175-189	3,126	1,013	<0.001	1.20 (1.15-1.25)	<0.001	1.17 (1.12-1.21)
	≥4.91	≥190	3,315	1,242	<0.001	1.43 (1.38-1.48)	<0.001	1.34 (1.29-1.40)
Hypertension	<1.42	<55	199	63	<0.001	1.49 (1.28-1.73)	0.003	1.26 (1.08-1.47)
	1.42-1.80	55-69	335	53	<0.001	1.40 (1.24-1.58)	<0.001	1.32 (1.17-1.49)
	1.81-2.19	70-84	587	43	0.027	1.12 (1.01-1.24)	0.107	1.09 (0.98-1.20)
	2.20-2.58	85-99	934	44	0.604	1.02 (0.94-1.11)	0.685	1.02 (0.93-1.11)
	2.59-2.96	100-114	1,174	48		1.00 (Reference)		1.00 (Reference)
	2.97-3.35	115-129	1,110	49	0.149	0.94 (0.87-1.02)	0.160	0.94 (0.87-1.02)
	3.36-3.74	130-144	942	56	0.397	0.96 (0.88-1.05)	0.358	0.96 (0.88-1.05)
	3.75-4.13	145-159	646	59	0.343	0.95 (0.87-1.05)	0.287	0.95 (0.86-1.05)
	4.14-4.52	160-174	399	65	0.853	0.99 (0.88-1.11)	0.575	0.97 (0.86-1.08)
	4.53-4.90	175-189	222	72	0.672	1.03 (0.89-1.19)	0.954	1.00 (0.86-1.15)
	≥4.91	≥190	244	91	0.003	1.24 (1.08-1.42)	0.036	1.16 (1.01-1.33)
Ischemic heart disease	<1.42	<55	764	243	<0.001	1.48 (1.37-1.60)	0.017	1.10 (1.02-1.19)
	1.42-1.80	55-69	946	151	0.005	1.11 (1.03-1.19)	0.746	0.99 (0.92-1.06)
	1.81-2.19	70-84	1,863	135	0.479	1.02 (0.97-1.08)	0.287	0.97 (0.92-1.03)
	2.20-2.58	85-99	3,073	143	0.922	1.00 (0.96-1.05)	0.642	0.99 (0.94-1.04)
	2.59-2.96	100-114	3,847	156		1.00 (Reference)		1.00 (Reference)
	2.97-3.35	115-129	4,158	184	<0.001	1.10 (1.05-1.15)	<0.001	1.10 (1.05-1.15)
	3.36-3.74	130-144	3,462	204	<0.001	1.15 (1.10-1.20)	<0.001	1.14 (1.09-1.20)
	3.75-4.13	145-159	2,662	244	<0.001	1.32 (1.26-1.39)	<0.001	1.30 (1.23-1.36)
	4.14-4.52	160-174	1,666	273	<0.001	1.45 (1.37-1.53)	<0.001	1.39 (1.31-1.47)
	4.53-4.90	175-189	957	310	<0.001	1.62 (1.51-1.74)	<0.001	1.53 (1.42-1.64)
	≥4.91	≥190	1,098	411	<0.001	2.14 (2.00-2.29)	<0.001	1.92 (1.80-2.06)
Myocardial infarction	<1.42	<55	551	175	<0.001	1.45 (1.32-1.59)	0.138	1.07 (0.98-1.18)
	1.42-1.80	55-69	717	114	0.001	1.14 (1.05-1.24)	0.637	1.02 (0.94-1.11)
	1.81-2.19	70-84	1,357	98	0.689	1.01 (0.95-1.08)	0.275	0.96 (0.90-1.03)
	2.20-2.58	85-99	2,266	106	0.786	1.01 (0.95-1.06)	0.847	0.99 (0.94-1.05)

