International Journal of Epidemiology, 2022, 1178–1189
https://doi.org/10.1093/ije/dyac029
Advance Access Publication Date: 26 February 2022
Original article

Cardiovascular Disease

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

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Received 26 October 2021; Editorial decision 27 January 2022; Accepted 3 February 2022

Abstract

Background: Limited information is available on detailed sex/age-specific associations between low-density lipoprotein cholesterol (LDL-C) and cardiovascular disease (CVD) mortality and 'the optimal range' associated with the lowest CVD mortality in the general population.
Methods: Korean adults ($N = 14\,884\,975$) who received routine health screenings during 2009–2010 were followed until 2018 for CVD mortality.
Results: During 8.8 years (mean) of follow-up, 94 344 individuals died from CVD. LDL-C had U-curve associations with mortality from CVD and its subtypes, except haemorrhagic stroke. Optimal range was 90–149 mg/dL for CVD; 70–114 for ischaemic heart disease; 85–129 for ischaemic stroke; ≥85 for subarachnoid haemorrhage; ≥130 for intracerebral haemorrhage; 115–159 for hypertension and heart failure; and 100–144 for sudden cardiac death. Assuming linear associations between 100 and 300 mg/dL, LDL-C was positively associated with CVD mortality [hazard ratio (HR) per 39-mg/dL (1-mmol/L) higher LDL-C = 1.10], largely due to ischaemic heart disease (HR = 1.26), followed by sudden cardiac death (HR = 1.13), ischaemic stroke (HR = 1.11) and heart failure (HR = 1.05). Intracerebral haemorrhage (HR = 0.90), but not subarachnoid haemorrhage, had inverse associations. Women and older adults had weaker positive associations than men and younger adults ($P_{interaction} < 0.001$ for both sex and age). Individuals aged 75–84 years had modest positive associations with CVD mortality, especially ischaemic heart disease and ischaemic stroke.

Conclusion: LDL-C had U-curve associations for CVD mortality. The associations and optimal ranges differed across CVD subtypes. Women and older adults had weaker positive associations than men and younger adults. Positive associations with ischaemic heart disease and ischaemic stroke were maintained in adults aged 75–84 years.

Key words: Low density lipoprotein cholesterol, cohort studies, heart disease, stroke, mortality

Key Messages

- Both low and high levels of low-density lipoprotein cholesterol were associated with increased mortality from cardiovascular disease (CVD), including ischaemic heart disease, ischaemic stroke, heart failure and sudden cardiac death, in the general population.
- The optimal range was 2.32–3.85 mmol/L (90–149 mg/dL) for overall CVD, whereas the range differed among CVD subtypes.
- Women had weaker positive associations above the optimal range than men.
- The positive associations above the optimal range with ischaemic heart disease and ischaemic stroke were maintained until 75–84 years of age, although they became weaker with advancing age.

Introduction

Low-density lipoprotein cholesterol (LDL-C)-lowering therapy is known to reduce cardiovascular disease (CVD) events and mortality in individuals with manifest CVD based on randomized–controlled trials (RCTs).[1] For primary prevention, most meta-analyses of RCTs have reported benefits,[2,3] but uncertainties remain, particularly for women, older adults and Asian populations.[3–8] Previous observational studies provided inconsistent results on the associations between LDL-C and CVD mortality,[9–16] reporting positive,[10–12] U-curve[13–15] and neutral associations.[16]

Precise and reliable estimates of the sex- and age-specific associations of LDL-C with CVD mortality in population-based cohort studies are important to address these knowledge gaps, pending further evidence from RCTs.[4] Meanwhile, current evidence on the association of LDL-C with CVD is centred on ischaemic heart disease (IHD) and ischaemic stroke.[9–12] The relationships between LDL-C and other subtypes of CVD, such as heart failure, sudden cardiac death (SCD) and subarachnoid haemorrhage (SAH), have rarely been examined.

Through a large prospective cohort study among ~15 million participants without known CVD/cancer and lipid-lowering medication use, we investigated the associations between LDL-C levels and mortality from CVD and its subtypes according to sex and age, and examined the LDL-C levels associated with the lowest CVD mortality ('the optimal range').

Methods

Study population and follow-up

The National Health Insurance Service (NHIS) provides mandatory health insurance and biennial health screening for 97% of the Korean population. From the 17 733 108 individuals aged 18–99 years who underwent routine health examinations from 2009 to 2010, persons with missing information ($n = 472\,530$) and known heart disease/stroke/cancer ($n = 1\,401\,077$) were excluded. After excluding 974 526 persons prescribed lipid-lowering agents, the remaining 14 884 975 participants were followed until 31 December 2018 through the national death statistics for CVD mortality (Supplementary Figure S1, available as Supplementary data at *IJE* online).

The International Classification of Diseases-10th Revision was used to define death from CVD (I00–I99) and subtypes of CVD were classified into hypertensive disease (I10–I15), IHD (I20–I25), acute myocardial infarction (AMI, I21), total stroke (I60–I69), haemorrhagic stroke (I60–I62), SAH (I60), intracerebral haemorrhage (ICH, I61–I62), ischaemic stroke (I63), heart failure (I50) and SCD (I46).

The Institutional Review Board of Catholic Kwandong University approved the study and informed consent was waived because the NHIS provided anonymized data.

Data collection

Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglyceride and glucose levels were assayed using fasting serum samples by enzymatic methods. LDL-C was calculated by the Friedewald equation. Systolic blood pressure (SBP) was measured in a seated position after ≥5 min of rest. Body mass index (BMI) was calculated based on weight and height measurements (kg/m^2).[17] Smoking history, alcohol use, physical activity and known heart diseases/stroke/cancer were assessed by questionnaire. The data collection process followed a standard government-established protocol. External quality assessments for clinical chemistry were regularly performed.[18]

Statistical analysis

More details are described in the Supplemental Material (available as Supplementary data at *IJE* online). LDL-C levels were categorized into 17, 11 or 6 groups. 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. Analyses using a restricted cubic spline transformation of LDL-C with five pre-defined knots were performed to examine non-linear associations.

