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High-density lipoprotein cholesterol and all-cause mortality by sex and age: a prospective cohort study among 15.8 million adults

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Abstract

Background: The associations between high-density lipoprotein cholesterol (HDL-C) levels and all-cause mortality are unclear in young adults (<45 years) and in Asian populations.

Methods: In total, 15 860 253 Korean adults underwent routine health examinations during 2009–10 and were followed until June 2018 for all-cause mortality. Hazard ratios (HRs) were calculated using Cox proportional hazard models.

Results: During a mean 8.4 years of follow-up, 555 802 individuals died. U-curve associations were found between HDL-C levels and mortality, irrespective of sex or age. The HDL-C ranges associated with the lowest mortality were 40–59 and 50–69 mg/dL (1.03–1.54 and 1.29–1.80 mmol/L) in men aged <65 and ≥65 years, respectively, and the corresponding ranges were 40–69 and 50–79 mg/dL (1.03–1.80 and 1.29–2.06 mmol/L) in women aged <45 and ≥45 years, respectively. For HDL-C ranges of 60–149 mg/dL (1.55–3.86 mmol/L), each 39 mg/dL (1 mmol/L) increase in HDL-C was associated with higher mortality [men: HR = 1.39; 95% confidence interval (CI) = 1.36–1.42; women: HR = 1.15, 95% CI = 1.11–1.18], adjusting for age. These positive associations were generally stronger at younger than older ages, whereas inverse associations for HDL-C ranges <60 mg/dL (1.55 mmol/L) were strongest in middle age (45–64 years). The U-curve associations were generally unchanged after adjustment for various confounders.

Conclusions: Korean adults showed U-curve associations of HDL-C with mortality, regardless of sex, and age. Younger adults had a lower optimal range and a stronger positive association with mortality than older adults in the high HDL-C range. Even

moderately high HDL-C levels are not necessarily a sign of good health, especially in young adults.

Key words: Lipids, HDL-cholesterol, mortality, Asians, general population, epidemiology

Key Messages

- U-curve relationships were found between high-density lipoprotein-cholesterol (HDL-C) and all-cause mortality, regardless of sex and age.
- The HDL-C levels associated with the lowest mortality were 40–59 mg/dL (1.03–1.54 mmol/L) in men and 50–79 mg/dL (1.29–2.06 mmol/L) in women.
- Younger adults had slightly lower optimal ranges than older adults in both sexes, although the youngest adults had the highest mean HDL-C levels in each sex.
- Even moderately high HDL-C levels are not necessarily a sign of good health, especially in young adults (<45 years).

Introduction

During the past several decades, high-density lipoprotein-cholesterol (HDL-C) has been widely considered to be 'good cholesterol', and the notion that 'the higher, the better' applies to HDL-C levels has been widespread in the medical community,[1] although clinical trials and Mendelian randomization studies showed no beneficial effects of higher HDL-C levels.[2–5] Recently, several cohort studies have suggested that HDL-C has U-shaped associations and that very high levels of HDL-C are associated with increased mortality.[6–11] However, the HDL-C levels associated with the lowest mortality were different among those cohort studies, and it is unclear whether moderately high levels, such as 60–89 mg/dL (1.55–2.32 mmol/L), increase mortality. Most participants in the previous studies were in their 50 s and 60 s; therefore, it is unclear whether these U-curve associations exist in young adults (<45 years). Early adulthood, roughly 18–44 years, is an important period of opportunity for disease prevention. A precise understanding of the patterns of these associations and an accurate estimate of mortality associated with HDL-C levels by age could help inform decision making regarding the identification of high-risk groups and preventive care focused on younger adults, as well as older adults.[12]

Additionally, since the levels and composition of HDL-C differ by race and ethnicity, as well as by age and sex,[13–15] the associations of HDL-C with mortality and the levels associated with the lowest mortality may differ among racial and ethnic groups. Among Asian populations, three Japanese studies (two population-based prospective and one hospital-based retrospective studies) did not show associations of higher all-cause mortality with high HDL-C levels.[8,16,17] In contrast, a Korean retrospective study reported U-curve associations,[18] although the highest HDL-C group had only modestly higher mortality [hazard ratio (HR) = 1.17 for men and 1.12 for women; $P \geq 0.05$) than those with HDL-C levels of 1.6–1.79 mmol/L. Overall, evidence is lacking for U-curve associations of HDL-C with all-cause mortality in Asian populations from population-based prospective studies.

Through a large prospective cohort study among over 15 million adults in the Korean general population, we examined whether the shape and magnitude of the association between HDL-C and all-cause mortality varied by sex and age, and estimated the sex- and age-specific levels of HDL-C associated with the lowest mortality. Additionally, detailed estimates of the mean (and median) concentrations of HDL-C according to sex and age are presented.

Methods

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

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 NHIS beneficiaries aged 18–99 who underwent routine health examinations from 2009 to 2010, persons with missing information ($n = 470\ 529$) on serum total cholesterol (TC), fasting glucose, blood pressure, body mass

index (BMI), HDL-C, low-density lipoprotein cholesterol (LDL-C), and triglycerides were excluded, as were 1194 individuals with a missing date of the health examination. After further exclusion of those with known heart disease, stroke, cancer or other diseases ($n = 1\ 401\ 132$), the remaining 15 860 253 participants were followed up until 30 June 2018 through the Resident Register of Korea for all-cause mortality.

The Institutional Review Board of Catholic Kwandong University approved the study with a waiver of the requirement for informed consent because this study analysed anonymized data that were constructed and provided by the NHIS following a protocol with strong protections for confidentiality.

Data collection

Serum HDL-C, TC, triglyceride and fasting glucose levels were assayed by enzymatic methods. LDL-C concentrations were calculated using the Friedewald equation. Blood pressure was measured once in a seated position. BMI was calculated by measured weight in kilograms divided by the square of measured height in metres (kg/m^2).[19] A self-administered questionnaire was used to assess physical activity, smoking history, alcohol use and a known history of heart disease, lipid disorder, cancer or other diseases. For the data collection process, including health examinations, a standard official protocol of the Ministry of Health and Welfare was used. Routine external quality assessments of clinical chemistry were conducted.[20]

Statistical analysis

Baseline HDL-C concentrations were categorized into 11 groups (mg/dL; <20, 20–29 to 100–109 in increments of 10, ≥110). The HDL-C category with the lowest mortality (40–49 mg/dL) in all participants was used as the reference. Three groups [<40 (low), 40–59 (reference, normal) and ≥60 (high)], according to the National Cholesterol Education Program (NCEP) and the Korean guidelines for dyslipidaemia,[1,21] were used in an additional analysis. In the spline analysis, a restricted cubic spline transformation of HDL-C with four predefined knots (5th, 35th, 65th and 95th percentiles) was used to evaluate non-linear associations.