CVD subtypes	LDL -C		No. of Deaths	Crude rate per 10^6	Sex, and age adjusted[b]		Multivariable adjusted[c]	
	mmol/L	mg/dL			p-value	HR (95% CI)	p-value	HR (95% CI)
	2.59-2.96	100-114	2,825	115		1.00 (Reference)		1.00 (Reference)
	2.97-3.35	115-129	3,117	138	<0.001	1.12 (1.06-1.18)	<0.001	1.12 (1.06-1.18)
	3.36-3.74	130-144	2,622	155	<0.001	1.18 (1.12-1.25)	<0.001	1.17 (1.11-1.24)
	3.75-4.13	145-159	2,010	184	<0.001	1.36 (1.28-1.44)	<0.001	1.33 (1.25-1.40)
	4.14-4.52	160-174	1,269	208	<0.001	1.50 (1.40-1.60)	<0.001	1.43 (1.34-1.53)
	4.53-4.90	175-189	724	235	<0.001	1.67 (1.53-1.81)	<0.001	1.56 (1.44-1.70)
	≥4.91	≥190	849	318	<0.001	2.25 (2.08-2.43)	<0.001	2.01 (1.86-2.17)
Stroke	<1.42	<55	1,402	446	<0.001	1.72 (1.62-1.82)	<0.001	1.44 (1.36-1.53)
	1.42-1.80	55-69	1,898	303	<0.001	1.36 (1.29-1.43)	<0.001	1.26 (1.20-1.33)
	1.81-2.19	70-84	3,584	260	<0.001	1.19 (1.14-1.23)	<0.001	1.14 (1.09-1.19)
	2.20-2.58	85-99	5,196	242	0.709	1.01 (0.97-1.04)	0.753	0.99 (0.96-1.03)
	2.59-2.96	100-114	6,585	267		1.00 (Reference)		1.00 (Reference)
	2.97-3.35	115-129	6,457	285	0.238	0.98 (0.95-1.01)	0.372	0.98 (0.95-1.02)
	3.36-3.74	130-144	5,068	299	0.003	0.95 (0.91-0.98)	0.006	0.95 (0.92-0.99)
	3.75-4.13	145-159	3,461	317	0.006	0.94 (0.91-0.98)	0.008	0.95 (0.91-0.99)
	4.14-4.52	160-174	2,183	358	0.449	1.02 (0.97-1.07)	0.707	1.01 (0.96-1.06)
	4.53-4.90	175-189	1,099	356	0.498	0.98 (0.92-1.04)	0.226	0.96 (0.90-1.02)
	≥4.91	≥190	1,152	432	<0.001	1.14 (1.07-1.21)	0.009	1.09 (1.02-1.16)
Hemorrhagic stroke	<1.42	<55	677	215	<0.001	2.11 (1.94-2.30)	<0.001	1.77 (1.62-1.93)
	1.42-1.80	55-69	915	146	<0.001	1.67 (1.55-1.80)	<0.001	1.54 (1.42-1.66)
	1.81-2.19	70-84	1,566	114	<0.001	1.30 (1.22-1.38)	<0.001	1.25 (1.17-1.33)
	2.20-2.58	85-99	2,122	99	0.262	1.03 (0.98-1.09)	0.498	1.02 (0.96-1.08)
	2.59-2.96	100-114	2,625	107		1.00 (Reference)		1.00 (Reference)
	2.97-3.35	115-129	2,528	112	0.115	0.96 (0.91-1.01)	0.156	0.96 (0.91-1.02)
	3.36-3.74	130-144	1,939	114	<0.001	0.90 (0.85-0.96)	<0.001	0.90 (0.85-0.96)
	3.75-4.13	145-159	1,247	114	<0.001	0.85 (0.79-0.91)	<0.001	0.85 (0.79-0.90)
	4.14-4.52	160-174	784	129	0.023	0.91 (0.84-0.99)	0.011	0.90 (0.83-0.98)
	4.53-4.90	175-189	397	129	0.017	0.88 (0.79-0.98)	0.006	0.86 (0.78-0.96)
	≥4.91	≥190	378	142	0.192	0.93 (0.84-1.04)	0.027	0.89 (0.79-0.99)
Subarachnoid hemorrhage	<1.42	<55	176	56	<0.001	1.72 (1.47-2.03)	<0.001	1.46 (1.24-1.73)
	1.42-1.80	55-69	289	46	<0.001	1.55 (1.36-1.77)	<0.001	1.45 (1.27-1.66)
	1.81-2.19	70-84	488	35	0.008	1.16 (1.04-1.29)	0.031	1.13 (1.01-1.26)
	2.20-2.58	85-99	732	34	0.705	1.02 (0.92-1.12)	0.786	1.01 (0.92-1.12)
	2.59-2.96	100-114	915	37		1.00 (Reference)		1.00 (Reference)
	2.97-3.35	115-129	935	41	0.723	1.02 (0.93-1.11)	0.773	1.01 (0.93-1.11)
	3.36-3.74	130-144	761	45	0.711	1.02 (0.92-1.12)	0.899	1.01 (0.91-1.11)
	3.75-4.13	145-159	528	48	0.645	1.03 (0.92-1.14)	0.895	1.01 (0.90-1.12)
	4.14-4.52	160-174	324	53	0.295	1.07 (0.94-1.22)	0.537	1.04 (0.92-1.18)

