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Total cholesterol and mortality from ischemic heart disease and overall cardiovascular disease in Korean adults

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Abstract

It is not completely clear whether "the lower, the better" cholesterol hypothesis for cardiovascular disease (CVD) and ischemic heart disease (IHD) can be applied to general populations with a low risk of heart disease mortality.

We prospectively followed up 503,340 Koreans who participated in routine health checkups during 2002–2003 until 2013 via linkage to national mortality records.

Nonlinear associations with total cholesterol (TC) were found: U-curves for overall CVD (I00-I99; nadir at 180–200 mg/dL) and a reverse-L-curve for IHD (I20-I25). Assuming a linear association in the lower range (<200 mg/dL), TC was inversely associated with CVD mortality (HR per 39 mg/dL [1 mmol/L] increase = 0.90). In the upper range (200–349 mg/dL), TC was positively associated with CVD mortality, largely due to IHD (HR = 1.19), especially acute myocardial infarction (HR = 1.23). The associations were generally similar in men versus women and in middle-aged (40–64 years) versus elderly (≥65 years) adults.

TC levels of 180–200 mg/dL were associated with the lowest CVD mortality. Below 200 mg/dL, TC had no graded positive associations with IHD mortality. It remains unclear whether the lowest cholesterol levels are associated with the least mortality from CVD and IHD in Korean adults with a low risk of heart disease.

Abbreviations: AMI = acute myocardial infarction, BMI = body mass index, CVD = cardiovascular disease, IHD = ischemic heart disease, LDL-C = low-density lipoprotein cholesterol, SBP = systolic blood pressure, TC = total cholesterol.

Keywords: Asians, blood cholesterol, cardiovascular disease, cohort studies, heart disease

1. Introduction

Ischemic heart disease (IHD) is a leading cause of death worldwide.[1,2] Reduction of total cholesterol (TC) has been an integral part of public health campaigns. TC has also been a major part of cardiovascular disease (CVD) risk prediction and prevention models.[3–5] For IHD prevention, "the lower, the better" cholesterol hypothesis has been accepted in the medical community for persons with a high risk of heart disease, especially men with manifest CVD, in whom heart disease mortality constituted approximately 50% of all deaths.[6] In the Korean general population with a relatively low risk of heart disease, however, it is less clear whether the lower the cholesterol levels are, the lower the mortality risks of IHD are.[7]

Through a large prospective cohort study including 503,340 Korean participants, we set out to obtain detailed information on the association between TC and mortality from IHD and overall CVD, and to estimate the cholesterol levels associated with the lowest mortality. In Koreans, IHD mortality constituted approximately 5% of all-cause mortality. Further, detailed estimates of the relative risk associated with TC levels <140 mg/dL could help inform decision-making in the clinical and public health settings for CVD prevention and management.

2. Methods

2.1. Data statement

Access to the data analyzed in this study is available from the National Health Insurance Service (NHIS) of Korea for researchers, upon review and approval of their study protocol by the NHIS.[8,9]

2.2. Study population and follow-up

Compulsory health insurance is provided by the NHIS to 97% of the population of Korea.[10] The cohort of this study (n = 514,795) comprised a random sample of 10% of the 5.15 million individuals covered by the NHIS who were 40–79 years of age in

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2002 and underwent health examinations in 2002 or 2003. From this sample, 11,455 subjects were excluded because information was missing on TC (n = 1710), body mass index (BMI), systolic blood pressure (SBP), or fasting glucose; because they had an extremely high BMI (≥50 kg/m^2, n = 52); or because they had a history of heart disease and stroke (n = 9693). Record linkage with national death records was used to identify CVD deaths among the remaining 503,340 subjects through December 31, 2013. International Classification of Diseases-10th Revision codes were used to define cause-specific death: I00-I99 for CVD, I20-I25 for IHD, and I21 for acute myocardial infarction (AMI). This study was approved by the Institutional Review Board of Catholic Kwandong University, Republic of Korea. The requirement for informed consent was waived due to the use of anonymized data provided by the NHIS following thorough confidentiality protocols.[11]

2.3. Data collection

Enzymatic methods were used to assay fasting serum TC and glucose levels. SBP was measured using a standard mercury sphygmomanometer, with the participant seated. Height was measured to the nearest centimeter and weight was measured to the nearest kilogram.[10] BMI was calculated as weight (kilograms) divided by the square of height (meters) (kg/m^2). Physical activity, alcohol use, and smoking history were assessed via a questionnaire. All health examinations and the data collection process followed a standard protocol officially registered by the Ministry of Health and Welfare. The Korean Association of Quality Assurance for Clinical Laboratory supervised external quality assessment for clinical chemistry, such as TC measurements, in participating hospitals, with regular assessments of assay quality.[12]

2.4. Statistical analysis

Participants were subdivided into 8 groups by TC levels (<140, 140–159, 160–179, 180–199 [reference], 200–219, 220–239, 240–259, and ≥260 mg/dL). The reference category was defined as the category with the lowest CVD mortality. Log risk was regressed on TC as a continuous variable within the ranges of <200 mg/dL (the lower range), 200–349 mg/dL (the upper range), and <350 mg/dL (the full range), resulting in HRs per 39 mg/dL (1 mmol/L) increase in TC within each range. The data were also analyzed using a restricted cubic spline transformation analysis of TC with 3 knots (150, 190, and 230 mg/dL).