The hazard ratios (HRs) for mortality were calculated using Cox models stratified by baseline age.[17,19,20] In the multivariable model, the following variables were adjusted: age, sex, income status, smoking status, alcohol use frequency, physical activity, SBP, fasting glucose, BMI, log-transformed triglyceride and HDL-C levels. Based on qualitative observations of the curvilinear association, the intervals of 44 mg/dL (roughly 1.1 mmol/L) with the lowest risk (the lowest unweighted geometric mean of HRs in three consecutive LDL-C categories in the 11-group analysis) were identified as optimal. An analysis excluding the first 3 years of follow-up was performed. In the Cox model, the cause-specific hazard method was used to handle competing risks; individuals who experienced other causes of death or reached the end of follow-up were treated as censored. Schoenfeld residuals were used to test the proportional hazard assumption. Subgroup analyses and 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 two-sided. All analyses used SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

During a mean 8.8 years of follow-up, 94 344 persons (56 057 men and 38 287 women) died from CVD (Supplementary Table S1, available as Supplementary data at *IJE* online). At baseline, the mean age was 46.6 ± 13.8 years, the mean LDL-C level was 114.5 ± 33.4 mg/dL (Table 1) and 9.0% of individuals had LDL-C levels of ≥160 mg/dL (Supplementary Figure S2, available as Supplementary data at *IJE* online). Higher LDL-C levels were associated with older age, female sex, never smoking, infrequent alcohol use and higher SBP, fasting glucose levels and BMI (Table 1). Women had higher LDL-C levels than men in the age groups of 18–23 and ≥48 years (Supplementary Figure S3 and Supplementary Table S2, available as Supplementary data at *IJE* online).

U-curve associations between LDL-C and CVD mortality were found and the optimal range was 90–149 mg/dL (Figure 1 and Supplementary Figure S4, available as Supplementary data at *IJE* online). Women had substantially lower excess mortality above the optimum (110–159 mg/dL) than men. The youngest group (<45 years) had the lowest optimal range (70–114 mg/dL) in the categorical analysis and U-curve associations weakened with advancing age (Figure 2 and Supplementary Figure S5, available as Supplementary data at *IJE* online). In the oldest (≥85 years), the associations of higher LDL-C levels with CVD mortality were less apparent, whereas adults aged 75–84 years had higher CVD mortality associated with LDL-C categories of ≥160 mg/dL.

For the subtypes of CVD, U-curve associations were generally found, with the exception that haemorrhagic stroke and its subtypes had L-curve associations. The optimal LDL-C range differed between subtypes of CVD (Figure 3). IHD (including AMI) had an optimal range of 70–114 mg/dL and stronger positive associations in higher LDL-C ranges than other CVD subtypes. For stroke, the optimal range was 85–129 mg/dL for ischaemic stroke, ≥85 mg/dL for SAH and ≥130 mg/dL for ICH. The optimal ranges were 115–159 mg/dL for hypertensive disease, 115–159 mg/dL for heart failure and 100–144 mg/dL for SCD. Adjustment for confounders generally yielded no substantial changes in the associations (Supplementary Table S3, available as Supplementary data at *IJE* online). A sensitivity analysis excluding the first 3 years of deaths showed no material change (Supplementary Figure S6, available as Supplementary data at *IJE* online). In the age-