CVD subtypes	LDL -C		No. of Deaths	Crude rate per 10^6	Sex, and age adjusted[b]		Multivariable adjusted[c]	
	mmol/L	mg/dL			p-value	HR (95% CI)	p-value	HR (95% CI)
	4.53-4.90	175-189	164	53	0.773	1.02 (0.87-1.21)	0.889	0.99 (0.84-1.17)
	≥ 4.91	≥190	149	56	0.804	1.02 (0.86-1.22)	0.691	0.97 (0.81-1.15)
Intracerebral hemorrhage	<1.42	<55	501	159	<0.001	2.29 (2.07-2.53)	<0.001	1.87 (1.69-2.08)
	1.42-1.80	55-69	626	100	<0.001	1.71 (1.56-1.87)	<0.001	1.56 (1.42-1.71)
	1.81-2.19	70-84	1,078	78	<0.001	1.36 (1.26-1.47)	<0.001	1.29 (1.20-1.40)
	2.20-2.58	85-99	1,390	65	0.344	1.03 (0.96-1.11)	0.634	1.02 (0.95-1.09)
	2.59-2.96	100-114	1,710	69		1.00 (Reference)		1.00 (Reference)
	2.97-3.35	115-129	1,593	70	0.040	0.93 (0.87-1.00)	0.066	0.94 (0.88-1.00)
	3.36-3.74	130-144	1,178	69	<0.001	0.85 (0.79-0.92)	<0.001	0.86 (0.80-0.92)
	3.75-4.13	145-159	719	66	<0.001	0.76 (0.70-0.83)	<0.001	0.77 (0.70-0.84)
	4.14-4.52	160-174	460	75	0.001	0.84 (0.76-0.93)	<0.001	0.84 (0.75-0.93)
	4.53-4.90	175-189	233	75	0.004	0.82 (0.71-0.94)	0.002	0.81 (0.70-0.93)
	≥ 4.91	≥190	229	86	0.155	0.90 (0.79-1.04)	0.033	0.86 (0.75-0.99)
Ischemic stroke	<1.42	<55	361	115	<0.001	1.42 (1.27-1.59)	0.005	1.18 (1.05-1.32)
	1.42-1.80	55-69	477	76	0.064	1.10 (0.99-1.21)	0.759	1.02 (0.92-1.12)
	1.81-2.19	70-84	1,017	74	0.026	1.09 (1.01-1.17)	0.243	1.05 (0.97-1.13)
	2.20-2.58	85-99	1,548	72	0.408	0.97 (0.91-1.04)	0.230	0.96 (0.90-1.03)
	2.59-2.96	100-114	2,019	82		1.00 (Reference)		1.00 (Reference)
	2.97-3.35	115-129	1,997	88	0.933	1.00 (0.94-1.06)	0.941	1.00 (0.94-1.07)
	3.36-3.74	130-144	1,659	98	0.476	1.02 (0.96-1.09)	0.393	1.03 (0.96-1.10)
	3.75-4.13	145-159	1,211	111	0.010	1.10 (1.02-1.18)	0.009	1.10 (1.02-1.18)
	4.14-4.52	160-174	767	126	<0.001	1.19 (1.10-1.30)	<0.001	1.18 (1.08-1.28)
	4.53-4.90	175-189	368	119	0.113	1.09 (0.98-1.22)	0.217	1.07 (0.96-1.20)
	≥ 4.91	≥190	421	158	<0.001	1.40 (1.26-1.55)	<0.001	1.33 (1.20-1.48)
Heart failure	<1.42	<55	201	64	<0.001	1.70 (1.46-1.98)	<0.001	1.58 (1.36-1.85)
	1.42-1.80	55-69	297	47	<0.001	1.41 (1.24-1.60)	<0.001	1.36 (1.19-1.54)
	1.81-2.19	70-84	532	39	0.009	1.15 (1.04-1.28)	0.042	1.11 (1.00-1.24)
	2.20-2.58	85-99	890	41	0.028	1.11 (1.01-1.21)	0.053	1.09 (1.00-1.19)
	2.59-2.96	100-114	1,035	42		1.00 (Reference)		1.00 (Reference)
	2.97-3.35	115-129	969	43	0.115	0.93 (0.85-1.02)	0.167	0.94 (0.86-1.03)
	3.36-3.74	130-144	748	44	0.003	0.87 (0.79-0.95)	0.008	0.88 (0.80-0.97)
	3.75-4.13	145-159	515	47	0.007	0.86 (0.78-0.96)	0.020	0.88 (0.79-0.98)
	4.14-4.52	160-174	392	64	0.093	1.11 (0.98-1.24)	0.062	1.12 (0.99-1.26)
	4.53-4.90	175-189	190	62	0.954	1.00 (0.86-1.17)	0.880	1.01 (0.87-1.18)
	≥ 4.91	≥190	209	78	0.014	1.21 (1.04-1.40)	0.014	1.21 (1.04-1.40)
Sudden cardiac death	<1.42	<55	299	95	<0.001	1.71 (1.51-1.94)	<0.001	1.38 (1.21-1.57)
	1.42-1.80	55-69	404	64	<0.001	1.39 (1.25-1.56)	<0.001	1.27 (1.13-1.42)
	1.81-2.19	70-84	779	57	<0.001	1.25 (1.15-1.37)	<0.001	1.20 (1.09-1.31)

CVD subtypes	LDL -C		No. of Deaths	Crude rate per 10^6	Sex, and age adjusted[b]		Multivariable adjusted[c]	
	mmol/L	mg/dL			p-value	HR (95% CI)	p-value	HR (95% CI)
	2.20-2.58	85-99	1,136	53	0.027	1.09 (1.01-1.18)	0.067	1.08 (0.99-1.17)
	2.59-2.96	100-114	1,300	53		1.00 (Reference)		1.00 (Reference)
	2.97-3.35	115-129	1,387	61	0.036	1.08 (1.01-1.17)	0.026	1.09 (1.01-1.18)
	3.36-3.74	130-144	1,083	64	0.118	1.07 (0.98-1.16)	0.097	1.07 (0.99-1.16)
	3.75-4.13	145-159	780	71	0.002	1.15 (1.05-1.26)	0.002	1.15 (1.05-1.25)
	4.14-4.52	160-174	472	77	<0.001	1.22 (1.10-1.35)	<0.001	1.20 (1.08-1.33)
	4.53-4.90	175-189	282	91	<0.001	1.42 (1.25-1.62)	<0.001	1.38 (1.21-1.57)
	≥4.91	≥190	255	96	<0.001	1.48 (1.30-1.70)	<0.001	1.39 (1.22-1.59)

CI, confidence interval; HR, hazard ratio; LDL-C, low density lipoprotein-cholesterol

[a] HRs were calculated by Cox models after adjustment for risk factors.