Cox proportional hazard models were used to calculate the HRs for CVD mortality stratified by baseline age (40–44, 45–54, 55–64, 65–74, and 75–80 years) after adjusting for baseline age (continuous variable; within each age group), sex, alcohol use (frequency; monthly or less, 2 days/month to 2 days/week, 3–7 days/week, and missing information [n = 9458]), smoking status (current smoker, former smoker, never smoker, and missing information [n = 21,282]), physical activity (at least once a week; yes or no), beneficiary income status (deciles; below 4 [low income], 4–7, 8–10 [high income]), SBP (continuous variable), fasting glucose (continuous variable), and BMI (continuous variable). In a sensitivity analysis, further adjustment was made for baseline lipid-lowering medication use (yes [n = 7742] or no).

The nonlinear associations of TC with CVD mortality were assessed with a likelihood ratio test. In this test, the model with only the linear term was compared to the corresponding model with both the linear and the cubic spline terms. Sensitivity analyses were conducted using subgroups with varying categories of TC.

All *P* values were 2-sided. All analyses used SAS version 9.4 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Participants

During a mean 10.5 years of follow-up, 2770 women and 4206 men died from CVD. The number of deaths from IHD, AMI, total stroke, hemorrhagic stroke, and ischemic stroke were 1313, 1008, 1927, 631, and 622, respectively, in men and 606, 467, 1456, 553, and 422, respectively, in women. At baseline the mean TC level was 200.4 ± 38.7 mg/dL (202.5 ± 39.4 mg/dL in women; 198.7 ± 38.1 mg/dL in men) and the mean age was 52.9 ± 9.7 years (Table 1). Individuals with higher TC values tended to be older, female, never smokers, and infrequent alcohol users, and more likely to have higher blood pressure, fasting glucose, and BMI (Table S1, http://links.lww.com/MD/D210).

3.2. TC and CVD mortality

The associations between TC and CVD mortality were generally nonlinear. In the sex- and age-adjusted analysis, U-curve associations between TC and overall CVD mortality were found, with a nadir at 180–199 mg/dL (Fig. 1). Both above and below this range, progressive excess mortality from CVD was observed. Among the CVD subtypes, mortality from IHD (including AMI) increased with cholesterol ≥200 mg/dL, but it was not associated with TC < 200 mg/dL (a reverse L-curve).

After adjustment for other confounders, the associations generally did not substantially change (Table S2, http://links.lww.com/MD/D210). Further adjustment for lipid-lowering medication use at baseline yielded no substantial change (Table S3, http://links.lww.com/MD/D210).

In the restricted cubic spline analysis, the patterns of associations and TC values associated with the lowest mortality were generally same as in the categorical analysis of TC, and the nonlinear associations were statistically confirmed (Fig. 2).

Assuming a linear association below 200 mg/dL, TC was inversely associated with CVD mortality (Fig. 3; HR per 39 mg/dL higher level = 0.90). Assuming a linear association in the upper range, TC was positively associated with CVD mortality, largely due to a strong association with IHD (HR = 1.19), especially AMI (HR = 1.23). In the full range (<350 mg/dL), assuming linear relationships, TC was positively associated with mortality from overall CVD, including IHD.

3.3. Subgroup analysis

Women had lower HRs for overall CVD mortality in the upper range of cholesterol (Fig. 4). For IHD mortality, HRs in the upper range were generally lower in women than in men, but with overlapping confidence intervals (Figs. 5 and 6). In a linear analysis in the upper range of cholesterol, middle-aged adult did not have significantly stronger associations than elderly adults (Figs. S1 and S2, http://links.lww.com/MD/D210), while men did not have significantly higher HRs than women for IHD mortality (Figs. S3 and S4, http://links.lww.com/MD/D210; e.g., for AMI mortality, the HR in men was 1.27 [95% CI = 1.12–1.43], whereas it was 1.16 in women [1.00–1.35], $P_{\text{heterogeneity}} = 0.374$).

Table 1

Characteristics of participants according to total cholesterol categories.