Table 1 Participants' characteristics at baseline by 11 LDL-C categories

Variables	Characteristics			LDL-C < 55 mg/dL		55–69 mg/dL		70–84 mg/dL		85–99 mg/dL		100–114 mg/dL		115–129 mg/dL		130–144 mg/dL		145–159 mg/dL		160–174 mg/dL		175–189 mg/dL		≥ 190 mg/dL	
				<1.42 mmol/L		1.42–1.80 mmol/L		1.81–2.19 mmol/L		2.20–2.58 mmol/L		2.59–2.96 mmol/L		2.97–3.35 mmol/L		3.36–3.74 mmol/L		3.75–4.13 mmol/L		4.14–4.52 mmol/L		4.53–4.90 mmol/L		≥ 4.91 mmol/L	
		$N = 14\,884\,975$		$n = 358\,984$		$n = 710\,498$		$n = 1\,558\,683$		$n = 2\,423\,212$		$n = 2\,781\,543$		$n = 2\,556\,276$		$n = 1\,916\,191$		$n = 1\,236\,071$		$n = 690\,341$		$n = 349\,802$		$n = 303\,374$	
Age	years	46.6	± 13.8	44.4	± 14.4	42.0	± 14.3	42.3	± 14.1	43.9	± 13.9	45.8	± 13.7	47.6	± 13.4	49.2	± 13.1	50.5	± 12.8	51.5	± 12.5	52.3	± 12.3	53.1	± 12.2
LDL-C[a]	mg/dL	114.5	± 33.4	41.8	± 11.9	63.2	± 4.2	77.8	± 4.3	92.4	± 4.3	107.0	± 4.3	121.8	± 4.3	136.5	± 4.3	151.4	± 4.3	166.2	± 4.3	181.1	± 4.3	209.5	± 24.2
HDL-C[a]	mg/dL	55.3	± 13.8	57.6	± 21.0	57.5	± 16.4	56.8	± 15.0	56.1	± 14.1	55.3	± 13.5	54.6	± 13.0	54.2	± 12.7	53.9	± 12.4	53.9	± 12.3	54.1	± 12.3	54.4	± 12.9
Body mass index	kg/m^2	23.6	± 3.5	23.2	± 3.4	22.7	± 3.3	22.7	± 3.2	23.0	± 3.6	23.4	± 3.7	23.8	± 3.1	24.1	± 3.1	24.4	± 4.2	24.5	± 4.0	24.7	± 3.1	24.8	± 3.1
Total cholesterol[a]	mg/dL	196.1	± 36.4	150.2	± 35.6	150.9	± 24.8	160.2	± 20.6	173.0	± 18.4	187.0	± 17.2	201.5	± 16.5	216.6	± 16.3	231.8	± 16.2	247.2	± 16.4	262.9	± 16.8	292.9	± 32.1
Log-transformed TG	mg/dL	4.7	± 0.6	5.2	± 0.9	4.7	± 0.7	4.6	± 0.7	4.6	± 0.6	4.6	± 0.6	4.7	± 0.5	4.7	± 0.5	4.8	± 0.5	4.8	± 0.5	4.8	± 0.5	4.9	± 0.5
Fasting glucose[b]	mg/dL	96.5	± 22.7	99.9	± 30.3	95.1	± 23.8	94.2	± 21.5	94.6	± 21.0	95.5	± 21.2	96.6	± 21.8	97.7	± 22.6	98.7	± 23.6	99.7	± 24.8	100.8	± 26.3	103.0	± 30.2
Systolic blood pressure	mm Hg	121.9	± 15.1	123.9	± 16.0	120.4	± 15.2	119.7	± 14.9	120.1	± 14.8	121.2	± 14.8	122.2	± 14.9	123.2	± 15.0	124.0	± 15.1	124.7	± 15.3	125.2	± 15.4	126.0	± 15.8
Sex	Women	7 045 784	(47.3)	120 135	(33.5)	315 425	(44.4)	739 330	(47.4)	1 155 943	(47.7)	1 306 196	(47.0)	1 189 491	(46.5)	901 911	(47.1)	603 342	(48.8)	350 934	(50.8)	187 504	(53.6)	175 573	(57.9)
Smoking status	Never smoker	9 010 837	(60.5)	166 941	(46.5)	399 091	(56.2)	929 431	(59.6)	1 474 309	(60.8)	1 692 532	(60.8)	1 551 719	(60.7)	1 170 006	(61.1)	764 976	(61.9)	435 090	(63.0)	225 047	(64.3)	201 695	(66.5)
	Past smoker	2 038 480	(13.7)	48 640	(13.5)	86 561	(12.2)	190 800	(12.2)	313 217	(12.9)	385 422	(13.9)	371 370	(14.5)	282 363	(14.7)	180 054	(14.6)	96 906	(14.0)	46 950	(13.4)	36 197	(11.9)
	Current smoker	3 763 277	(25.3)	142 123	(39.6)	221 473	(31.2)	430 489	(27.6)	623 533	(25.7)	689 581	(24.8)	620 722	(24.3)	454 538	(23.7)	285 128	(23.1)	155 104	(22.5)	76 316	(21.8)	64 270	(21.2)
	Missing	72 381	(0.5)	1280	(0.4)	3373	(0.5)	7963	(0.5)	12 153	(0.5)	14 008	(0.5)	12 465	(0.5)	9284	(0.5)	5913	(0.5)	3241	(0.5)	1489	(0.4)	1212	(0.4)
Alcohol use,	<1 day/week	7 508 864	(50.4)	120 594	(33.6)	290 643	(40.9)	697 534	(44.8)	1 150 266	(47.5)	1 383 833	(49.8)	1 324 512	(51.8)	1 033 884	(54.0)	696 878	(56.4)	404 447	(58.6)	213 128	(60.9)	193 145	(63.7)
Frequency	1–2 days/week	5 249 644	(35.3)	135 447	(37.7)	279 866	(39.4)	606 684	(38.9)	914 092	(37.7)	1 008 952	(36.3)	890 701	(34.8)	637 564	(33.3)	390 216	(31.6)	207 677	(30.1)	99 164	(28.3)	79 281	(26.1)
	3–4 days/week	1 419 202	(9.5)	64 099	(17.9)	92 853	(13.1)	170 278	(10.9)	241 104	(9.9)	261 040	(9.4)	229 082	(9.0)	164 007	(8.6)	99 467	(8.0)	51 966	(7.5)	25 074	(7.2)	20 232	(6.7)
	5–7 days/week	573 560	(3.9)	36 608	(10.2)	41 393	(5.8)	70 369	(4.5)	95 083	(3.9)	101 865	(3.7)	88 479	(3.5)	63 213	(3.3)	38 440	(3.1)	20 236	(2.9)	9548	(2.7)	8326	(2.7)
	Missing	133 705	(0.9)	2236	(0.6)	5743	(0.8)	13 818	(0.9)	22 667	(0.9)	25 853	(0.9)	23 502	(0.9)	17 523	(0.9)	11 070	(0.9)	6015	(0.9)	2888	(0.8)	2390	(0.8)
Physical activity	No	8 435 887	(56.7)	206 815	(57.6)	406 151	(57.2)	884 616	(56.8)	1 367 037	(56.4)	1 562 858	(56.2)	1 438 520	(56.3)	1 082 016	(56.5)	704 370	(57.0)	398 048	(57.7)	203 899	(58.3)	181 557	(59.8)
	1 day/week	2 122 187	(14.3)	52 522	(14.6)	106 686	(15.0)	234 945	(15.1)	360 792	(14.9)	405 801	(14.6)	361 452	(14.1)	264 030	(13.8)	165 690	(13.4)	89 575	(13.0)	44 123	(12.6)	36 571	(12.1)
	≥2 days/week	4 326 901	(29.1)	99 647	(27.8)	197 661	(27.8)	439 122	(28.2)	695 383	(28.7)	812 884	(29.2)	756 304	(29.6)	570 145	(29.8)	366 011	(29.6)	202 718	(29.4)	101 780	(29.1)	85 246	(28.1)
Age group, years	18–44	6 970 970	(46.8)	195 430	(54.4)	439 363	(61.8)	953 446	(61.2)	1 365 299	(56.3)	1 386 955	(49.9)	1 114 517	(43.6)	728 219	(38.0)	412 622	(33.4)	206 469	(29.9)	94 686	(27.1)	73 964	(24.4)
	45–64	6 182 656	(41.5)	124 545	(34.7)	207 719	(29.2)	470 358	(30.2)	827 677	(34.2)	1 094 705	(39.4)	1 133 307	(44.3)	930 898	(48.6)	642 868	(52.0)	376 381	(54.5)	198 194	(56.7)	176 004	(58.0)
	65–74	1 348 019	(9.1)	30 830	(8.6)	48 733	(6.9)	103 312	(6.6)	177 086	(7.3)	232 089	(8.3)	241 127	(9.4)	201 893	(10.5)	142 191	(11.5)	84 619	(12.3)	44 521	(12.7)	41 618	(13.7)
	75–84	350 581	(2.4)	7442	(2.1)	13 170	(1.9)	28 368	(1.8)	47 999	(2.0)	61 772	(2.2)	61 846	(2.4)	50 812	(2.7)	35 523	(2.9)	21 217	(3.1)	11 501	(3.3)	10 931	(3.6)
	85–99	32 749	(0.2)	737	(0.2)	1513	(0.2)	3199	(0.2)	5151	(0.2)	6022	(0.2)	5479	(0.2)	4369	(0.2)	2867	(0.2)	1655	(0.2)	900	(0.3)	857	(0.3)
Income status, quartile	1 (low-income)	3 070 463	(20.6)	82 611	(23.0)	162 091	(22.8)	341 760	(21.9)	510 474	(21.1)	568 211	(20.4)	510 616	(20.0)	378 161	(19.7)	243 994	(19.7)	137 496	(19.9)	71 203	(20.4)	63 846	(21.0)
	2	3 234 389	(21.7)	92 855	(25.9)	184 925	(26.0)	390 222	(25.0)	567 093	(23.4)	606 436	(21.8)	525 614	(20.6)	375 742	(19.6)	236 860	(19.2)	130 082	(18.8)	65 454	(18.7)	59 106	(19.5)
	3	3 998 276	(26.9)	98 361	(27.4)	193 254	(27.2)	426 495	(27.4)	663 430	(27.4)	752 544	(27.1)	683 089	(26.7)	507 371	(26.5)	323 809	(26.2)	179 726	(26.0)	91 304	(26.1)	78 893	(26.0)
	4	4 581 847	(30.8)	85 157	(23.7)	170 228	(24.0)	400 206	(25.7)	682 215	(28.2)	854 352	(30.7)	836 957	(32.7)	654 917	(34.2)	431 408	(34.9)	243 037	(35.2)	121 841	(34.8)	101 529	(33.5)
Body mass index, kg/m^2	<18.5	607 278	(4.1)	24 750	(6.9)	58 267	(8.2)	115 383	(7.4)	139 061	(5.7)	115 369	(4.1)	75 352	(2.9)	41 336	(2.2)	20 434	(1.7)	9544	(1.4)	4201	(1.2)	3581	(1.2)
	18.5–24.9	9 724 620	(65.3)	229 724	(64.0)	491 895	(69.2)	1 095 543	(70.3)	1 684 001	(69.5)	1 872 622	(67.3)	1 653 671	(64.7)	1 188 540	(62.0)	740 502	(59.9)	401 292	(58.1)	198 461	(56.7)	168 369	(55.5)
	25–29.9	4 066 600	(27.3)	92 802	(25.9)	144 053	(20.3)	313 243	(20.1)	540 066	(22.3)	712 363	(25.6)	739 222	(28.9)	610 985	(31.9)	421 836	(34.1)	247 310	(35.8)	129 769	(37.1)	114 951	(37.9)
	≥30	486 477	(3.3)	11 708	(3.3)	16 283	(2.3)	34 514	(2.2)	60 084	(2.5)	81 189	(2.9)	88 031	(3.4)	75 330	(3.9)	53 299	(4.3)	32 195	(4.7)	17 371	(5.0)	16 473	(5.4)