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. In the multivariable model, the following variables were adjusted for: age (continuous variable within each age stratum), sex, income status (vigintile: ≤5 (low income), 6–10, 11–15 and >15], 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 of ≥30 min at least once a week: yes or no), systolic blood pressure (continuous variable), fasting glucose (continuous variable), BMI (<18.5, 18.5–24.9, 25–29.9 or ≥30 kg/m^2), LDL-C level (continuous variable), triglyceride level (<150, 150–199 or ≥200 mg/dL), or known lipid disorder (yes, no). BMI and triglyceride were used as categorical variables due to non-linear associations with mortality in our data.[19]

Based on qualitative observations of the curvilinear association, the intervals of 20 mg/dL (roughly 0.5 mmol/L) for males and 30 mg/dL (roughly 0.75 mmol/L) for females with the lowest risk (the lowest unweighted geometric mean of HRs in 2–3 consecutive HDL-C categories) were considered to be the 'optimal ranges'. The optimal range refers to the HDL-C range associated with the lowest mortality in this study. Subgroup analyses by sex and age, as well as various categorical, spline and linear analyses, served as sensitivity analyses. Cochran's Q statistic was used as the interaction test to examine the difference in the effect size of HDL-C between sex and age groups. All *P*-values were two-sided. All analyses used SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Data availability

The data supporting the findings of this study are available from the NHIS, but restrictions apply to the availability of these data, which were used under licence for the current study; therefore, the data are not publicly accessible.

Results

During a median 8.6 years (interquartile range: 7.9–8.9 years) of follow-up, 363 142 men and 192 660 women died. At baseline, the participants' mean±standard deviation (SD) age was 47.4 ± 14.0 years, their mean HDL-C level was 55.2 ± 13.8 mg/dL (Table 1) and 33.8% of participants had high HDL-C levels (≥60 mg/dL). Individuals with higher HDL-C levels tended: to be younger, female, less likely to be current smokers and more frequent alcohol users; to have lower levels of fasting glucose, systolic blood pressure and BMI; and to have higher levels of TC (Table 1). LDL-C levels were the highest in the normal HDL-C group. In the 11-group analysis, LDL-C levels were highest in those with an HDL-C level 40–49 mg/dL and lowest in those with an HDL-C level ≥110 mg/dL (Supplementary Table S1, available as Supplementary data at *IJE* online). The number of individuals was highest in the groups with HDL-C levels of 45–49 mg/dL in men and 50–54 mg/dL in women (Figure 1).

Table 1 Participants' characteristics at baseline by HDL-C categories

Variables	Characteristics	Total	Low	Normal	High
			<40 mg/dL	40–59	≥60 mg/dL
			<1.03 mmol/L	1.03–1.54	≥1.55 mmol/L
		n = 15 860 253	*n* = 1 658 105	*n* = 8 845 603	*n* = 5 356 545
Age	years	47.4 ± 14.0	50.2 ± 13.9	47.9 ± 13.9	45.7 ± 14.0
HDL-C[a]	mg/dL	55.2 ± 13.8	35.0 ± 3.8	49.7 ± 5.5	70.4 ± 10.2
LDL-C[a]	mg/dL	113.8 ± 33.9	110.3 ± 35.5	116.4 ± 33.5	110.6 ± 33.6
Body mass index	kg/m^2	23.7 ± 3.5	25.0 ± 4.0	24.0 ± 3.4	22.7 ± 3.4
Total cholesterol[a]	mg/dL	195.6 ± 36.9	185.8 ± 37.3	194.0 ± 36.6	201.2 ± 36.4
Fasting glucose[b]	mg/dL	97.4 ± 23.9	101.6 ± 29.1	98.0 ± 24.2	95.2 ± 21.1
Systolic blood pressure	mm Hg	122.3 ± 15.2	124.7 ± 14.8	122.8 ±15.0	120.6 ± 15.3
Sex	Women	7 584 272 (47.8)	488 064 (29.4)	3 811 635 (43.1)	3 284 573 (61.3)
Lipid disorder	Yes	434 887 (2.7)	53 187 (3.2)	249 884 (2.8)	131 816 (2.5)
Smoking status	Never smoker	9 663 216 (60.9)	803 213 (48.4)	5 139 252 (58.1)	3 720 751 (69.5)
	Past smoker	2 197 947 (13.9)	283 247 (17.1)	1 318 410 (14.9)	596 290 (11.1)
	Current smoker	3 921 747 (24.7)	563 643 (34.0)	2 342 937 (26.5)	1 015 167 (19.0)
	Missing	77 343 (0.5)	8002 (0.5)	45 004 (0.5)	24 337 (0.5)
Alcohol use	<1 day/week	8 141 279 (51.3)	895 442 (54.0)	4 552 017 (51.5)	2 693 820 (50.3)
	1–2 days/week	5 467 729 (34.5)	564 381 (34.0)	3 076 253 (34.8)	1 827 095 (34.1)
	3–4 days/week	1 496 667 (9.4)	129 918 (7.8)	815 940 (9.2)	550 809 (10.3)
	5–7 days/week	612 066 (3.9)	52 019 (3.1)	318 796 (3.6)	241 251 (4.5)
	Missing	142 512 (0.9)	16 345 (1.0)	82 597 (0.9)	43 570 (0.8)
Physical activity	Yes	6 859 070 (43.2)	705 065 (42.5)	3 845 394 (43.5)	2 308 611 (43.1)
Age group, years	18–34	3 284 180 (20.7)	239 164 (14.4)	1 711 569 (19.3)	1 333 447 (24.9)
	35–44	3 770 400 (23.8)	389 639 (23.5)	2 127 015 (24.0)	1 253 746 (23.4)
	45–54	4 133 714 (26.1)	426 002 (25.7)	2 302 211 (26.0)	1 405 501 (26.2)
	55–64	2 640 648 (16.6)	315 219 (19.0)	1 526 489 (17.3)	798 940 (14.9)
	65–74	1 594 068 (10.1)	218 777 (13.2)	928 857 (10.5)	446 434 (8.3)
	75–99	437 243 (2.8)	69 304 (4.2)	249 462 (2.8)	118 477 (2.2)
Income status, ventile	≤5 (low-income)	3 263 906 (20.6)	302 933 (18.3)	1 753 872 (19.8)	1 207 101 (22.5)
	6–10	3 394 453 (21.4)	318 132 (19.2)	1 832 720 (20.7)	1 243 601 (23.2)
	11–15	4 234 966 (26.7)	453 053 (27.3)	2 383 558 (26.9)	1 398 355 (26.1)
	>15	4 966 928 (31.3)	583 987 (35.2)	2 875 453 (32.5)	1 507 488 (28.1)
BMI, kg/m^2	<18.5	615 025 (3.9)	20 804 (1.3)	244 044 (2.8)	350 177 (6.5)
	18.5–24.9	10 204 043 (64.3)	857 387 (51.7)	5 489 969 (62.1)	3 856 687 (72.0)
	25–29.9	4 485 938 (28.3)	681 604 (41.1)	2 764 716 (31.3)	1 039 618 (19.4)
	≥30	555 247 (3.5)	98 310 (5.9)	346 874 (3.9)	110 063 (2.1)
Triglycerides, mg/dL	<150	11 247 979 (70.9)	680 450 (41.0)	5 964 766 (67.4)	4 602 763 (85.9)
	150–199	2 157 508 (13.6)	335 382 (20.2)	1 388 764 (15.7)	433 362 (8.1)
	≥200	2 454 766 (15.5)	642 273 (38.7)	1 492 073 (16.9)	320 420 (6.0)
HDL-C, mg/dL (mmol/L)	<20 (<0.51)	7175 (0.0)	7175 (0.4)	0 (0.0)	0 (0.0)
	20–29 (0.51–0.76)	131 384 (0.8)	131 384 (7.9)	0 (0.0)	0 (0.0)
	30–39 (0.77–1.02)	1 519 546 (9.6)	1 519 546 (91.6)	0 (0.0)	0 (0.0)
	40–49 (1.03–1.28)	4 256 182 (26.8)	0 (0.0)	4 256 182 (48.1)	0 (0.0)
	50–59 (1.29–1.54)	4 589 421 (28.9)	0 (0.0)	4 589 421 (51.9)	0 (0.0)
	60–69 (1.55–1.80)	3 105 336 (19.6)	0 (0.0)	0 (0.0)	3 105 336 (58.0)
	70–79 (1.81–2.06)	1 428 982 (9.0)	0 (0.0)	0 (0.0)	1 428 982 (26.7)
	80–89 (2.07–2.32)	547 041 (3.4)	0 (0.0)	0 (0.0)	547 041 (10.2)
	90–99 (2.33–2.58)	185 041 (1.2)	0 (0.0)	0 (0.0)	185 041 (3.5)
	100–109 (2.59–2.84)	55 841 (0.4)	0 (0.0)	0 (0.0)	55 841 (1.0)
	≥110 (≥2.85)	34 304 (0.2)	0 (0.0)	0 (0.0)	34 304 (0.6)