[b] Adjustment for age at baseline, and sex

[c] Adjustment for age at baseline, sex, smoking status, alcohol use, physical activity, household income, body mass index, systolic blood pressure, fasting glucose, triglyceride and high density lipoprotein-cholesterol.

To convert LDL-C from mg/dL to mmol/L, multiply by 0.02586.

Table S4. HRs[a] per each 39 mg/dL (1 mmol/L) increase in LDL-C for deaths from CVD and subtypes according to LDL-C range and sex

LDL-C range	CVD subtypes	Total			Men				Women		
		No. of death	p-value	HR (95% CI)	No. of death	p-value	HR (95% CI)	$P_{interaction}$ (sex)	No. of death	p-value	HR (95% CI)
LDL-C < 100 mg/dL											
< 2.59 mmol/L	CVD	28,639	<0.001	0.78 (0.76-0.81)	19,593	<0.001	0.78 (0.76-0.80)	0.796	9,046	<0.001	0.79 (0.75-0.83)
(Total, n=5,051,377)	Hypertension	2,055	<0.001	0.76 (0.68-0.84)	1,199	<0.001	0.74 (0.66-0.84)	0.693	856	0.003	0.78 (0.66-0.92)
(Men, n= 2,720,544)	Ischemic heart disease	6,646	<0.001	0.89 (0.85-0.95)	5,000	0.001	0.90 (0.85-0.96)	0.229	1,646	0.002	0.83 (0.74-0.93)
(Women, n= 2,330,833)	Myocardial infarction	4,891	0.004	0.91 (0.85-0.97)	3,685	0.011	0.91 (0.85-0.98)	0.625	1,206	0.063	0.88 (0.76-1.01)
	Stroke	12,080	<0.001	0.74 (0.71-0.77)	8,048	<0.001	0.73 (0.70-0.77)	0.286	4,032	<0.001	0.77 (0.71-0.83)
	Hemorrhagic stroke	5,280	<0.001	0.65 (0.61-0.69)	3,432	<0.001	0.62 (0.58-0.67)	0.042	1,848	<0.001	0.71 (0.64-0.80)
	Subarachnoid hemorrhage	1,685	<0.001	0.75 (0.67-0.84)	844	<0.001	0.74 (0.64-0.86)	0.809	841	<0.001	0.72 (0.61-0.85)
	Intracerebral hemorrhage	3,595	<0.001	0.62 (0.58-0.66)	2,588	<0.001	0.59 (0.55-0.64)	0.032	1,007	<0.001	0.71 (0.61-0.83)
	Ischemic stroke	3,403	<0.001	0.86 (0.79-0.93)	2,328	0.002	0.86 (0.79-0.95)	0.948	1,075	0.050	0.86 (0.74-1.00)
	Heart failure	1,920	<0.001	0.71 (0.64-0.79)	1,116	<0.001	0.71 (0.62-0.81)	0.970	804	<0.001	0.71 (0.60-0.84)
	Sudden cardiac death	2,618	<0.001	0.81 (0.74-0.88)	2,016	<0.001	0.79 (0.71-0.87)	0.402	602	0.156	0.86 (0.71-1.06)
LDL-C 100-300 mg/dL											
2.59-7.76 mmol/L	CVD	65,656	<0.001	1.10 (1.09-1.11)	36,439	<0.001	1.16 (1.14-1.18)	<0.001	29,217	<0.001	1.04 (1.02-1.05)
(Total, n=9,830,896)	Hypertension	4,736	0.467	1.02 (0.97-1.06)	1,941	0.306	1.04 (0.97-1.11)	0.414	2,795	0.984	1.00 (0.95-1.05)
(Men, n= 5,117,327)	Ischemic heart disease	17,827	<0.001	1.26 (1.24-1.29)	11,517	<0.001	1.31 (1.27-1.34)	<0.001	6,310	<0.001	1.18 (1.14-1.22)
(Women, n= 4,713,569)	Myocardial infarction	13,397	<0.001	1.28 (1.25-1.31)	8,677	<0.001	1.32 (1.28-1.36)	<0.001	4,720	<0.001	1.20 (1.15-1.24)
	Stroke	25,994	0.266	1.01 (0.99-1.03)	13,452	<0.001	1.05 (1.02-1.08)	<0.001	12,542	0.101	0.98 (0.96-1.00)
	Hemorrhagic stroke	9,893	<0.001	0.93 (0.90-0.96)	4,800	0.026	0.95 (0.91-0.99)	0.216	5,093	<0.001	0.91 (0.88-0.95)
	Subarachnoid hemorrhage	3,773	0.935	1.00 (0.96-1.05)	1,421	0.798	1.01 (0.93-1.10)	0.505	2,352	0.427	0.98 (0.92-1.04)
	Intracerebral hemorrhage	6,120	<0.001	0.90 (0.86-0.93)	3,379	0.007	0.93 (0.88-0.98)	0.088	2,741	<0.001	0.86 (0.82-0.91)