Data are expressed as mean ± SD or *n* (%).

The *P*-values, which were calculated by the chi-square test and one-way ANOVA across the LDL-C groups, were <0.001 for each variable.

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

[b]To convert glucose from mg/dL to mmol/L, multiply by 0.0555.

ANOVA, analysis of variance; HDL-C, high-density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglyceride.

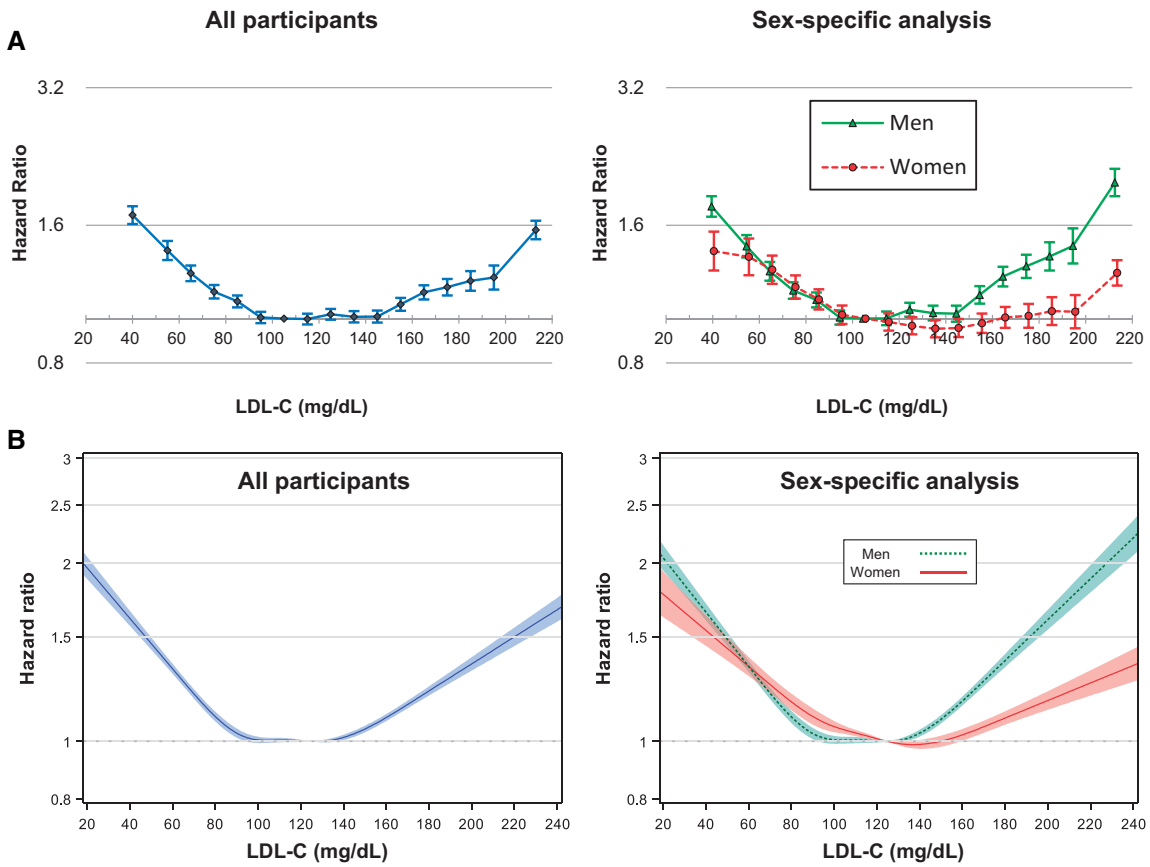

Figure 1 Age- and sex-adjusted hazard ratios across 17 categories of LDL-C for CVD mortality. (A) LDL-C categories (mg/dL: <50, 50–59 to 190–199 by 10, ≥200, 100–109 as reference). The midpoint was used as a representative value of each LDL-C category, except both ends (40 and 213) for which the median was used. (B) Restricted cubic splines of LDL-C with five knots (5th, 27.5th, 50th, 72.5th and 95th percentiles) and 125 mg/dL as a reference were used. Hazard ratios and 95% CIs were calculated using Cox proportional-hazards models with adjustment for sex (for all participants only) and age at baseline as a continuous variable. CVD, cardiovascular disease; LDL-C, low density lipoprotein cholesterol. To convert LDL-C from mg/dL to mmol/L, multiply by 0.02586

stratified analyses, positive associations in the upper range for mortality from IHD, AMI, ischaemic stroke and SCD generally decreased with age, as did inverse associations in the lower range for mortality from stroke, specifically haemorrhagic stroke (especially ICH) (Supplementary Figure S7, available as Supplementary data at *IJE* online). The youngest group (<45 years) generally had a linear association with IHD including AMI.