Variables	Characteristics	Total	Women	Men
		n = 503,340	n = 229,865	n = 273,475
Total cholesterol	mg/dL	200.4 ± 38.7	202.5 ± 39.4	198.7 ± 38.1
Age	years	52.9 ± 9.7	53.8 ± 9.8	52.1 ± 9.4
Systolic blood pressure	mm Hg	127.1 ± 18.2	125.2 ± 18.9	128.7 ± 17.5
Fasting serum glucose	mg/dL	98.3 ± 34.6	96.0 ± 32.9	100.2 ± 35.9
Body mass index	kg/m^2	24.0 ± 3.0	24.0 ± 3.1	24.0 ± 2.8
Sex	Women	229,865 (45.7)	229,865 (100.0)	0 (0.0)
	Men	273,475 (54.3)	0 (0.0)	273,475 (100.0)
Smoking status	Never smoker	322,696 (64.1)	212,804 (92.6)	109,892 (40.2)
	Past smoker	42,543 (8.5)	2,099 (0.9)	40,444 (14.8)
	Current smoker	116,820 (23.2)	6,281 (2.7)	110,539 (40.4)
	Missing	21,281 (4.2)	8,681 (3.8)	12,600 (4.6)
Alcohol use frequency, days	≤1/month	278,394 (55.3)	184,697 (80.4)	93,697 (34.3)
	2/month-2/week	158,360 (31.5)	35,386 (15.4)	122,974 (45.0)
	3–7/week	57,128 (11.3)	4,208 (1.8)	52,920 (19.4)
	Missing	9,458 (1.9)	5,574 (2.4)	3,884 (1.4)
Physical activity	≥1 times/week	206,821 (41.1)	73,571 (32.0)	133,250 (48.7)
Income status, decile	<4 (low-income)	115,882 (23.0)	66,265 (28.8)	49,617 (18.1)
	4–7	163,984 (32.6)	73,928 (32.2)	90,056 (32.9)
	>7 (high-income)	223,474 (44.4)	89,672 (39.0)	133,802 (48.9)
Total cholesterol, mg/dL	<140	19,167 (3.8)	7,776 (3.4)	11,391 (4.2)
	140-159	46,068 (9.2)	19,938 (8.7)	26,130 (9.6)
	160-179	86,874 (17.3)	38,266 (16.6)	48,608 (17.8)
	180-199	109,349 (21.7)	48,897 (21.3)	60,452 (22.1)
	200-219	99,108 (19.7)	45,336 (19.7)	53,772 (19.7)
	220-239	69,991 (13.9)	32,899 (14.3)	37,092 (13.6)
	240-259	39,913 (7.9)	19,470 (8.5)	20,443 (7.5)
	≥260	32,870 (6.5)	17,283 (7.5)	15,587 (5.7)

Data are expressed as mean ± SD or n (%). *P* values, which were calculated by the chi-square test and one-way ANOVA between sex, were <.001 for each variable, except body mass index (*P* = .631). To convert total cholesterol from mg/dL to mmol/L, multiply by 0.02586. To convert glucose from mg/dL to mmol/L, multiply by 0.0555.

In the categorical analyses, except for the highest (≥260 mg/dL) and lowest (<140 mg/dL) TC categories, TC categories were not associated with statistically significantly higher mortality from CVD or IHD compared to the reference category (Table S2, http://links.lww.com/MD/D210).

Middle-aged (40–64 years old) and non-hypertensive persons (SBP < 140 mm Hg) had higher estimated relative risks for mortality from CVD or IHD than elderly (aged ≥60 years) and hypertensive (SBP ≥140 mm Hg) persons both in the lower and upper range, although the confidence intervals overlapped between comparison groups (Figs. 4–6). In the elderly, the HRs were 1.11 (95% CI = 1.04–1.18) for overall CVD, 1.16 (1.04–1.31) for IHD, and 1.19 (1.05–1.36) for AMI, in the upper range.

3.4. Sensitivity analysis using standard classification of TC

High TC levels (≥240 mg/dL), but not borderline levels (200–239 mg/dL), were associated with greater CVD mortality, compared to the desirable level of <200 mg/dL (Tables S4 and S5, http://links.lww.com/MD/D210). For IHD, both borderline and high levels were associated with greater mortality.

4. Discussion

TC had nonlinear associations with CVD mortality, U-curve associations for overall CVD, and reverse-L-curve associations for IHD, including AMI. CVD mortality was lowest at TC levels of 180–199 mg/dL, while above and below this range, progressive excess mortality from CVD was found. For IHD mortality, a positive graded association was found in the upper range (≥200 mg/dL), while no association was found in the lower range (<200 mg/dL).

4.1. ischemic heart disease (IHD)

Many previous studies have reported a continuous graded association of cholesterol levels with IHD. Surprisingly, however, few studies have provided information on the risks of IHD associated with detailed TC categories covering the range <180 mg/dL,[13–16] perhaps due to the small number of individuals with TC<180 mg/dL in European-origin populations. Upon closer scrutiny, previous studies have provided evidence that TC is strongly and directly related to IHD mortality, without evidence of a threshold, down to around 180–200 mg/dL but not below this range,[13–16] and our study yielded further supporting evidence of this finding. This nonlinear association of TC with IHD is a novel, but not improbable, finding given the evidence of a nonlinear association of SBP with CVD, including IHD [17]. Several studies found similar results: below around 180–200 mg/dL, there were no positive associations between cholesterol levels and IHD.[13,15,18,19] These studies, however, have not considered non-linear associations. Statin trials showed that more intensive statin use reduced IHD mortality more than less intensive use, although statin trials among Asian populations have shown no clear advantage against IHD mortality.[20,21] However, the lack of trials examining whether lower cholesterol targets have more beneficial effects indicates that evidence from clinical trials may not be definitive enough to confirm that "the lower, the