Data are expressed as mean±SD or *n* (%). The *P*-values, which were calculated by the chi square test and one-way analysis of variance (ANOVA) across the HDL cholesterol groups, were <0.001 for each variable.

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

[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.

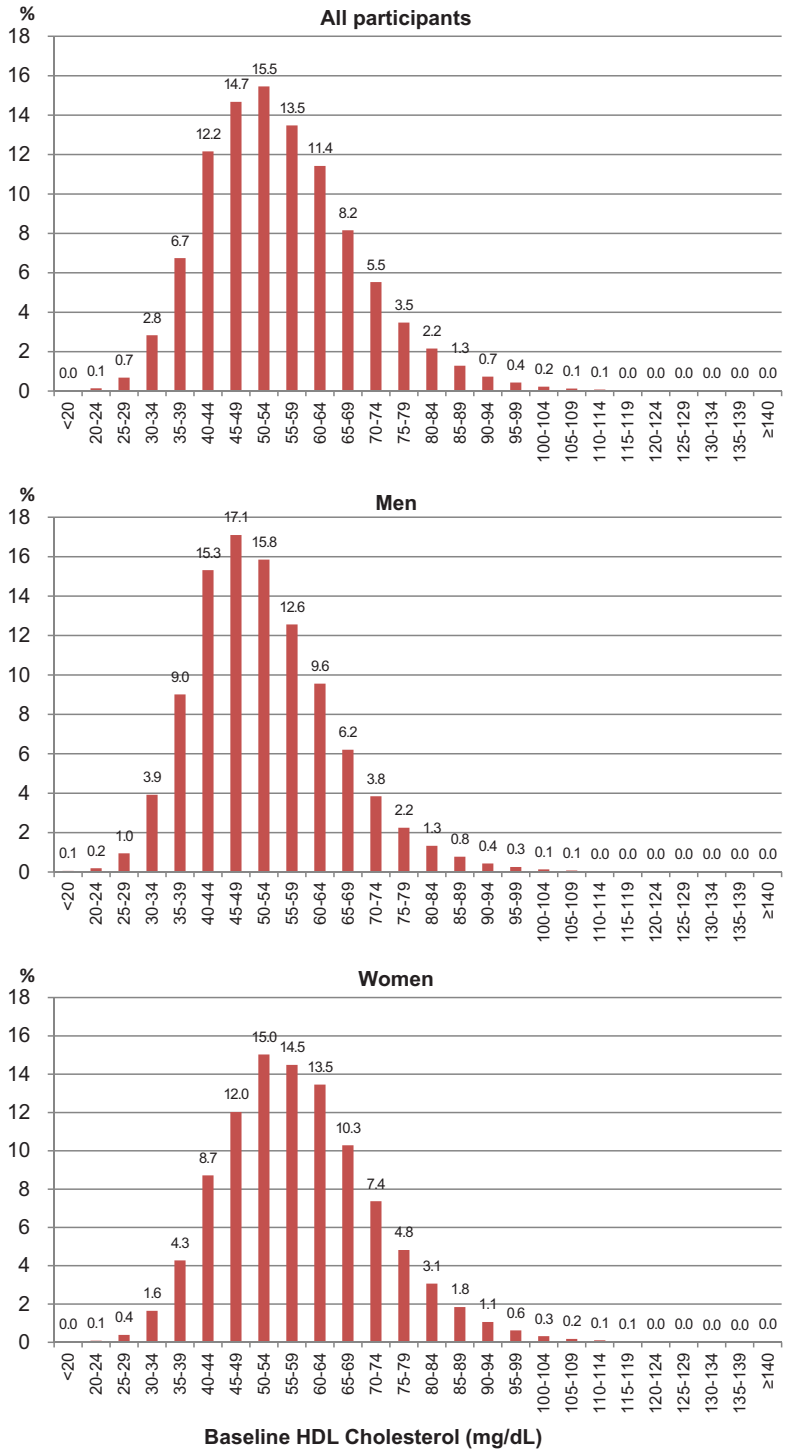

Figure 1. Distribution of high-density lipoprotein (HDL) cholesterol concentration in Korean adults. To convert cholesterol from mg/dL to mmol/L, multiply by 0.02586

HDL-C concentrations according to sex and age

Women had on average 6.2 mg/dL higher HDL-C levels than men. The difference was the largest at the age of 28–31 years (9.7 mg/dL), decreased with advancing age and was the lowest at the age of 86–99 years (0.6 mg/dL) (Figure 2, Supplementary Table S2, available as Supplementary data at *IJE* online). Mean HDL-C levels reached a maximum of 56.0 mg/dL at 22–23 years in men and 64.0 mg/dL at 24–27 years in women. In women, after the peak values were reached, HDL-C levels gradually