LDL-C range	CVD subtypes	Total			Men				Women		
		No. of death	p-value	HR (95% CI)	No. of death	p-value	HR (95% CI)	$P_{interaction}$ (sex)	No. of death	p-value	HR (95% CI)
	Ischemic stroke	8,439	<0.001	1.11 (1.07-1.14)	4,572	<0.001	1.16 (1.11-1.21)	0.002	3,867	0.014	1.06 (1.01-1.10)
	Heart failure	4,054	0.034	1.05 (1.00-1.10)	1,701	0.047	1.08 (1.00-1.16)	0.364	2,353	0.252	1.03 (0.98-1.09)
	Sudden cardiac death	5,554	<0.001	1.13 (1.08-1.17)	3,591	<0.001	1.18 (1.13-1.24)	<0.001	1,963	0.429	1.02 (0.96-1.09)
LDL-C ≤ 300 mg/dL											
≤ 7.76 mmol/L	CVD	94,295	0.011	1.01 (1.00-1.02)	56,032	<0.001	1.03 (1.02-1.04)	<0.001	38,263	<0.001	0.98 (0.97-0.99)
(Total, n=14,882,273)	Hypertension	6,791	<0.001	0.95 (0.93-0.98)	3,140	<0.001	0.93 (0.89-0.97)	0.163	3,651	0.068	0.97 (0.93-1.00)
(Men, n= 7,837,871)	Ischemic heart disease	24,473	<0.001	1.17 (1.16-1.19)	16,517	<0.001	1.19 (1.17-1.21)	<0.001	7,956	<0.001	1.11 (1.09-1.14)
(Women, n= 7,044,402)	Myocardial infarction	18,288	<0.001	1.19 (1.17-1.21)	12,362	<0.001	1.21 (1.18-1.23)	<0.001	5,926	<0.001	1.13 (1.10-1.16)
	Stroke	38,074	<0.001	0.94 (0.93-0.95)	21,500	<0.001	0.94 (0.93-0.96)	0.854	16,574	<0.001	0.94 (0.92-0.95)
	Hemorrhagic stroke	15,173	<0.001	0.84 (0.83-0.86)	8,232	<0.001	0.81 (0.79-0.84)	<0.001	6,941	<0.001	0.87 (0.85-0.89)
	Subarachnoid hemorrhage	5,458	<0.001	0.93 (0.90-0.96)	2,265	<0.001	0.92 (0.87-0.96)	0.972	3,193	<0.001	0.92 (0.88-0.95)
	Intracerebral hemorrhage	9,715	<0.001	0.80 (0.79-0.82)	5,967	<0.001	0.78 (0.75-0.80)	0.003	3,748	<0.001	0.84 (0.81-0.87)
	Ischemic stroke	11,842	<0.001	1.05 (1.03-1.07)	6,900	<0.001	1.07 (1.05-1.10)	0.016	4,942	0.191	1.02 (0.99-1.05)
	Heart failure	5,974	<0.001	0.93 (0.90-0.96)	2,817	<0.001	0.92 (0.88-0.96)	0.387	3,157	0.003	0.94 (0.90-0.98)
	Sudden cardiac death	8,172	0.389	1.01 (0.99-1.04)	5,607	0.401	1.01 (0.98-1.04)	0.151	2,565	0.244	0.97 (0.93-1.02)

CI, confidence interval; HR, hazard ratio; LDL-C, low density lipoprotein-cholesterol;

[a] HRs were calculated by Cox models, after adjustment for age at baseline, sex, smoking status, alcohol use, physical activity, household income, body mass index, systolic blood pressure, fasting glucose, triglyceride, and high density lipoprotein-cholesterol.

To convert LDL-C from mg/dL to mmol/L, multiply by 0.02586

Table S5. HRs[a] per each 39 mg/dL (1 mmol/L) increase in LDL-C for deaths from CVD and subtypes according to LDL-C range and age