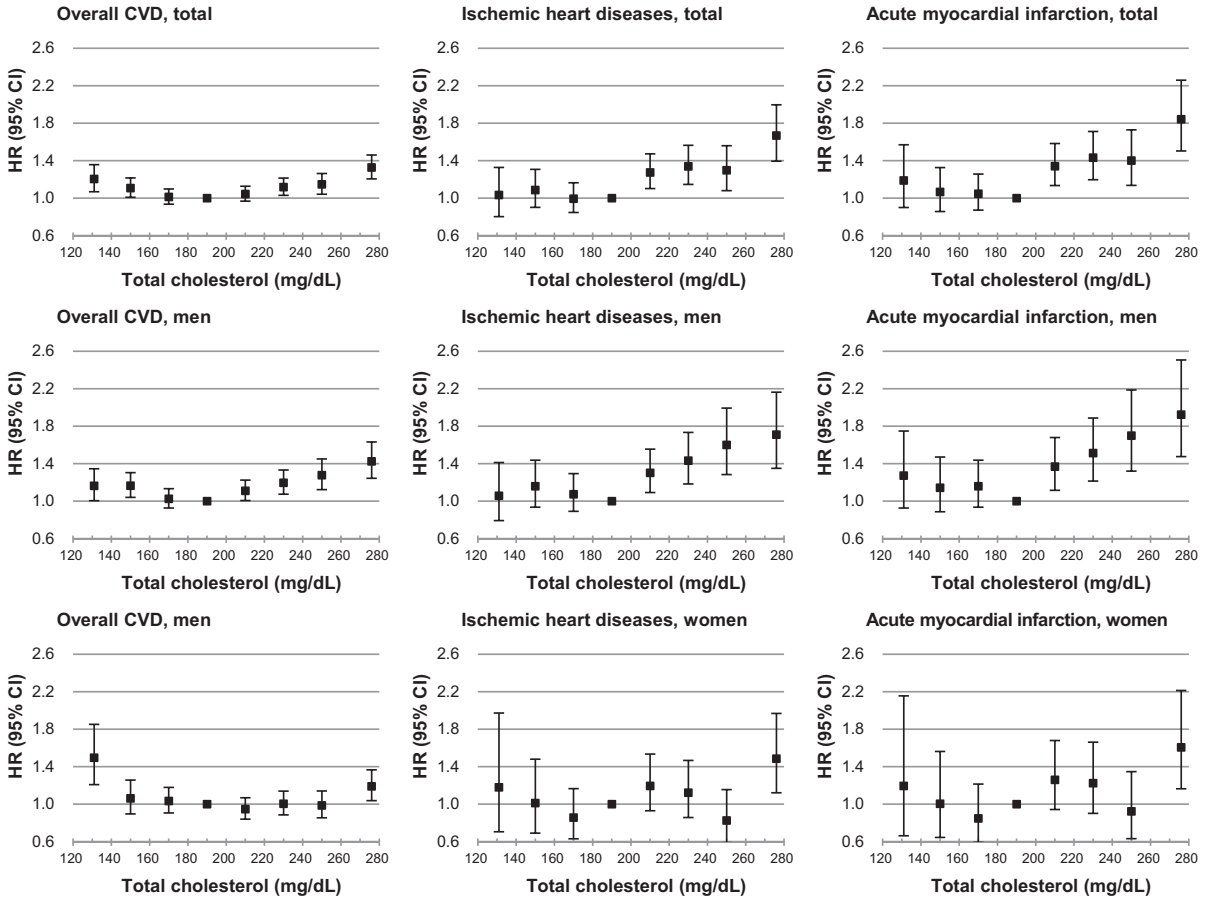


Figure 1. Age- and sex-adjusted HRs across 8 categories of baseline total cholesterol (TC) for CVD mortality. TC categories (<140, 140–159, 160–179, 180–199 [reference], 200–219, 220–239, 240–259, and ≥260 mg/dL). The midpoint was used as a representative value of each TC category, except both ends (131 and 276), for which the median was used. HRs and 95% CIs were calculated using Cox proportional hazard models stratified by baseline age (years: 40–44, 45–54, 55–64, 65–74, 75–80). CI = confidence interval, CVD = cardiovascular disease, HR = hazard ratio. To convert TC from mg/dL to mmol/L, multiply by 0.02586.

better."[22] Additionally, the achieved cholesterol levels had reverse-L-curve, or even U-curve, associations with vascular morbidity and mortality in some,[7,23,24] but not all,[25] observational studies in individuals taking statins. Overall, in Korean adults, the lowest cholesterol levels were not associated with the lowest mortality, and no positive association was found in the levels <200 mg/dL, whereas a positive association was found in the range ≥200 mg/dL.