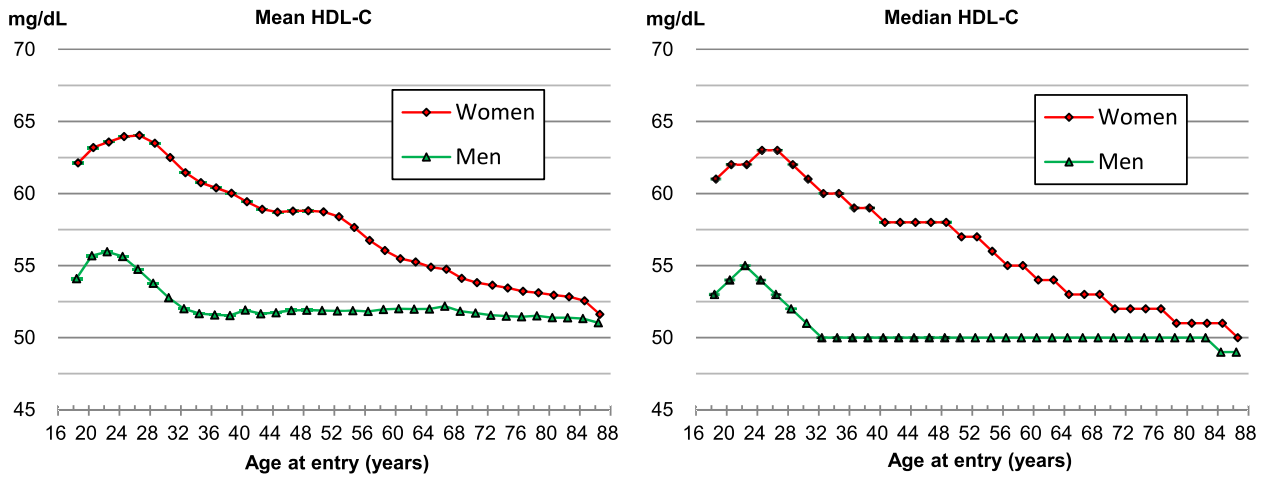

Figure 2. Mean and median concentrations of high-density lipoprotein cholesterol (HDL-C). To convert HDL-C from mg/dL to mmol/L, multiply by 0.02586. More detailed information is presented in Supplementary Table S1

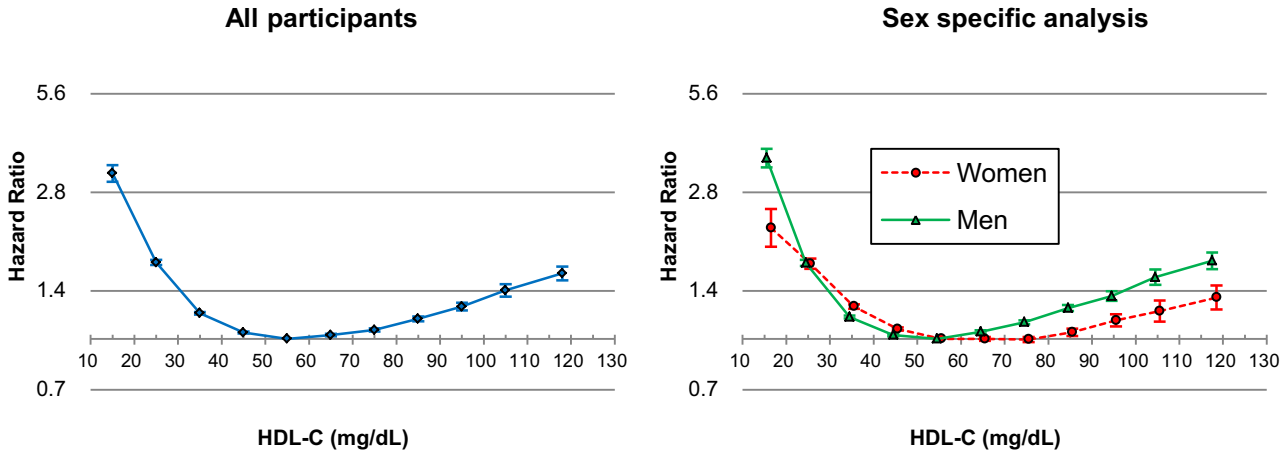

Figure 3. Age- and sex- adjusted HRs for all-cause mortality associated with 11 high-density lipoprotein cholesterol (HDL-C) categories, according to sex. HR, hazard ratio. HDL-C categories (mg/dL: <20, 20–29 to 100–109 by 10, ≥110, 50–59 as reference). The midpoint was used as a representative value for each HDL-C category, except for both ends (16 and 118), for which the median of all participants was used. HRs and 95% confidence intervals were calculated using Cox hazard models with adjustment for sex (for all participants only) and age at baseline as a continuous variable. To convert HDL-C from mg/dL to mmol/L, multiply by 0.02586. The exact numerical values of the HRs are presented in Supplementary Table S3

decreased with age, whereas after 10 years of decreasing, the levels were generally unchanged during the period of 32–83 years in men (Figure 2).

Associations between HDL-C and mortality

U-curve associations between HDL-C levels and mortality were found in both men and women (Figure 3). The HDL-C range associated with the lowest mortality was 40–59 mg/dL in men and 50–79 mg/dL in women in an age-adjusted analysis (Supplementary Table S3, available as Supplementary data at *IJE* online). When age was further stratified, U-curve associations were observed regardless of sex and age (Figure 4), and the optimal HDL-C range for survival was 40–59 mg/dL in men aged <65 years, 50–69 mg/dL in men aged ≥65 years, 40–69 mg/dL in women aged <45 years and 50–79 mg/dL in women aged ≥45 years, in an age-adjusted analysis. In the multivariable-adjusted analysis, the optimal ranges slightly shifted upward in men ≥55 yearsand the ranges in each age group were similar to the ranges of the age-adjusted analysis in women (Supplementary Table S4, available as Supplementary data at *IJE* online). Sensitivity analyses excluding female hormone users (n = 310 240) or the first 3 years of follow-up (n = 142 346) showed similar results to those of the main analyses (Supplementary Figures S1 and S2, available as Supplementary data at *IJE* online). In the spline analysis (Supplementary Figures S3 and S4, available as Supplementary data at *IJE* online), similar U-curve associations were shown.

When assuming linear associations for HDL-C ranges of <150 (full range), <60 (lower range) and 60–149 mg/dL