CVD subtypes (ICD10)	Age group, Years	LDL-C<100 mg/dL (n=5,051,377)				100-300 mg/dL (n=9,830,896)				LDL-C ≤ 300 mg/dL (n=14,882,273)			
		No. of death	p-value	HR (95% CI)	$P_{interaction}$ (age)	No. of death	p-value	HR (95% CI)	$P_{interaction}$ (age)	No. of death	p-value	HR (95% CI)	$P_{interaction}$ (age)
CVD	18-99	28,639	<0.001	0.78 (0.76-0.81)		65,656	<0.001	1.10 (1.09-1.11)		94,295	0.011	1.01 (1.00-1.02)	
	18-44	1,906	<0.001	0.76 (0.69-0.84)	<0.001	3,577	<0.001	1.24 (1.18-1.30)	<0.001	5,483	<0.001	1.11 (1.07-1.14)	<0.001
	45-64	7,028	<0.001	0.73 (0.69-0.77)		15,433	<0.001	1.14 (1.11-1.17)		22,461	0.304	1.01 (0.99-1.02)	
	65-74	9,715	<0.001	0.80 (0.76-0.83)		22,516	<0.001	1.10 (1.08-1.13)		32,231	0.036	1.01 (1.00-1.03)	
	75-84	8,166	<0.001	0.85 (0.81-0.90)		20,234	<0.001	1.06 (1.04-1.08)		28,400	0.921	1.00 (0.99-1.01)	
	85-99	1,824	0.005	0.85 (0.75-0.95)		3,896	0.941	1.00 (0.95-1.05)		5,720	0.019	0.96 (0.93-0.99)	
Hypertension	18-99	2,055	<0.001	0.76 (0.68-0.84)		4,736	0.467	1.02 (0.97-1.06)		6,791	<0.001	0.95 (0.93-0.98)	
	18-44	27	0.856	0.93 (0.41-2.10)	0.895	58	0.113	1.33 (0.93-1.90)	0.423	85	0.108	1.21 (0.96-1.53)	0.084
	45-64	275	0.020	0.74 (0.58-0.95)		498	0.927	0.99 (0.87-1.13)		773	0.010	0.90 (0.83-0.98)	
	65-74	604	<0.001	0.73 (0.61-0.87)		1,435	0.187	1.05 (0.98-1.13)		2,039	0.496	0.98 (0.93-1.03)	
	75-84	849	0.003	0.78 (0.66-0.92)		2,126	0.971	1.00 (0.94-1.06)		2,975	0.031	0.96 (0.92-1.00)	
	85-99	300	0.282	0.85 (0.64-1.14)		619	0.664	0.97 (0.87-1.10)		919	0.033	0.92 (0.85-0.99)	
Ischemic heart disease	18-99	6,646	<0.001	0.89 (0.85-0.95)		17,827	<0.001	1.26 (1.24-1.29)		24,473	<0.001	1.17 (1.16-1.19)	
	18-44	409	0.734	1.04 (0.83-1.29)	0.653	1,194	<0.001	1.50 (1.39-1.62)	<0.001	1,603	<0.001	1.44 (1.37-1.52)	<0.001
	45-64	1,933	0.011	0.88 (0.80-0.97)		5,221	<0.001	1.35 (1.30-1.40)		7,154	<0.001	1.22 (1.19-1.25)	
	65-74	2,271	0.005	0.88 (0.80-0.96)		5,945	<0.001	1.24 (1.20-1.29)		8,216	<0.001	1.15 (1.12-1.17)	
	75-84	1,670	0.218	0.93 (0.83-1.04)		4,621	<0.001	1.16 (1.11-1.20)		6,291	<0.001	1.10 (1.07-1.13)	
	85-99	363	0.376	0.89 (0.68-1.16)		846	0.197	1.07 (0.97-1.18)		1,209	0.291	1.04 (0.97-1.11)	
Myocardial infarction	18-99	4,891	0.004	0.91 (0.85-0.97)		13,397	<0.001	1.28 (1.25-1.31)		18,288	<0.001	1.19 (1.17-1.21)	
	18-44	279	0.541	1.09 (0.83-1.42)	0.545	828	<0.001	1.51 (1.38-1.65)	<0.001	1,107	<0.001	1.45 (1.36-1.55)	<0.001
	45-64	1,422	0.142	0.92 (0.82-1.03)		4,015	<0.001	1.36 (1.31-1.42)		5,437	<0.001	1.25 (1.21-1.28)	

CVD subtypes (ICD10)	Age group, Years	LDL-C<100 mg/dL (n=5,051,377)				100-300 mg/dL (n=9,830,896)				LDL-C ≤ 300 mg/dL (n=14,882,273)			
		No. of death	p-value	HR (95% CI)	$P_{interaction}$ (age)	No. of death	p-value	HR (95% CI)	$P_{interaction}$ (age)	No. of death	p-value	HR (95% CI)	$P_{interaction}$ (age)
	65-74	1,706	0.007	0.86 (0.78-0.96)		4,618	<0.001	1.25 (1.20-1.30)		6,324	<0.001	1.16 (1.13-1.19)	
	75-84	1,233	0.466	0.95 (0.83-1.09)		3,348	<0.001	1.17 (1.12-1.23)		4,581	<0.001	1.11 (1.07-1.14)	
	85-99	251	0.697	0.94 (0.68-1.29)		588	0.031	1.14 (1.01-1.28)		839	0.130	1.06 (0.98-1.15)	
Stroke	18-99	12,080	<0.001	0.74 (0.71-0.77)		25,994	0.266	1.01 (0.99-1.03)		38,074	<0.001	0.94 (0.93-0.95)	
	18-44	863	<0.001	0.67 (0.58-0.78)	<0.001	1,286	0.074	1.08 (0.99-1.18)	0.056	2,149	0.006	0.93 (0.88-0.98)	<0.001
	45-64	2,938	<0.001	0.67 (0.62-0.72)		5,703	0.136	0.97 (0.93-1.01)		8,641	<0.001	0.87 (0.85-0.89)	
	65-74	4,253	<0.001	0.77 (0.72-0.82)		9,311	0.018	1.04 (1.01-1.07)		13,564	<0.001	0.96 (0.94-0.98)	
	75-84	3,395	<0.001	0.85 (0.78-0.92)		8,287	0.578	1.01 (0.98-1.04)		11,682	0.033	0.98 (0.96-1.00)	
	85-99	631	0.008	0.77 (0.63-0.93)		1,407	0.928	1.00 (0.93-1.09)		2,038	0.524	0.98 (0.93-1.04)	
Hemorrhagic stroke	18-99	5,280	<0.001	0.65 (0.61-0.69)		9,893	<0.001	0.93 (0.90-0.96)		15,173	<0.001	0.84 (0.83-0.86)	
	18-44	759	<0.001	0.65 (0.56-0.76)	0.009	1,067	0.363	1.05 (0.95-1.15)	0.121	1,826	<0.001	0.89 (0.84-0.94)	0.002
	45-64	1,915	<0.001	0.59 (0.54-0.65)		3,526	0.003	0.93 (0.88-0.97)		5,441	<0.001	0.81 (0.79-0.84)	
	65-74	1,557	<0.001	0.66 (0.59-0.74)		3,039	<0.001	0.90 (0.86-0.96)		4,596	<0.001	0.83 (0.80-0.86)	
	75-84	932	0.011	0.82 (0.70-0.95)		2,041	0.021	0.93 (0.87-0.99)		2,973	<0.001	0.89 (0.85-0.93)	
	85-99	117	0.222	0.75 (0.48-1.19)		220	0.967	1.00 (0.82-1.23)		337	0.165	0.91 (0.80-1.04)	
Subarachnoid hemorrhage	18-99	1,685	<0.001	0.75 (0.67-0.84)		3,773	0.935	1.00 (0.96-1.05)		5,458	<0.001	0.93 (0.90-0.96)	
	18-44	438	<0.001	0.69 (0.56-0.85)	0.568	614	0.392	1.06 (0.93-1.20)	0.161	1,052	0.007	0.90 (0.84-0.97)	0.127
	45-64	726	0.017	0.81 (0.69-0.96)		1,685	0.310	0.96 (0.90-1.04)		2,411	<0.001	0.91 (0.86-0.95)	
	65-74	339	<0.001	0.66 (0.51-0.83)		927	0.322	0.95 (0.87-1.05)		1,266	0.002	0.90 (0.85-0.96)	
	75-84	164	0.131	0.76 (0.53-1.09)		507	0.296	1.07 (0.94-1.21)		671	0.745	1.01 (0.93-1.11)	
	85-99	18	0.309	0.56 (0.18-1.71)		40	0.096	1.40 (0.94-2.09)		58	0.581	1.09 (0.81-1.46)	
Intracerebral hemorrhage	18-99	3,595	<0.001	0.62 (0.58-0.66)		6,120	<0.001	0.90 (0.86-0.93)		9,715	<0.001	0.80 (0.79-0.82)	