In the spline analysis, the associations of LDL-C with CVD mortality were generally similar to those in the categorical analysis and non-linear associations were statistically confirmed for CVD and each subtype (Supplementary Figure S8, , available as Supplementary data at *IJE* online; $P_{\text{nonlinearity}} < 0.001$ for each CVD subtype). Women had a higher optimal range than men for overall CVD mortality, but the difference in the optimal ranges between men and women for CVD subtypes was less apparent (Figure 4 and Supplementary Figures S9 and S10, available as Supplementary data at *IJE* online).

Assuming a linear association at <100 mg/dL, LDL-C was inversely associated with mortality from CVD [multivariable-adjusted HR per 39-mg/dL (1-mmol/L) higher level = 0.78] and its subtypes (Supplementary Table S4, available as Supplementary data at *IJE* online). The inverse associations were the strongest for haemorrhagic stroke (HR = 0.65), especially ICH (HR = 0.62), whereas they were the weakest for IHD (HR = 0.89) and ischaemic stroke (HR = 0.86). Assuming a linear association between 100 and 300 mg/dL, LDL-C was positively associated with CVD mortality, largely due to a strong association with IHD (HR = 1.26), especially AMI (HR = 1.28). SCD (HR = 1.13), ischaemic stroke (HR = 1.11) and heart failure (HR = 1.05) had positive associations, whereas haemorrhagic stroke (HR = 0.93), especially ICH (HR = 0.90), had an inverse association and SAH had no association. Assuming a linear association in the range ≤300 mg/dL, LDL-C generally had a modest positive association with CVD mortality (HR = 1.01).

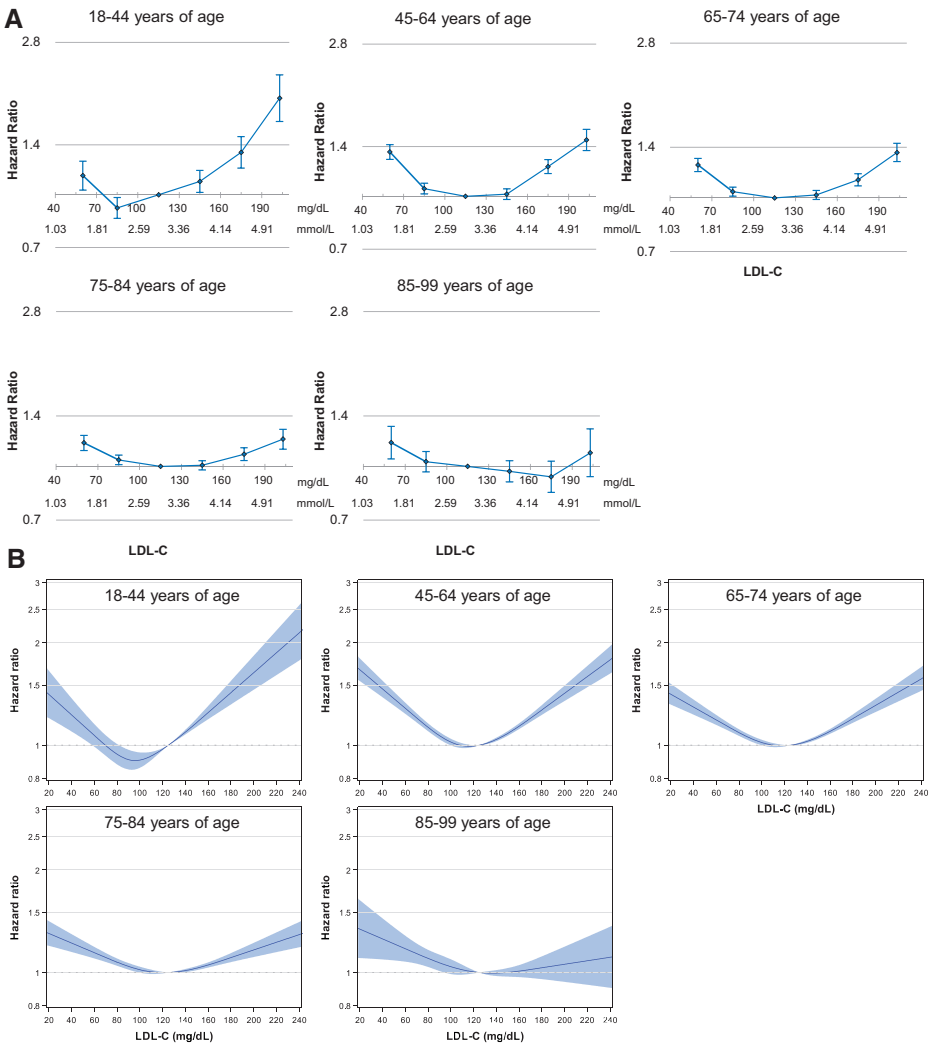

Figure 2 Hazard ratios of LDL-C for CVD mortality according to age. (A) LDL-C categories [mg/dL: <70, 70–99, 100–129 (reference), 130–159, 160–189, ≥190]. The midpoint was used as a representative value of each LDL-C category, except both ends (45 and 205) for which the median was used. (B) Restricted cubic splines of LDL-C with four knots (5th, 35th, 65th and 95th percentiles) and 125 mg/dL as a reference were used. Hazard ratios and 95% CIs were calculated using Cox proportional-hazards models with adjustment for age at baseline, sex, 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

In the upper LDL-C range, women had substantially weaker positive associations than men for mortality from overall CVD [HR 1.04 vs 1.16; $P_{\text{interaction}}(\text{sex}) < 0.001$] and its subtypes (Supplementary Table S4, available as Supplementary data at *IJE* online): IHD including AMI [both $P_{\text{interaction}}(\text{sex}) < 0.001$]; stroke, especially ischaemic stroke [both $P_{\text{interaction}}(\text{sex}) < 0.001$]; and SCD [$P_{\text{interaction}}(\text{sex}) < 0.001$]. In the lower LDL-C range, women generally had similar inverse associations to men except for ICH mortality.

Both the positive association in the upper range and the inverse association in the lower range weakened with advancing age (Supplementary Table S5, available as Supplementary data at *IJE* online). The oldest (≥85 years) generally did not have higher mortality from CVD, whereas the elderly aged 75–84 years had modestly higher mortality from CVD (especially IHD and ischaemic stroke) in the upper range.