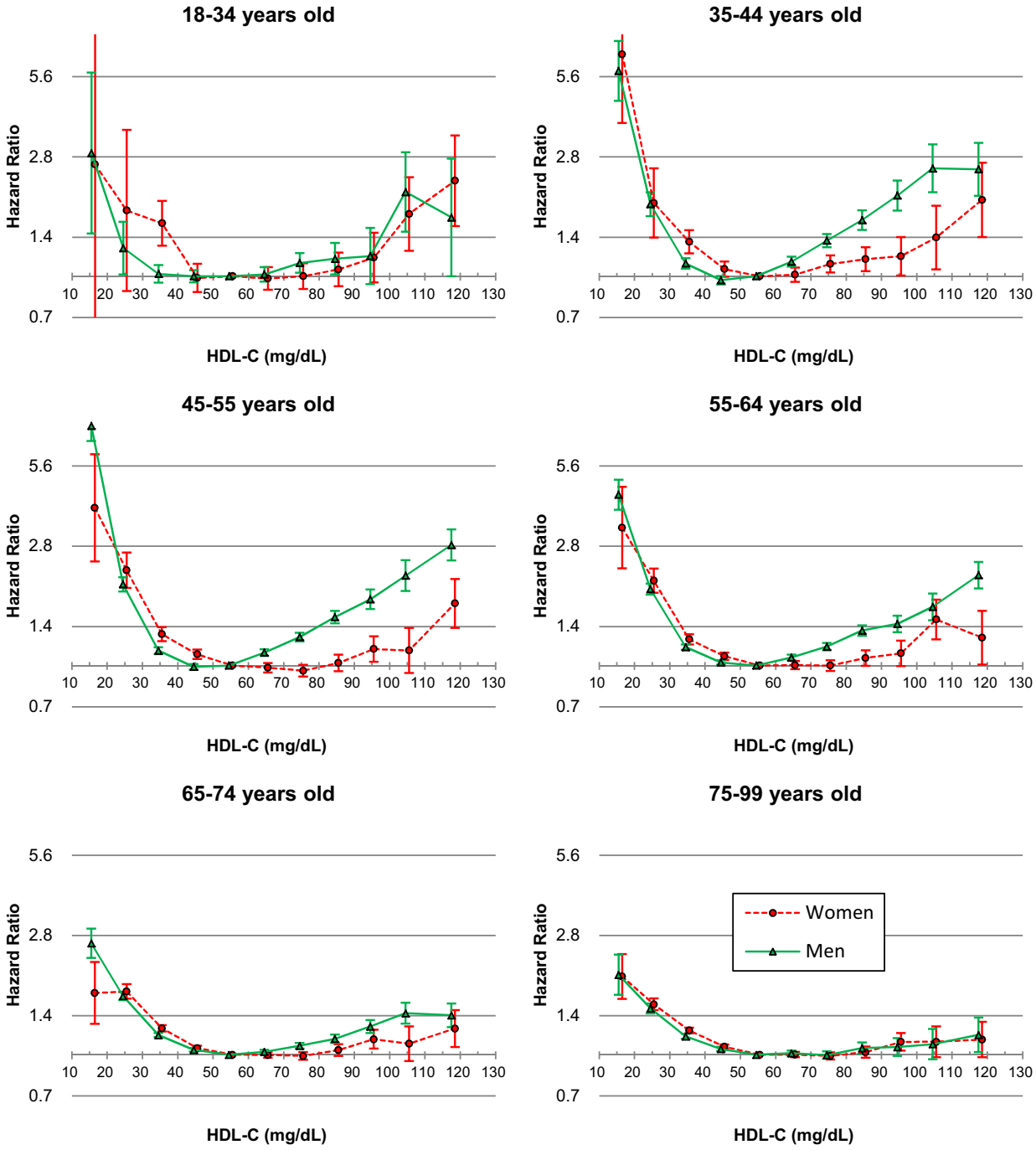

Figure 4. Age-adjusted HRs for all-cause mortality associated with 11 high-density lipoprotein cholesterol (HDL-C) categories, according to sex and age. HR, hazard ratio. HDL-C categories (mg/dL: <20, 20–29 to 100–109 by 10, ≥110, 50–59 as reference). The same level was used as a representative value for each HDL-C category as in Figure 3. HRs and 95% confidence intervals were calculated using the same method as in Figure 3. To convert HDL-C from mg/dL to mmol/L, multiply by 0.02586. The exact numerical values of the HRs are presented in Supplementary Table S4

(higher range), each 39 mg/dL (1 mmol/L) increase in HDL-C was associated with a 3% lower (HR = 0.97; 95% CI = 0.96–0.98), 37% lower (HR = 0.63; 95% CI = 0.62–0.65) and 39% higher (HR = 1.39; 95% CI = 1.36–1.42) mortality, respectively, in men and a 15% lower (HR = 0.85; 95% CI = 0.84–0.86), 40% lower (HR = 0.60; 95% CI = 0.58–0.61) and 15% higher (HR = 1.15; 95% CI = 1.11–1.18) mortality in women in the age-adjusted analysis (Figure 5). In the age-stratified analysis, when assuming linear associations for the full range of HDL-C, men aged <65 years and women aged <45 years had positive or no associations of HDL-C with all-cause mortality. Both men and women aged 18–34 years, who had the highest mean HDL-C levels in the age groups, had the