CVD subtypes (ICD10)	Age group, Years	LDL-C<100 mg/dL (n=5,051,377)				100-300 mg/dL (n=9,830,896)				LDL-C ≤ 300 mg/dL (n=14,882,273)			
		No. of death	p-value	HR (95% CI)	$P_{interaction}$ (age)	No. of death	p-value	HR (95% CI)	$P_{interaction}$ (age)	No. of death	p-value	HR (95% CI)	$P_{interaction}$ (age)
	18-44	321	<0.001	0.61 (0.48-0.77)	<0.001	453	0.622	1.04 (0.90-1.20)	0.356	774	0.005	0.88 (0.81-0.96)	<0.001
	45-64	1,189	<0.001	0.51 (0.45-0.57)		1,841	0.005	0.90 (0.84-0.97)		3,030	<0.001	0.76 (0.73-0.79)	
	65-74	1,218	<0.001	0.66 (0.59-0.75)		2,112	<0.001	0.88 (0.83-0.94)		3,330	<0.001	0.80 (0.77-0.83)	
	75-84	768	0.035	0.83 (0.70-0.99)		1,534	0.001	0.88 (0.81-0.95)		2,302	<0.001	0.85 (0.81-0.89)	
	85-99	99	0.373	0.80 (0.49-1.31)		180	0.441	0.91 (0.73-1.15)		279	0.077	0.88 (0.76-1.01)	
Ischemic stroke	18-99	3,403	<0.001	0.86 (0.79-0.93)		8,439	<0.001	1.11 (1.07-1.14)		11,842	<0.001	1.05 (1.03-1.07)	
	18-44	40	0.133	0.60 (0.31-1.17)	0.470	105	0.045	1.31 (1.01-1.70)	0.011	145	0.021	1.24 (1.03-1.48)	0.040
	45-64	469	0.282	0.90 (0.73-1.09)		1,132	0.022	1.10 (1.01-1.20)		1,601	0.042	1.06 (1.00-1.12)	
	65-74	1,317	0.137	0.91 (0.80-1.03)		3,200	<0.001	1.17 (1.11-1.23)		4,517	<0.001	1.09 (1.05-1.12)	
	75-84	1,300	0.022	0.86 (0.75-0.98)		3,334	0.007	1.07 (1.02-1.12)		4,634	0.079	1.03 (1.00-1.07)	
	85-99	277	0.023	0.72 (0.54-0.96)		668	0.634	0.97 (0.87-1.09)		945	0.900	1.00 (0.92-1.07)	
Heart failure	18-99	1,920	<0.001	0.71 (0.64-0.79)		4,054	0.034	1.05 (1.00-1.10)		5,974	<0.001	0.93 (0.90-0.96)	
	18-44	33	0.032	0.45 (0.22-0.94)	0.399	38	0.071	1.48 (0.97-2.28)	0.043	71	0.351	0.87 (0.66-1.16)	0.109
	45-64	222	<0.001	0.60 (0.45-0.79)		403	0.427	1.06 (0.92-1.22)		625	0.032	0.91 (0.83-0.99)	
	65-74	569	0.003	0.75 (0.63-0.91)		1,253	0.011	1.11 (1.02-1.20)		1,822	0.431	0.98 (0.93-1.03)	
	75-84	837	<0.001	0.72 (0.61-0.85)		1,879	0.176	1.05 (0.98-1.12)		2,716	0.004	0.94 (0.90-0.98)	
	85-99	259	0.173	0.80 (0.59-1.10)		481	0.093	0.89 (0.77-1.02)		740	<0.001	0.85 (0.78-0.93)	
Sudden cardiac death	18-99	2,618	<0.001	0.81 (0.74-0.88)		5,554	<0.001	1.13 (1.08-1.17)		8,172	0.389	1.01 (0.99-1.04)	
	18-44	303	0.028	0.76 (0.59-0.97)	0.523	522	0.009	1.19 (1.04-1.35)	0.011	825	0.200	1.05 (0.97-1.14)	0.177
	45-64	848	<0.001	0.76 (0.66-0.87)		1,773	<0.001	1.22 (1.14-1.30)		2,621	0.094	1.04 (0.99-1.08)	
	65-74	839	0.019	0.83 (0.71-0.97)		1,853	0.012	1.09 (1.02-1.17)		2,692	0.931	1.00 (0.96-1.04)	
	75-84	529	0.421	0.92 (0.75-1.13)		1,209	0.445	1.03 (0.95-1.12)		1,738	0.249	0.97 (0.92-1.02)	