Discussion

LDL-C had U-curve associations for mortality from overall CVD, including IHD, ischaemic stroke, heart failure and SCD, and L-curve associations for haemorrhagic stroke,

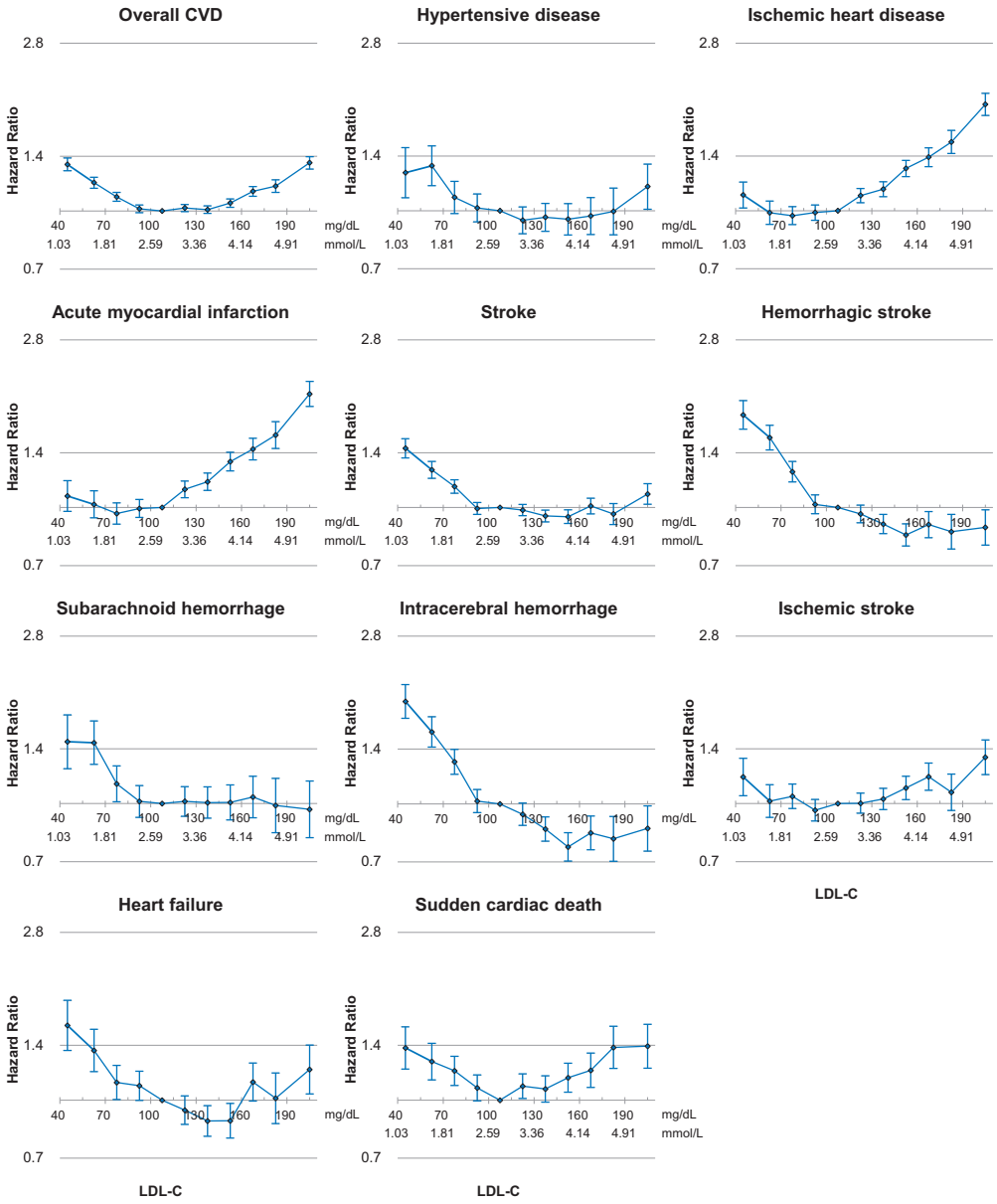

Figure 3 Hazard ratios across 11 categories of LDL-C for mortality from CVD and its subtypes. LDL-C categories (mg/dL: <55, 55–69 to 175–189 by 15, ≥190, 100–114 as reference). The midpoint was used as a representative value of each LDL-C category, except both ends (45 and 205) for which the median was used. Hazard ratios and 95% CIs were calculated using Cox proportional-hazards models after adjustment for the same variables as in Figure 2. CVD, cardiovascular disease; LDL-C, low density lipoprotein cholesterol. To convert LDL-C from mg/dL to mmol/L, multiply by 0.02586

including SAH and ICH. CVD mortality was lowest at LDL-C levels of 90–149 mg/dL. The optimal ranges were lowest for IHD and highest for ICH. The positive associations above the optimal level were generally weaker in women than in men, and became weaker with advancing age. However, the positive associations with IHD and ischaemic stroke were clearly maintained up until 75–84 years, but not after 85 years of age.

Ischaemic heart disease

LDL-C had U-curve (or J-curve) associations with mortality from IHD (including AMI) with an optimal range of 70–114 mg/dL, whereas LDL-C levels of 55–69 mg/dL had a similar risk and LDL-C levels <55 mg/dL had only a modestly higher risk. Previous studies have claimed a continuous graded association of LDL-C, non-HDL-C and TC with IHD.[10,13,21–23] Upon closer scrutiny, however,