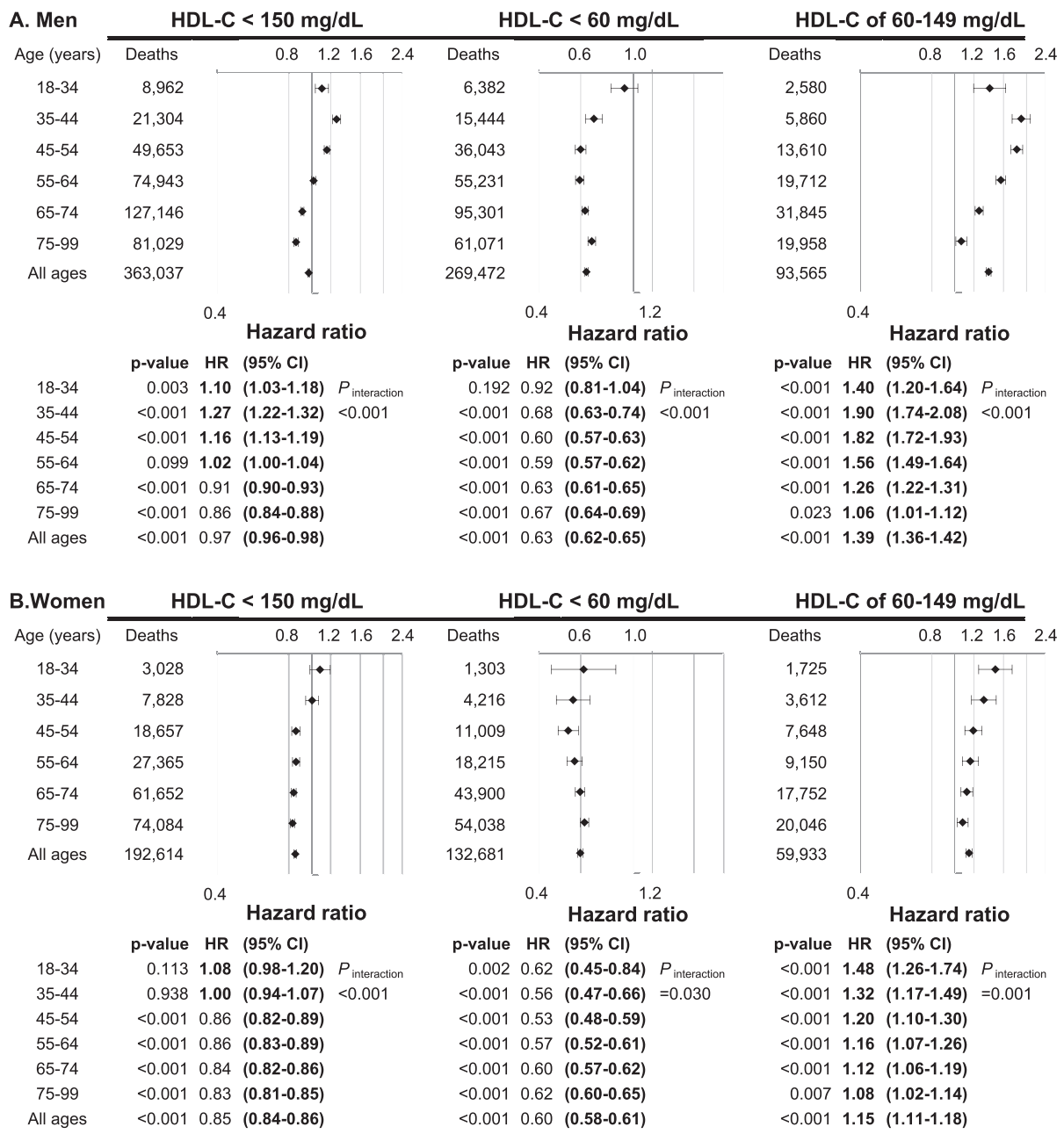

Figure 5. Age-adjusted HRs per each 39 mg/dL (1 mmol/L) increase in high-density lipoprotein cholesterol (HDL-C) for all-cause mortality, according to HDL-C range and age. A) Men, B) Women. HR, hazard ratio; Pinteraction, P value for interaction between age groups. HRs and 95% confidence intervals were calculated using Cox hazard models. To convert TC from mg/dL to mmol/L, multiply by 0.02586

weakest inverse association in the lower range, whereas in general the younger group had higher positive associations in the upper range (Table 2, Figure 5). The difference in HRs was greater in the upper range than in the lower range within sex-age subgroups.

Associations across three categories of HDL-C

In the age-adjusted analysis, compared with the normal levels of 40–59 mg/dL (Supplementary Table S5, available as Supplementary data at *IJE* online), high levels (≥60 mg/dL) were associated with a 9% higher risk in men and a 2% lower risk of mortality in women. When age was grouped into six categories, all men except for those aged 75–99 years had a higher mortality risk associated with high HDL-C, especially men aged 35–44 years (HR = 1.29) and 45–54 years (HR = 1.24), and in women, the excess risks/or beneficial effects associated with high HDL-C were ≤5% in each group.

Table 2 HRs[a] per 39 mg/dL (1 mmol/L) HDL-C increase according to sex, age and HDL-C range

HDL-C range, mg/dL (mmol/L)	Age group, years	Men			Women			*P*-value for interaction between sexes
		No. of deaths	*P*-value	HR (95% CI)	No. of deaths	*P*-value	HR (95% CI)	
<150	18–34	8962	0.004	1.11 (1.03–1.18)	3028	0.013	1.13 (1.03–1.25)	0.687
(<3.88)	35–44	21 304	<0.001	1.10 (1.05–1.14)	7828	0.434	1.03 (0.96–1.10)	0.095
	45–54	49 653	<0.001	0.95 (0.92–0.97)	18 657	<0.001	0.88 (0.84–0.91)	0.003
	55–64	74 943	<0.001	0.90 (0.88–0.92)	27 365	<0.001	0.88 (0.85–0.91)	0.271
	65–74	127 146	<0.001	0.85 (0.84–0.86)	61 652	<0.001	0.85 (0.83–0.87)	0.809
	75–99	81 029	<0.001	0.80 (0.79–0.82)	74 084	<0.001	0.81 (0.79–0.82)	0.861
	All ages	363 037	<0.001	0.89 (0.88–0.89)	192 614	<0.001	0.84 (0.83–0.86)	<0.001
<60	18–34	6382	0.850	0.99 (0.86–1.13)	1303	0.101	0.76 (0.55–1.05)	0.151
(<1.55)	35–44	15 444	<0.001	0.66 (0.61–0.72)	4216	<0.001	0.66 (0.56–0.78)	0.994
	45–54	36 043	<0.001	0.56 (0.53–0.59)	11 009	<0.001	0.58 (0.52–0.64)	0.697
	55–64	55 231	<0.001	0.59 (0.57–0.62)	18 215	<0.001	0.59 (0.55–0.64)	0.881
	65–74	95 301	<0.001	0.62 (0.60–0.64)	43 900	<0.001	0.62 (0.59–0.65)	0.903
	75–99	61 071	<0.001	0.63 (0.61–0.66)	54 038	<0.001	0.60 (0.58–0.63)	0.087
	All ages	269 472	<0.001	0.62 (0.61–0.63)	132 681	<0.001	0.60 (0.58–0.62)	0.104
60–149	18–34	2580	0.003	1.27 (1.09–1.49)	1725	<0.001	1.42 (1.21–1.68)	0.338
(1.55–3.87)	35–44	5860	<0.001	1.47 (1.34–1.61)	3612	0.004	1.19 (1.06–1.35)	0.007
	45–54	13 610	<0.001	1.35 (1.28–1.43)	7648	0.004	1.13 (1.04–1.23)	<0.001
	55–64	19 712	<0.001	1.26 (1.20–1.32)	9 150	0.005	1.12 (1.03–1.21)	0.011
	65–74	31 845	<0.001	1.11 (1.07–1.16)	17 752	0.010	1.08 (1.02–1.14)	0.371
	75–99	19 958	0.664	0.99 (0.94–1.04)	20 046	0.159	1.04 (0.99–1.10)	0.193
	All ages	93 565	<0.001	1.19 (1.16–1.21)	59 933	<0.001	1.09 (1.06–1.13)	<0.001

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

CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio.

[a]HRs were calculated by Cox models stratified by baseline age (using the STRATA statement, years: 18–24, 25–34, 35–44, 45–54, 55–64, 65–74, 75–84, 85–99) after adjustment for age at baseline, smoking status, alcohol use, physical activity, income status, body mass index, systolic blood pressure, fasting glucose, triglycerides, low-density lipoprotein cholesterol and known lipid disorder.

Discussion

A U-shaped relationship between HDL-C and all-cause mortality was observed in each age-sex group, perhaps except for the oldest group. The HDL-C levels associated with the lowest mortality were 40–59 mg/dL in men and 50–79 mg/dL in women. Younger adults had slightly lower optimal ranges than older adults in both sexes, despite the youngest adults having the highest mean HDL levels in each sex. The younger the age was, the stronger the positive association was in the HDL range of 60–149 mg/dL.