CVD subtypes (ICD10)	Age group, Years	LDL-C<100 mg/dL (n=5,051,377)				100-300 mg/dL (n=9,830,896)				LDL-C ≤ 300 mg/dL (n=14,882,273)			
		No. of death	p-value	HR (95% CI)	$P_{interaction}$ (age)	No. of death	p-value	HR (95% CI)	$P_{interaction}$ (age)	No. of death	p-value	HR (95% CI)	$P_{interaction}$ (age)
	85-99	99	0.958	0.99 (0.59-1.66)		197	0.712	0.96 (0.77-1.19)		296	0.340	0.94 (0.82-1.07)	

CI, confidence interval; HR, hazard ratio; LDL-C, low density lipoprotein-cholesterol;

[a] HRs were calculated by Cox models, after adjustment for age at baseline, sex, smoking status, alcohol use, physical activity, household income, body mass index, systolic blood pressure, fasting glucose, triglyceride, and high density lipoprotein-cholesterol.

To convert LDL-C from mg/dL to mmol/L, multiply by 0.02586

Table S6. HRs[a] per each 39 mg/dL (1 mmol/L) increase in LDL-C for deaths from CVD and subtypes in the LDL-C range 130-300 mg/dL

LDL-C range	CVD subtypes	Total			Men				Women		
	CVD subtypes	No. of death	p-value	HR (95% CI)	No. of death	p-value	HR (95% CI)	$P_{interaction}$ (sex)	No. of death	p-value	HR (95% CI)
LDL-C 130-300 mg/dL											
2.59-7.76 mmol/L	CVD	33,964	<0.001	1.16 (1.14-1.18)	17,395	<0.001	1.26 (1.22-1.29)	<0.001	16,569	<0.001	1.08 (1.06-1.11)
(Total, n=4,493,077)	Hypertension	2,452	0.113	1.06 (0.99-1.13)	869	0.003	1.20 (1.06-1.35)	0.012	1,583	0.966	1.00 (0.92-1.08)
	Ischemic heart disease	9,822	<0.001	1.30 (1.26-1.35)	5,983	<0.001	1.36 (1.31-1.42)	<0.001	3,839	<0.001	1.22 (1.17-1.28)
	Myocardial infarction	7,455	<0.001	1.31 (1.26-1.36)	4,551	<0.001	1.36 (1.30-1.43)	0.008	2,904	<0.001	1.23 (1.17-1.30)
	Stroke	12,952	<0.001	1.07 (1.04-1.10)	6,054	<0.001	1.15 (1.10-1.20)	<0.001	6,898	0.285	1.02 (0.98-1.06)
	Hemorrhagic stroke	4,740	0.886	1.00 (0.95-1.05)	2,069	0.277	1.05 (0.96-1.13)	0.123	2,671	0.266	0.96 (0.90-1.03)
	Subarachnoid hemorrhage	1,923	0.936	1.00 (0.93-1.09)	666	0.659	0.97 (0.84-1.12)	0.654	1,257	0.887	1.01 (0.92-1.11)
	Intracerebral hemorrhage	2,817	0.972	1.00 (0.94-1.07)	1,403	0.095	1.09 (0.99-1.20)	0.022	1,414	0.114	0.93 (0.85-1.02)
	Ischemic stroke	4,423	<0.001	1.13 (1.08-1.19)	2,188	<0.001	1.20 (1.11-1.29)	0.054	2,235	0.016	1.08 (1.02-1.16)
	Heart failure	2,050	<0.001	1.18 (1.10-1.27)	738	<0.001	1.30 (1.15-1.47)	0.089	1,312	0.003	1.14 (1.05-1.24)
	Sudden cardiac death	2,867	<0.001	1.16 (1.09-1.23)	1,745	<0.001	1.25 (1.16-1.36)	0.003	1,122	0.475	1.04 (0.94-1.14)

CI, confidence interval; HR, hazard ratio; LDL-C, low density lipoprotein-cholesterol;

[a] HRs were calculated by Cox models, after adjustment for age at baseline, sex, smoking status, alcohol use, physical activity, household income, body mass index, systolic blood pressure, fasting glucose, triglyceride, and high density lipoprotein-cholesterol.

To convert LDL-C from mg/dL to mmol/L, multiply by 0.02586