

Review

Criticism of Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases

Cholesterol Is Not the Cause of Heart Attacks. Then What Is?

Translated and revised from Med Check (in Japanese) Jul 2026: 26 (126): p76-82.

MedCheck Editorial Team

Supplementary Appendix

2026/8/31

MedCheck Editorial Team

Supplement 1: Inverse association between cholesterol and all-cause deaths.

1-A : Summary list of newly found researches on association between cholesterol level and all-cause mortality

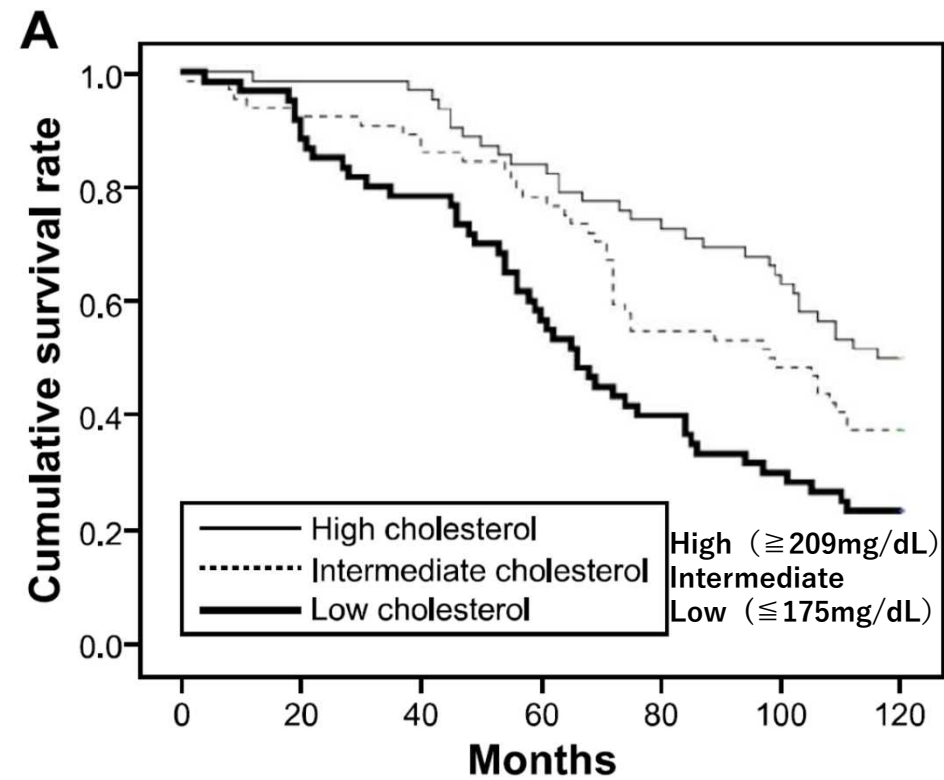
Ref. No	References	Country	Age	Total/LDL	Cholesterol Groups	Primary Outcome	Association
13	Tuikkala P, Hartikainen S, Korhonen MJ et al. Serum total cholesterol levels and all-cause mortality in a home-dwelling elderly population: a six-year follow-up. Scand J Prim Health Care. 2010 Jun;28(2):121-7. doi: 10.3109/02813432.2010.487371.PMID: 20470020	Finland	75–	Total	3	All-cause mortality.	INV
14	Takata Y, Ansai T, Soh I et al. Serum total cholesterol concentration and 10-year mortality in an 85-year-old population. Clin Interv Aging. 2014 Feb 13;9:293-300. doi: 10.2147/CIA.S53754. eCollection 2014.PMID: 24611005	Japan	85	Total	3	All-cause mortality.	INV
15	He GD A nonlinear association of total cholesterol with all-cause and cause-specific mortality. Nutr Metab (Lond). 2021 Mar 10;18(1):25. doi: 10.1186/s12986-021-00548-1.PMID: 33691735	US	≥65 <65	Total	6	All-cause, CVD, Cancer mortality	INV INV *a
16	Kawamoto R, Kikuchi A, Akase T et al. Low density lipoprotein cholesterol and all-cause mortality rate: findings from a study on Japanese community-dwelling persons. Lipids Health Dis. 2021 Sep 12;20(1):105. doi: 10.1186/s12944-021-01533-6.PMID: 34511127	Japan	Av:64	LDL	4	All-cause mortality.	INV
17	Taravatmanesh S, Parsa N, Trevisan M et al. The Association Between Low Serum Cholesterol and Non-Cardiovascular Mortality among Italian Males and Females: A Nine- Year Prospective Cohort Study. Asian Pac J Cancer Prev. 2019 May 25;20(5):1361-1368. doi: 10.31557/APJCP.2019.20.5.1361.PMID: 31127892	Italia	20–69	Total	10	All-cause mortality.	INV
18	Nago N, Ishikawa S, Goto T, Kayaba K Low cholesterol is associated with mortality from stroke, heart disease, and cancer: the Jichi Medical School Cohort Study. J Epidemiol. 2011;21(1):67-74. doi: 10.2188/jea.je20100065. Epub 2010 Dec 11.PMID: 21160131	Japan	40–69	Total	4	All-cause mortality.	INV
19	Bassole Epse Brou MAM, Fujiyoshi A, Higashiyama A et al.J-MICC Study Group. Liver diseases and low serum albumin as potential confounders in the association between low total cholesterol and elevated all-cause and cancer mortality: The Japan Multi-Institutional Collaborative Cohort (J-MICC) study. J Clin Lipidol. 2026 Feb;20(2):357-367. doi: 10.1016/j.jacl.2025.11.009. Epub 2025 Nov 15.PMID: 41484028	Japan	35–69	Total	4	All-cause, CVD, Cancer mortality	INV *b