Shape of the association

Our study found clear U-curve associations of HDL-C with all-cause mortality, in accordance with several recent cohort studies.[6–11] Early epidemiological studies reported inverse associations,[22,23] largely because individuals with very high and modestly high HDL-C concentrations were often grouped together.[6,7] Additionally, non-linear associations were rarely considered in those studies. Upon closer scrutiny, some early studies, especially the MRFIT study, showed the possibility of U-curve associations between HDL-C and all-cause mortality.[22] The weaker positive associations with high HDL-C levels in older than in younger adults may partly account for the inverse associations observed in previous studies, in which the participants were mainly older adults.[24]

Optimal HDL-C ranges for survival

The optimal ranges for survival were 40–59 mg/dL in men and 50–79 mg/dL in women in our study. In other studies, the optimal levels were: 58–77 mg/dL (1.5–1.99 mmol/L) in a general population in the UK[7]; 54–77 mg/dL (1.4–2.0 mmol/L) in Danish men and 69–97 mg/dL (1.8–2.5 mmol/L) in Danish women[6]; 51–70 mg/dL in men and 61–90 mg/dL in women among Canadian outpatients[11]; and 70–79 mg/dL in the US general population aged over 50 years.[9] Overall, our study population had lower optimal levels than other general populations, although they had similar or higher mean HDL-C values than some other populations[8,9] especially for men.[6] Similar results were

reported for BMI, in that Koreans did not have a lower optimal BMI range than other populations, despite having a generally leaner body shape than Western populations.[19]

In our study, younger adults had lower optimal ranges than older adults, despite their higher average HDL-C levels. These results were unexpected. As shown for BMI and TC, the young adults had the lowest BMI and TC values and the optimal ranges for survival were also the lowest among the various age groups.[19,25] The young adults were therefore expected to have the highest optimal range for HDL-C, since they had the highest mean HDL-C values across all age groups. Our results showed the contrary. Additionally, assuming linear associations for HDL-C ranges of 60–149 mg/dL, positive associations were generally stronger at younger ages than at older ages. The weakest inverse associations in the youngest age group (<45 years) for HDL-C levels <60 mg/dL (1.55 mmol/L) were partially explained by the fact that they had the lowest optimal levels.

HDL-C concentrations by sex and age

HDL-C levels peaked at 22–23 years in men and at 24–27 years in women. After the peak age, HDL-C levels gradually decreased in women as age advanced, with a plateau in their 40 s, whereas in men, the levels decreased until 30–31 years and then were generally unchanged during the period of 32–83 years. The distribution of HDL-C levels by sex and age was generally different from those of other, mostly Western, populations[1,26–28] in which older adults have generally higher levels than younger adults, especially in women. However, Japanese people showed a similar pattern to that found in our study, where HDL levels gradually decreased with advancing age in women and generally showed no change with age in men aged 30 or more.[29] The lower prevalence of hormone replacement therapy (HRT) use in Korean women, at only 4.5%,[30] than in European-origin women[31,32] might have partially contributed to this finding, as HRT users tend to have higher HDL-C levels than non-users.[33] The exact mechanism behind this difference needs to be elucidated.

Clinical relevance

Our results showed that the common perception that the higher the HDL-C, the better, does not hold for even moderately high levels, especially in younger adults and particularly in men. The belief that high levels of HDL-C are a protective factor needs to come under close scrutiny.[1] Even moderately high HDL-C levels, such as 60–89 mg/dL (1.55–2.32 mmol/L) in men and 70–89 mg/dL (1.81–2.32 mmol/L) in women, may be associated with higher mortality, although very high HDL-C levels >90 mg/dL (2.33 mmol/L) are acknowledged to be associated with higher risk in some clinical guidelines.[34] Overall, it is important for clinicians to recognize that individuals with high HDL-C levels—particularly younger adults—may be at an elevated risk for all-cause mortality.[6]

The most common cut-off point for low HDL-C levels is around 40 mg/dL (1.0 mmol/L) in men and around 50 mg/dL (1.3 mmol/L) in women. Our study showed that the excess risk associated with 40–49 mg/dL was generally <10% in both sexes for mortality. Our results suggest that setting a different cut-off point for low HDL-C for men and women is not absolutely necessary to identify high-risk individuals.[1]

HDL-C levels might be a marker of general health, rather than a marker specific for cardiovascular disease (CVD).[11] The diseases associated with both low and high HDL-C levels and potential mechanisms have not been conclusively identified. Therefore, establishing which medical conditions are linked to low and high HDL-C levels, and clarifying the underlying mechanisms, is likely to be a fruitful line of future research with potential to improve health outcomes at the population level.[25]

Strengths and limitations of the study

The prospective design, large number of individuals from the general population and complete follow-up for death are the main strengths of this study. Furthermore, the participants were drawn from an ethnically homogeneous population who received coverage from the same health care system in a broadly similar environment; these factors reduce the possible impact of unknown confounders and therefore represent a major strength of this study. However, there are limitations. Due to the observational nature, this study cannot confirm causality. Thus, adjusting HDL-C levels to 'the optimal range' may not modify the risk of death. The lack of cause-specific mortality is a limitation of study. The study participants were homogeneously Korean. During 2003–18, 4 177 303 Koreans died (CVD 22%, cancer 28% and non-CVD-non-cancer 50%). Some results (e.g. the exact optimal ranges) may not be generalizable to other ethnicities with different distributions of causes of death. The specific findings of this study, such as the magnitude of relative risk associated with HDL-C levels and the optimal range of HDL-C, may vary across ethnic groups that have different levels and composition of HDL-C.

Conclusions

U-curve relationships between HDL-C and all-cause mortality were found, regardless of sex and age, perhaps except for the oldest adults. The HDL-C levels associated with the

lowest mortality were 40–59 mg/dL (1.03–1.54 mmol/L) in men and 50–79 mg/dL (1.29–2.06 mmol/L) in women. In both sexes, the optimal ranges of HDL-C level were slightly lower in younger adults than in older adults, although the highest mean HDL-C levels were found in the youngest adults. HDL-C levels ≥60 mg/dL (1.55 mmol/L) are not necessarily a sign of good health, especially in younger adults. Identification and proper management of diseases associated with both low and high HDL-C levels might improve survival.

Supplementary Data

Supplementary data are available at *IJE* online.

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Author Contributions

S.W.Y. initiated the study concept and design, statistically analysed the data and wrote the first draft. S.W.Y. and H.K. acquired the data. S.W.Y., S.J.P., J.J.Y., H.O. and H.K. analysed and interpreted the data and contributed to critical revision of the manuscript. All authors have read and approved the final submitted version of the manuscript. S.W.Y. is the study guarantor.

Conflict of Interest

The authors have no financial or non-financial competing interests to declare.