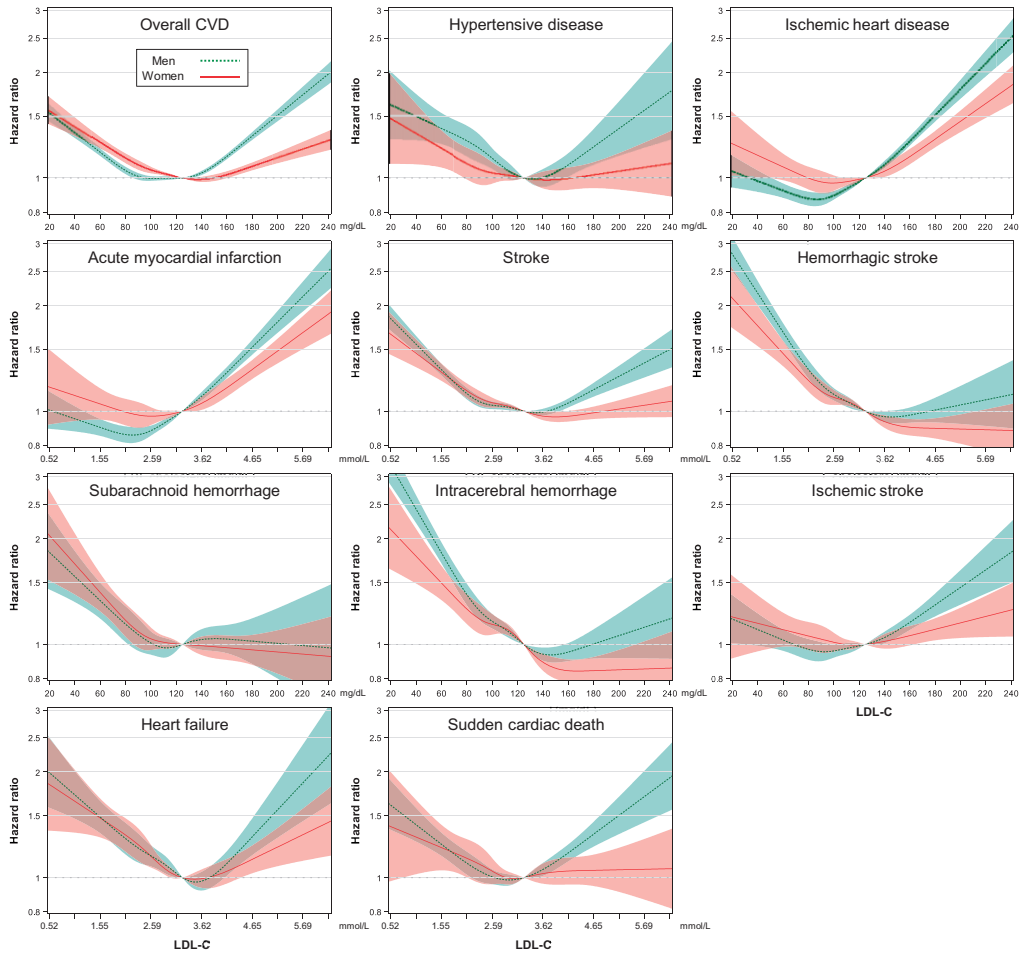

Figure 4 Hazard ratios for mortality from CVD subtypes by sex using spline analysis. Restricted cubic splines of low-density lipoprotein cholesterol (LDL-C) with five knots (5th, 27.5th, 50th, 72.5th and 95th percentiles) and 125 mg/dL as a reference were used. Hazard ratios and 95% CIs were calculated using Cox proportional-hazards models after adjustment for the same variables as in Figure 2. CVD, cardiovascular disease; LDL-C, low density lipoprotein cholesterol. To convert cholesterol from mg/dL to mmol/L, multiply by 0.02586

previous large cohort studies showed evidence of non-linear associations in a non-HDL-C range at ≤140 mg/dL,[10] a TC range around ≤200 mg/dL,[22,24] a TC range at ≤181 mg/dL[21] and an LDL-C range at ≤100 mg/dL.[23] This non-linear association is plausible given the evidence of a J-curve association of SBP with IHD.[25] The non-linear association may partly explain the findings of RCTs that lipid lowering was generally more beneficial in people with baseline LDL-C of ≥100 mg/dL than <100 mg/dL.[26–28]

Haemorrhagic stroke

LDL-C had L-curve associations with haemorrhagic stroke including SAH and ICH. A recent systematic review suggested a similar non-linear association.[29] Several statin RCTs and meta-analyses reported increased risk of ICH with *P*-value ≥ 0.05,[30–32] whereas more recent meta-analyses of statins at higher doses and for secondary prevention reported that statin users had higher risk of ICH.[33,34] Prospective cohort studies have generally reported inverse relationships between LDL-C and ICH/SAH.[29,35,36] These discrepancies may partly be resolved by the non-linear associations observed herein. The different associations of SAH and ICH are a novel finding. Inverse associations were found only at <85 mg/dL for SAH and <130 mg/dL for ICH. Men and women had almost identical associations for SAH. SAH is most often caused by a ruptured aneurysm,[37] whereas the most important risk factor for ICH is hypertension.[38] Our study suggests that lower LDL-C levels (<85 mg/dL) may be associated with aneurysm rupture risk.

Ischaemic stroke

Evidence from RCTs on whether LDL-C lowering reduces ischaemic stroke mortality is unclear, despite the clear effects

on non-fatal ischaemic stroke.[1] In observational studies, incident ischaemic stroke generally had weaker positive associations with cholesterol than IHD[10,22,39,40] and the association was inconsistent for ischaemic stroke mortality.[22,40,41] Our study showed a clear U-curve association with the optimum at 85–129 mg/dL. Previous large prospective studies of TC support a non-linear association with ischaemic stroke mortality.[22,40] A systematic review of RCTs reported no beneficial effect of statins on stroke in women[42] and few studies have examined the association (or the effect of cholesterol-lowering therapy) in the very old.[43] In the current study, the LDL-C range of ≥100 mg/dL showed a positive, although modest, association in women and in older adults except for the oldest (≥85 years old).

Overall stroke

Due to a higher proportion of deaths from haemorrhagic stroke and a weaker association with ischaemic stroke mortality, women had no association of LDL-C with overall stroke mortality in the LDL-C range of ≥100 mg/dL, whereas men had a weak positive association. Considering the substantial difference in the associations between ischaemic stroke and haemorrhagic stroke mortality, the association of LDL-C with overall stroke mortality may reflect the population-specific distribution of stroke subtypes.

Heart failure

Few studies have examined the association between LDL-C and heart failure in the general population.[13] In persons with heart failure, observational studies generally found associations between low cholesterol levels and poor prognoses.[44–46] Our study found a U-curve association between LDL-C and heart failure mortality, with the optimal range at 130–159 mg/dL. A recent study in Denmark reported a potential U-curve association,[13] whereas positive associations above the optimum were stronger and clearer in our study. In RCTs, statins showed no beneficial effects on primary and secondary prevention for heart failure deaths.[47] Moderate hypercholesterolemia at baseline and LDL-C levels of <130 mg/dL during follow-up in RCTs may partly explain those findings.[48–50] In our study, positive associations were found in the range of ≥130 mg/dL in adults aged up to 75–84 years. Assuming causality, LDL-C-lowering therapy targeting 130–159 mg/dL might be beneficial for heart failure.