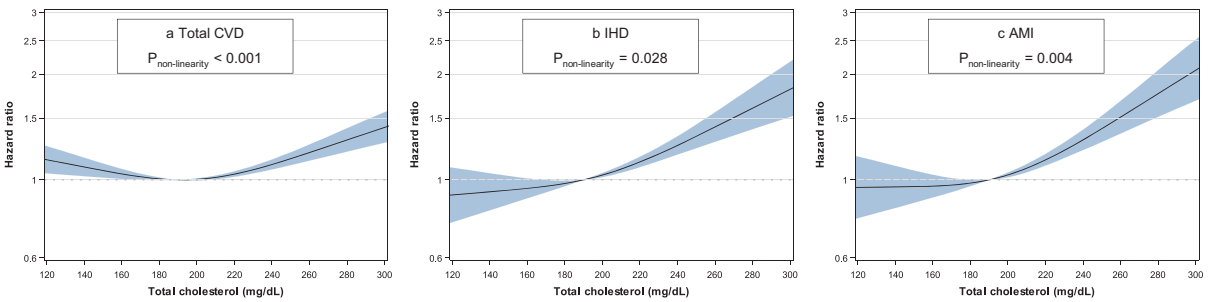
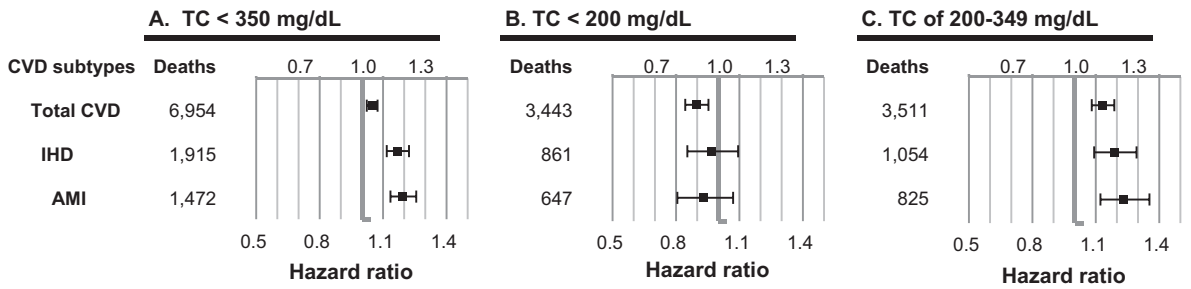


Figure 2. HRs for mortality from CVD and IHD using restrictive cubic spline analysis. Restricted cubic splines of total cholesterol with 3 knots (150, 190, and 230 mg/dL) and 190 mg/dL as a reference were used for individuals with total cholesterol values <350 mg/dL (n = 502,369). Hazard ratios and 95% CIs were calculated using Cox proportional hazards models stratified by baseline age (years: 40–44, 45–54, 55–64, 65–74, 75–80), after adjustment for age at baseline (continuous variable), smoking status, alcohol use, income status, physical activity, body mass index, systolic blood pressure, and fasting glucose levels. AMI = acute myocardial infarction, CI = confidence interval, CVD = cardiovascular diseases, HR = hazard ratio, IHD = ischemic heart disease. To convert cholesterol from mg/dL to mmol/L, multiply by 0.02586.



	A. TC < 350 mg/dL		B. TC < 200 mg/dL		C. TC of 200-349 mg/dL	
	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)
Total CVD	<0.001	**1.05** (1.02-1.07)	<0.001	**0.90** (0.84-0.95)	<0.001	**1.13** (1.08-1.19)
IHD	<0.001	**1.17** (1.12-1.22)	0.585	**0.97** (0.85-1.09)	<0.001	**1.19** (1.09-1.29)
AMI	<0.001	**1.19** (1.13-1.26)	0.307	**0.93** (0.81-1.07)	<0.001	**1.23** (1.12-1.35)

Figure 3. HRs per each 39 mg/dL (1 mmol/L) increase in total cholesterol (TC), according to TC range. *HRs and 95% CIs were calculated using Cox proportional hazard models stratified by baseline age (years: 40–44, 45–54, 55–64, 65–74, 75–80), after adjustment for the same variables as in Figure 2. The same abbreviations are used as in Figure 2. To convert glucose from mg/dL to mmol/L, multiply by 0.02586.

Our estimated relative risks associated with 1 mmol/L increases in TC (HR = 1.19, in the upper range) were comparable to those in a recent systematic review,[26] but were lower than those reported in a large US study including men aged 35–57 years.[16]

4.2. Overall CVD

U-curve associations were found between TC and CVD in our study. A recent review claimed that cholesterol had no association or an inverse association with CVD mortality in