References

1. NCEP Expert Panel. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;**106**:3143–421.
2. Keene D, Price C, Shun-Shin MJ, Francis DP. Effect on cardiovascular risk of high density lipoprotein targeted drug treatments niacin, fibrates, and CETP inhibitors: meta-analysis of randomised controlled trials including 117,411 patients. *BMJ* 2014;**349**:g4379.
3. Voight BF, Peloso GM, Orho-Melander M *et al.* Plasma HDL cholesterol and risk of myocardial infarction: a Mendelian randomisation study. *Lancet* 2012;**380**:572–80.
4. Holmes MV, Asselbergs FW, Palmer TM *et al.*; on behalf of the UCLEB consortium. Mendelian randomization of blood lipids for coronary heart disease. *Eur Heart J* 2015;**36**:539–50.
5. Richardson TG, Sanderson E, Palmer TM *et al.* Evaluating the relationship between circulating lipoprotein lipids and apolipoproteins with risk of coronary heart disease: a multivariable Mendelian randomisation analysis. *PLoS Med* 2020;**17**:e1003062.
6. Madsen CM, Varbo A, Nordestgaard BG. Extreme high high-density lipoprotein cholesterol is paradoxically associated with high mortality in men and women: two prospective cohort studies. *Eur Heart J* 2017;**38**:2478–86.
7. Hamer M, O'Donovan G, Stamatakis E. High-density lipoprotein cholesterol and mortality: too much of a good thing? *Arterioscler Thromb Vasc Biol* 2018;**38**:669–72.
8. Hirata A, Sugiyama D, Watanabe M *et al.* Association of extremely high levels of high-density lipoprotein cholesterol with cardiovascular mortality in a pooled analysis of 9 cohort studies including 43,407 individuals: The EPOCH-JAPAN study. *J Clin Lipidol* 2018;**12**:674–84.e5.
9. Li ZH, Lv YB, Zhong WF *et al.* High-density lipoprotein cholesterol and all-cause and cause-specific mortality among the elderly. *J Clin Endocrinol Metab* 2019;**104**:3370–78.
10. Bowe B, Xie Y, Xian H, Balasubramanian S, Zayed MA, Al-Aly Z. High density lipoprotein cholesterol and the risk of all-cause mortality among U.S. Veterans. Clin J Am Soc Nephrol 2016;**11**:1784–93.
11. Ko DT, Alter DA, Guo H *et al.* High-density lipoprotein cholesterol and cause-specific mortality in individuals without previous cardiovascular conditions: the CANHEART study. *J Am Coll Cardiol* 2016;**68**:2073–83.
12. Holman DM, White MC, Shoemaker ML *et al.* Cancer prevention during early adulthood: highlights from a meeting of experts. *Am J Prev Med* 2017;**53**:S5–13.
13. Holzer M, Trieb M, Konya V, Wadsack C, Heinemann A, Marsche G. Aging affects high-density lipoprotein composition and function. *Biochim Biophys Acta* 2013;**1831**:1442–48.
14. Woudberg NJ, Goedecke JH, Blackhurst D *et al.* Association between ethnicity and obesity with high-density lipoprotein (HDL) function and subclass distribution. *Lipids Health Dis* 2016;**15**:92.
15. Carroll MD, Fryar CD, Nguyen DT. Total and high-density lipoprotein cholesterol in adults: United States, 2015-2016. *NCHS Data Brief* 2017;**290**:1–8.
16. Hirata A, Okamura T, Sugiyama D *et al.*; the NIPPON DATA90 Research Group. The relationship between very high levels of serum high-density lipoprotein cholesterol and cause-specific mortality in a 20-year follow-up study of Japanese general population. *J Atheroscler Thromb* 2016;**23**:800–09.
17. Kobayashi D, Noto H, Shimbo T *et al.* Repeated measures of extremely high levels of high-density lipoprotein cholesterol and subsequent all-cause mortality and cardiovascular events: a longitudinal study. *Atherosclerosis* 2019;**288**:17–25.
18. Oh IH, Hur JK, Ryoo JH *et al.* Very high high-density lipoprotein cholesterol is associated with increased all-cause mortality in South Koreans. *Atherosclerosis* 2019;**283**:43–51.
19. 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**:1696–705.
20. Min WK, Ko C, Kim YK *et al.* Annual report on external quality assessment in clinical chemistry in Korea (2009). *J Lab Med Qual Assur* 2010;**32**:1–10.
21. Committee of Clinical Practice Guideline of the Korean Society of Lipid and Atherosclerosis. *Korean Guidelines for the*

Management of Dyslipidemia. 4th edn. https://www.lipid.or.kr/bbs/skin/default/download.php? code=care&number=1314 (14 June 2020, date last accessed).
22. Gordon DJ, Probstfield JL, Garrison RJ *et al.* High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. *Circulation* 1989;**79**:8–15.
23. Wilson PW, Abbott RD, Castelli WP. High density lipoprotein cholesterol and mortality. The Framingham Heart Study. *Arteriosclerosis* 1988;**8**:737–41.
24. Corti MC, Guralnik JM, Salive ME *et al.* HDL cholesterol predicts coronary heart disease mortality in older persons. *JAMA* 1995;**274**:539–44.
25. 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**:1596.
26. Gupta R, Sharma M, Goyal NK, Bansal P, Lodha S, Sharma KK. Gender differences in 7 years trends in cholesterol lipoproteins and lipids in India: Insights from a hospital database. *Indian J Endocr Metab* 2016;**20**:211–18.
27. Rouvre M, Vol S, Gusto G *et al.* Low high density lipoprotein cholesterol: prevalence and associated risk-factors in a large French population. *Ann Epidemiol* 2011;**21**:118–27.
28. Thelle DS, Forde OH, Arnesen E. Distribution of high-density lipoprotein cholesterol according to age, sex, and ethnic origin: cardiovascular disease study in Finnmark 1977. *J Epidemiol Community Health* 1982;**36**:243–47.
29. Arai H, Yamamoto A, Matsuzawa Y *et al.* Serum lipid survey and its recent trend in the general Japanese population in 2000. *J Atheroscler Thromb* 2005;**12**:98–106.
30. Cho MK, Park HM. The National Use of Hormonal Therapy in Postmenopausal Women in 2010. *J Korean Soc Menopause* 2011;**17**:150–54.
31. Nagel G, Lahmann PH, Schulz M, Boeing H, Linseisen J. Use of hormone replacement therapy (HRT) among women aged 45-64 years in the German EPIC-cohorts. *Maturitas* 2007;**56**:436–46.
32. Ness J, Aronow WS. Prevalence and causes of persistent use of hormone replacement therapy among postmenopausal women: a follow-up study. *Am J Ther* 2006;**13**:109–12.
33. Crespo CJ, Smit E, Snelling A, Sempos CT, Andersen RE; NHANES III. Hormone replacement therapy and its relationship to lipid and glucose metabolism in diabetic and nondiabetic postmenopausal women: results from the Third National Health and Nutrition Examination Survey (NHANES III). *Diabetes Care* 2002;**25**:1675–80.
34. Mach F, Baigent C, Catapano AL *et al.*; ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;**41**:111–88.

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Commentary: Big data bring big controversies: HDL cholesterol and mortality

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No matter how large a study, how richly it is phenotyped or how intriguing the findings that emerge, it behoves us to be sceptical in interpreting evidence arising from observational epidemiological studies. Various intractable sources of error, including reverse causality and residual confounding, hinder interpretations on potential causal relationships between exposures and outcomes in observational study settings.[1]

High-density lipoprotein cholesterol (HDL-C) serves as an excellent cautionary example on over-reliance on observational epidemiology when studying and interpreting the potential clinical role of a biomarker. For decades, in a