SCD

Since most people with SCD are considered to have IHD,[51] SCD shares risk factors with IHD. In the current study, however, the U-curve associations were somewhat different between SCD and IHD. SCD had a higher optimal range, a stronger inverse association in the LDL-C range of <100 mg/dL and a weaker positive association at ≥100 mg/dL than IHD. A potential explanation is that a substantial portion of SCD is caused by heart failure and primary arrhythmogenic disorders.[51] A Finnish study of 2612 men found a potential U-shaped association, in accordance with the current study.[52]

Overall CVD

LDL-C had U-curve associations with CVD mortality, as in a recent Korean study.[14] The optimal range was higher in women than in men. However, it was not substantially different between sexes for each subtype of CVD, although it was substantially different between CVD subtypes. An explanation for the higher optimal range in women than in men may be that women have weaker positive associations for atherosclerotic CVD, a lower proportion of IHD deaths and a higher proportion of haemorrhagic stroke deaths. The substantial differences in associations across CVD subtypes suggest that the associations of LDL-C with overall CVD mortality may depend upon population-specific distributions of CVD subtypes.

Reverse causality may partly explain the inverse association in the lower LDL-C range.[14,23] In the current study, individuals with known heart disease, stroke and cancer were excluded. Younger adults (<45 years) with fewer comorbidities also showed U-curve associations. Exclusion of the first 3 years of deaths yielded little change in the associations, whereas in statin users, U-curve associations were less apparent.[13,23] Additionally, inverse associations in the lower range were stronger for all-cause mortality than for CVD mortality (Supplementary Figure S11, available as Supplementary data at *IJE* online). Meanwhile, LDL-C levels decrease during infections[53] and in anaemia,[54] both of which may increase CVD risk.[55,56] Upon further adjustment for anaemia, the higher CVD mortality associated with lower LDL-C levels was modestly weakened (Supplementary Figure S12, available as Supplementary data at *IJE* online). Low LDL-C levels may be a predictor or a mediator, at least partly, of the effect of LDL-C-lowering diseases on CVD. The exact role of prolonged low LDL-C levels in haemorrhagic stroke and other CVD subtypes requires further elucidation.

Sex- and age-specific associations

In the upper LDL-C range, women had substantially weaker positive associations than men for mortality from overall CVD ($P_{interaction} < 0.001$ for sex) including IHD, AMI, stroke (especially ischaemic stroke) and SCD.

Hypertensive disease and heart failure showed weaker positive associations in women than in men in the LDL-C range of 130–300 mg/dL (Supplementary Table S6, available as Supplementary data at *IJE* online). These findings generally concur with RCTs showing weaker effects of statins in women than in men, especially for vascular mortality.[5] In the age-stratified analysis, the youngest adults (<45 years) had the lowest optimal range. Similar results have been shown for BMI, TC and HDL-C, but for all-cause mortality.[17,19,20] The positive associations in the upper range for IHD, ischaemic stroke, heart failure and SCD weakened with advancing age, as shown in statin trials.[57] Although the oldest (≥85 years) generally had no higher mortality from CVD, adults aged 75–84 years had modestly higher mortality from CVD, especially IHD and ischaemic stroke (and perhaps also heart failure in the range of 130–300 mg/dL). Assuming causality, LDL-C-lowering therapy may be beneficial in adults aged 75–84 years as primary CVD prevention.

Strengths and limitations

The prospective design of the concurrent cohort,[11] the complete follow-up for death and CVD-causes of death through national mortality data, and the large number of participants are the main strengths of the study. Second, extensive adjustment for potential confounders was performed. Third, our study recruited ethnically homogeneous individuals living in a similar environment covered by the same healthcare system. Fourth, our study estimated the risk associated with LDL-C levels down to <50 mg/dL. There are several limitations. First, the observational study design makes causal inference difficult, especially for inverse associations in the lower ranges. Thus, adjusting LDL-C levels to 'the optimal range' may not modify the risk of CVD death. Second, the estimated relative risk based on a single measurement of LDL-C may underestimate the true association, considering the regression dilution effect.[22] Third, LDL-C levels were calculated by the Friedewald equation. However, direct and Friedewald-estimated measurements are closely correlated in Korean adults.[58,59] Additionally, since the calculated levels are mostly lower than direct measurements in Koreans, using direct measurements would yield higher estimated HRs associated with lower LDL-C levels and the optimal ranges would move higher than the current results (Supplementary Figures S13 and S14, available as Supplementary data at *IJE* online). Fourth, the homogeneous study population might affect the generalizability. For instance, Asians had a greater risk of bleeding complications related to warfarin and antiplatelet therapy than Caucasians.[60] The associations and optimal ranges may differ by ethnicity due to varying LDL-C levels, healthcare utilization, distribution of CVD subtypes, and environmental and individual risk factors.

Conclusion

Both low and high LDL-C levels were associated with higher mortality from CVD including IHD, ischaemic stroke, heart failure and SCD in the Korean general population, except SAH and ICH, for which only low levels had higher mortality. CVD mortality was lowest at LDL-C levels of 90–149 mg/dL (2.32–3.85 mmol/L). The optimal ranges differed by CVD subtypes: they were lowest for IHD and highest for ICH. Women had weaker positive associations above the optimal range than men. Although the positive associations with CVD, especially IHD and ischaemic stroke, became weaker with advancing age, the associations were maintained up to 75–84 years of age. Our detailed findings could help inform clinical and public health decision-making for CVD prevention and management.

Ethics approval

This study was approved by the Institutional Review Board of Catholic Kwandong University (Gangneung, Republic of Korea: CKU-19–01-0202).

Data availability

The data supporting the findings of this study are available from the NHIS (https://nhiss.nhis.or.kr/bd/ab/bdaba021eng.do), which provides access to researchers upon review and approval of their proposal.

Supplementary data

Supplementary data are available at *IJE* online.

Author contributions

S.W.Y. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. S.W.Y. and H.O. conceived of the study concept and design. S.W.Y. acquired the data, statistically analysed the data and wrote the first draft. S.J.A., H.B.P. and J.J.Y. conducted the literature review and helped to prepare the Introduction and the Discussion. All authors contributed to the analysis, interpretation of the results and critical revision of the manuscript. All authors read and approved the final submitted version of the manuscript. S.W.Y. is the study guarantor.

Funding

There was no specific funding for the current work.

Acknowledgements

The authors thank the staff at the Big Data Steering Department at the NHIS for providing the data and support.

Conflict of interest

None declared.

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