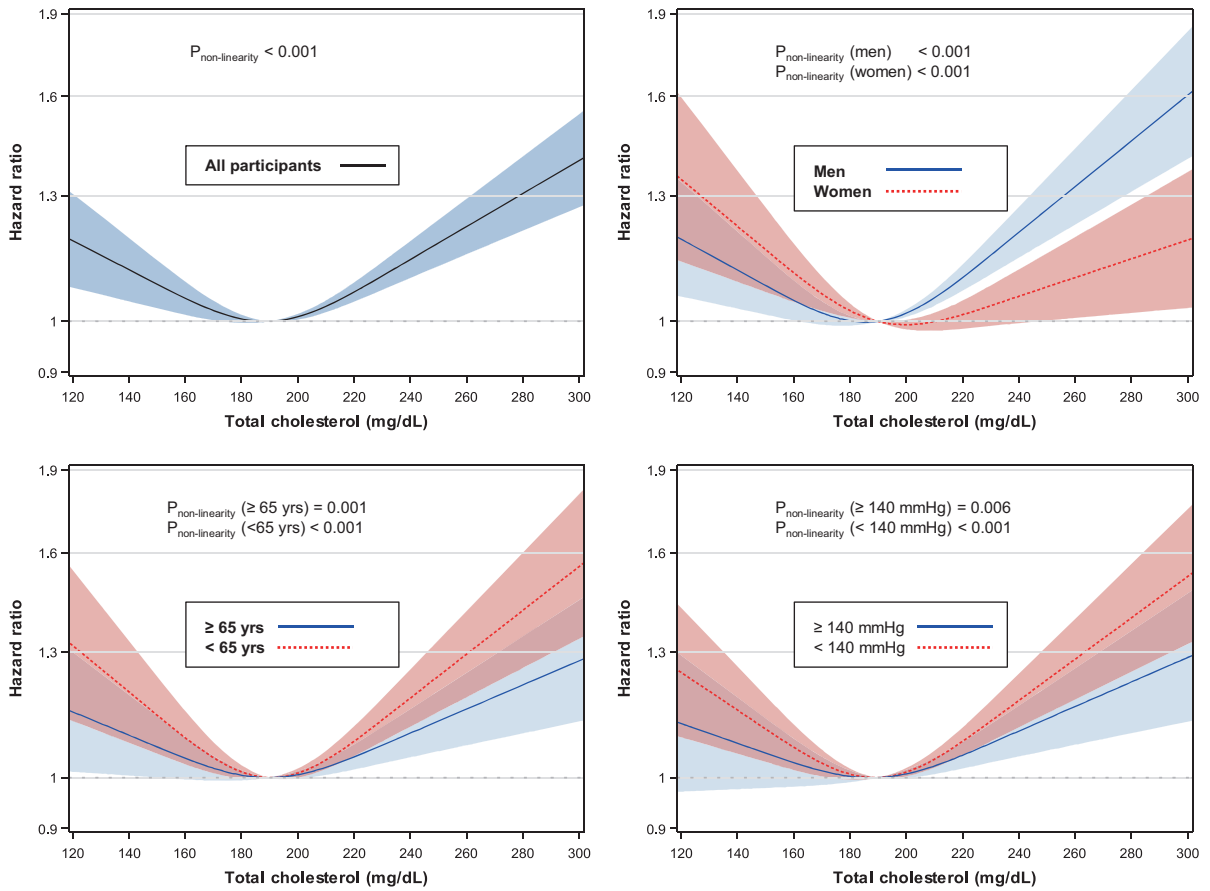


Figure 4. HRs for CVD mortality using restrictive cubic spline analysis according to sex, age, and systolic blood pressure. The same methods and abbreviations are used as in Figure 2. To convert cholesterol from mg/dL to mmol/L, multiply by 0.02586.

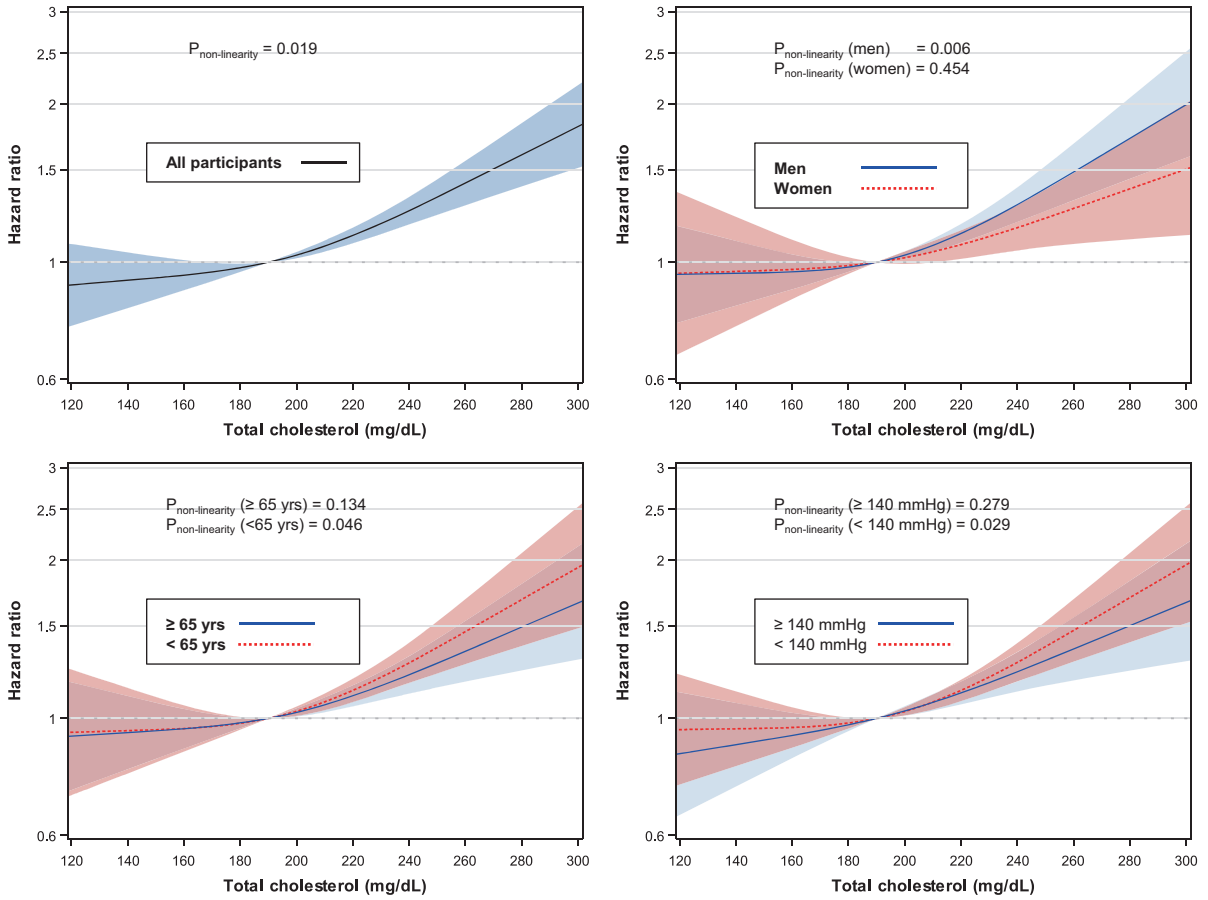


Figure 5. HRs for IHD mortality using restrictive cubic spline analysis according to sex, age, and systolic blood pressure. The same methods and abbreviations are used as in Figure 2. To convert cholesterol from mg/dL to mmol/L, multiply by 0.02586.

the elderly.[27] Their conclusion, however, did not consider subtypes of CVD or nonlinear associations between cholesterol and CVD. The shape of the association of TC with mortality was different across CVD subtypes: a reverse L-curve for IHD was found in the current study; U-curves for total stroke, and an L-curve for hemorrhagic stroke, especially intracerebral hemorrhage, were found in our previous study of the same study population.[9] The negative association in the lower range is mostly explained by hemorrhagic stroke,[9] while the positive association in the upper range is largely accounted for by IHD. In our study, in the upper range, each 1 mmol/L higher TC was associated with 11% higher mortality from CVD (95% CI, 4%–18%), 16% for IHD (4%–31%), and 19% for AMI (5%–36%) in the elderly (Figs. 4–6). The corresponding risk associated with stroke mortality was 11% (2%–21%) in the elderly, as shown in our previous research.[9] Additionally, in the upper range, no CVD subtypes had negative associations with TC, while in the lower range, mortality from CVD, especially ICH, was inversely associated with TC.[9] These inverse associations of TC remained stable after adjusting for high-density lipoprotein cholesterol in Korean and Japanese populations.[28,29] The higher mortality from CVD associated with lower cholesterol levels might be the effect of a long-term period of lower levels, or reflect the effect of this factor in individuals with a low risk of heart disease, which most randomized trials cannot reflect. Additionally, the results from a recent systematic review, stating that a greater reduction of cardiovascular mortality was not found in groups with more intensive cholesterol-lowering regimens compared those with less intensive regimens when the baseline low-density lipoprotein cholesterol (LDL-C) level was less than 100 mg/dL, agrees with the current study to some degree.[30]

Both cubic spline and categorical analysis plots suggested that women had a higher TC range associated with the lowest CVD mortality (around 200–220 mg/dL; approximately equivalent to 125–140 mg/dL of LDL-C in Koreans) than men (around 180–200 mg/dL; roughly equivalent to 110–125 mg/dL of LDL-C), and that women might have weaker positive associations in the upper range than men. However, women had no materially weaker associations with overall CVD or any subtype. Upon closer scrutiny, combining the impacts of a modestly lower HR in the upper range in women than in men with the larger proportion of hemorrhagic stroke deaths and lower proportion of IHD deaths among CVD mortality in women than in men in Korea during the follow-up period [9,31] would explain this finding. This result suggests that for overall CVD, the pattern of associations and the TC range associated with the lowest risk may differ across regional and ethnic populations or different time periods in a population, since the distribution of CVD subtypes varies by time period, region, and ethnicity.[32,33]

The patterns of associations for CVD and its subtypes were generally similar between middle-aged (40–64 years) and elderly (≥65 years) adults, as well as non-hypertensive and hypertensive

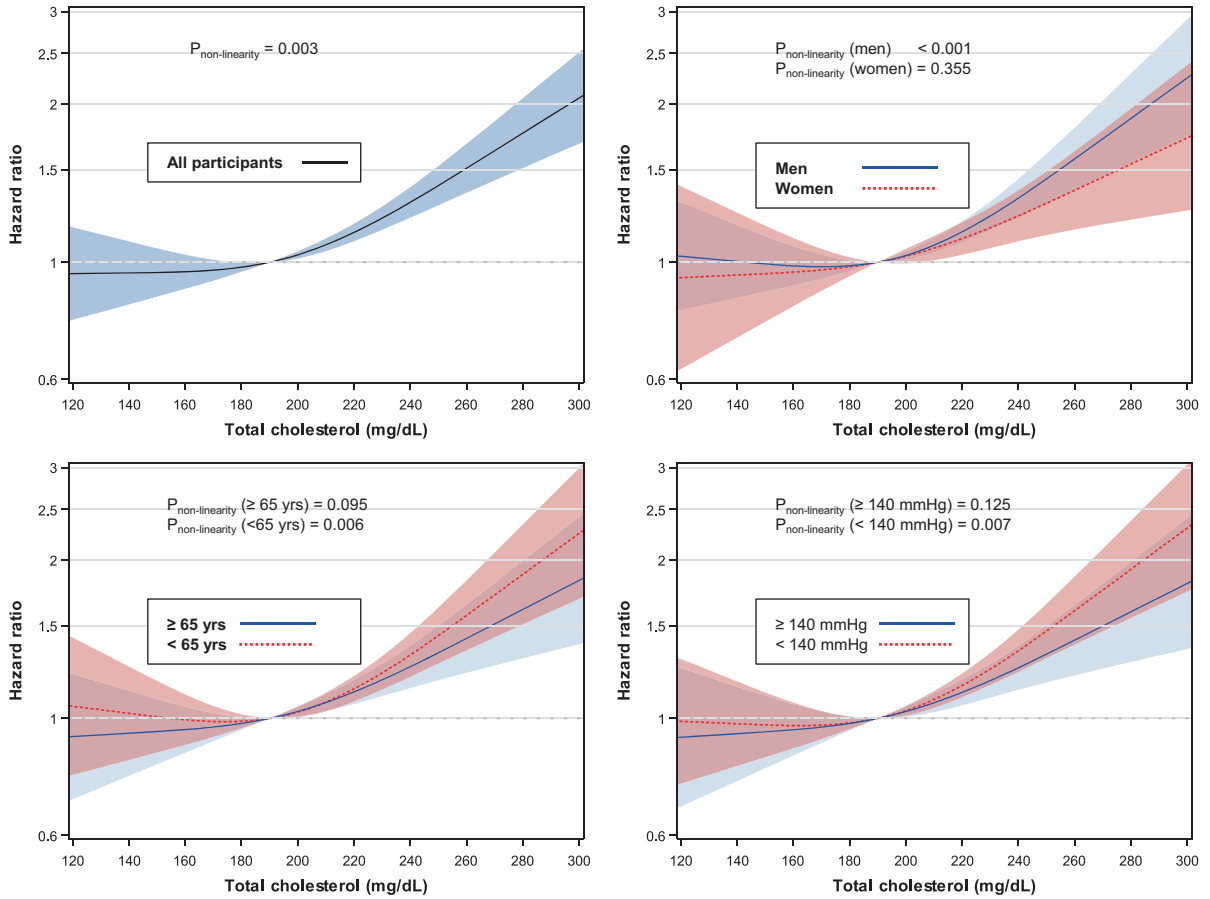


Figure 6. HRs for AMI mortality using restrictive cubic spline analysis according to sex, age, and systolic blood pressure. The same methods and abbreviations are used as in Figure 2. To convert cholesterol from mg/dL to mmol/L, multiply by 0.02586.

persons, which may be in discordance with a collaborative study in which age and blood pressure seemed to affect the strength and the direction of the association. That collaborative study, however, collected information from 61 prospective studies with different regions, ethnicities, and time periods.[9,14] An analysis of 65,594 Japanese adults reported that the associations between TC levels and deaths from IHD were similar in each sex and age subgroup, except for elderly women, while the confidence interval associated with each TC category generally overlapped across sex and age subgroups.[34] The Evidence for Cardiovascular Prevention from Observational Cohorts in Japan (EPOCH–JAPAN) and the Asia Pacific Cohort Studies Collaboration (APCSC) suggested a significant interaction between SBP and TC for CVD; however, the suggested patterns of interaction were different between those studies.[35,36] The EPOCH-JAPAN study reported that the HRs associated with TC were greater in persons with higher SBP, whereas the associations were greater in persons with lower SBP in the APCSC study.

4.3. Strengths and limitations of the study

The main strengths of this study include its prospective design, large sample size, and complete follow-up for mortality. Another strength is the fact that our study population consisted of ethnically homogeneous individuals covered by the same health care system and living in a similar environment.[37] A further strength is that our study estimated the risk associated with TC levels including those lower than 140 mg/dL. Nonetheless, this study has several limitations. First, the fact that the study population was homogenously Korean may affect the generalizability of our findings. The cholesterol-lowering effects of statins have reported to be stronger in Asians than in Western populations.[38] The beneficial effects of intensive statin therapy over moderate-dose therapy have not been confirmed in Asian populations.[21] The genetic factors related to cholesterol biosynthesis, cholesterol transport, and statin metabolism may be different across ethnic groups to some degree.[38] Considering these differences between ethnic groups, some results, such as the magnitude of relative risk associated with TC for CVD and IHD deaths and the TC range associated with the lowest mortality, may need further assessment in other populations with varying TC levels, health care utilization, distribution of CVD subtypes, and distribution of environmental and individual risk factors. Second, cholesterol-lowering therapy use during follow-up was unaccounted for in the analysis. However, due to relatively lower statin use in the Korean population (<10% in persons with hypercholesterolemia),[39] the effects of not considering lipid-lowering medication during follow-up were assumed to be modest. Third, this study used a single measurement of TC at baseline. The estimated relative risk may underestimate the true

association, due to a regression dilution effect.[14] Fourth, information on the cause of death obtained from death certificates may be imperfect due to misclassifications, but a comparison of death certificates with medical records in Korea showed them to be reasonably valid.[40] Additionally, the pattern of potential misclassification tends not to vary according to TC levels, so this factor is not likely to have resulted in an overestimation of the risk.

5. Conclusions

U-curve and reverse L-curve associations were found between TC and mortality from overall CVD and IHD, respectively, in Korean adults who had a relatively low risk of heart disease mortality. For overall CVD, TC levels of 180–200 mg/dL were associated with the lowest mortality. TC had no positive associations with IHD mortality in the lower range. The shape of the association for overall CVD, however, might be different across ethnic groups, particularly due to the distribution of CVD subtypes in a population. The associations for CVD and IHD mortality were generally similar in men versus women and in middle-aged (40–64 years) versus elderly (≥65 years) adults.

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Investigation: Sang-Wook Yi.
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