CVD: cardiovascular disease, POS: positive association, NO: no association , INV: inverse association

Supplement 1: Inverse association between cholesterol and all-cause deaths.

1-B: 14) Takata et al. Serum total cholesterol concentration and 10-year mortality in an 85-year-old population
Clin Interv Aging. 2014 Feb 13;9:293-300. doi: 10.2147/CIA.S53754. eCollection 2014.

Figure 1 Survival curves of the participants who survived during the 10-year follow-up period among the three total cholesterol (TC) groups: for all participants (A),



Abstract

Little is known about the association between total cholesterol (TC) and all-cause mortality in the elderly (especially the very elderly). Here we examined the association between TC and all-cause mortality in 207 very elderly (85-year-old) participants. In 2003, we performed a baseline laboratory blood examination, and blood pressure (BP) and body mass index (BMI) measurements, and lifestyle questionnaires were completed by the participants. The participants were followed for the subsequent 10 years. As of 2013, of the 207 participants in 2003, 70 participants had survived, 120 individuals had died, and 17 were lost to follow up. The TC values were divided into high-TC (≥ 209 mg/dL), intermediate-TC (176-208 mg/dL), and low-TC (≤ 175 mg/dL) categories. With the Kaplan-Meier method, we found that both the high-TC and intermediate-TC participants survived longer than the low-TC participants. The men with high TC survived longer than those with low TC, but no corresponding difference was found for the women. A multivariate Cox proportional hazards regression model, with adjustment for gender, smoking, alcohol intake, history of stroke or heart disease, serum albumin concentration, BMI, and systolic BP, revealed that the total mortality in the low-TC group was 1.7-fold higher than that in the high-TC group. Mortality, adjusted for the same factors, decreased 0.9% with each 1 mg/dL increase in the serum TC concentration and decreased 0.8% with each 1 mg/dL increase in the serum (low-density lipoprotein) LDL-cholesterol (LDL-C) concentration. Our results indicate an association between lower serum TC concentrations and increased all-cause mortality in a community-dwelling, very elderly population. Mortality decreased with the increases in both TC and LDL-C concentrations, after adjustment for various confounding factors. These findings suggest that low TC and low LDL-C may be independent predictors of high mortality in the very elderly.

Supplement 1: Inverse association between cholesterol and all-cause deaths.

1-C (1): 16) Kawamoto et al. Low density lipoprotein cholesterol and all-cause mortality rate: findings from a study on Japanese community-dwelling persons. *Lipids Health Dis.* 2021 Sep 12;20(1):105. doi: 10.1186/s12944-021-01533-6.

Abstract

Background: Low-density lipoprotein cholesterol (LDL-C) independently impacts aging-related health outcomes and plays a critical role in cardiovascular diseases (CVDs). However, there are limited predictive data on all-cause mortality, especially for the Japanese community population. In this study, it was examined whether LDL-C is related to survival prognosis based on 7 or 10 years of follow-up.

Methods: Participants included 1610 men (63 ± 14 years old) and 2074 women (65 ± 12 years old) who participated in the Nomura cohort study conducted in 2002 (first cohort) and 2014 (second cohort) and who continued throughout the follow-up periods (follow-up rates: 94.8 and 98.0%). Adjusted relative risk estimates were obtained for all-cause mortality using a basic resident register. The data were analyzed by a Cox regression with the time variable defined as the length between the age at the time of recruitment and that at the end of the study (the age of death or censoring), and risk factors including gender, age, body mass index (BMI), presence of diabetes, lipid levels, renal function, serum uric acid levels, blood pressure, and history of smoking, drinking, and CVD.

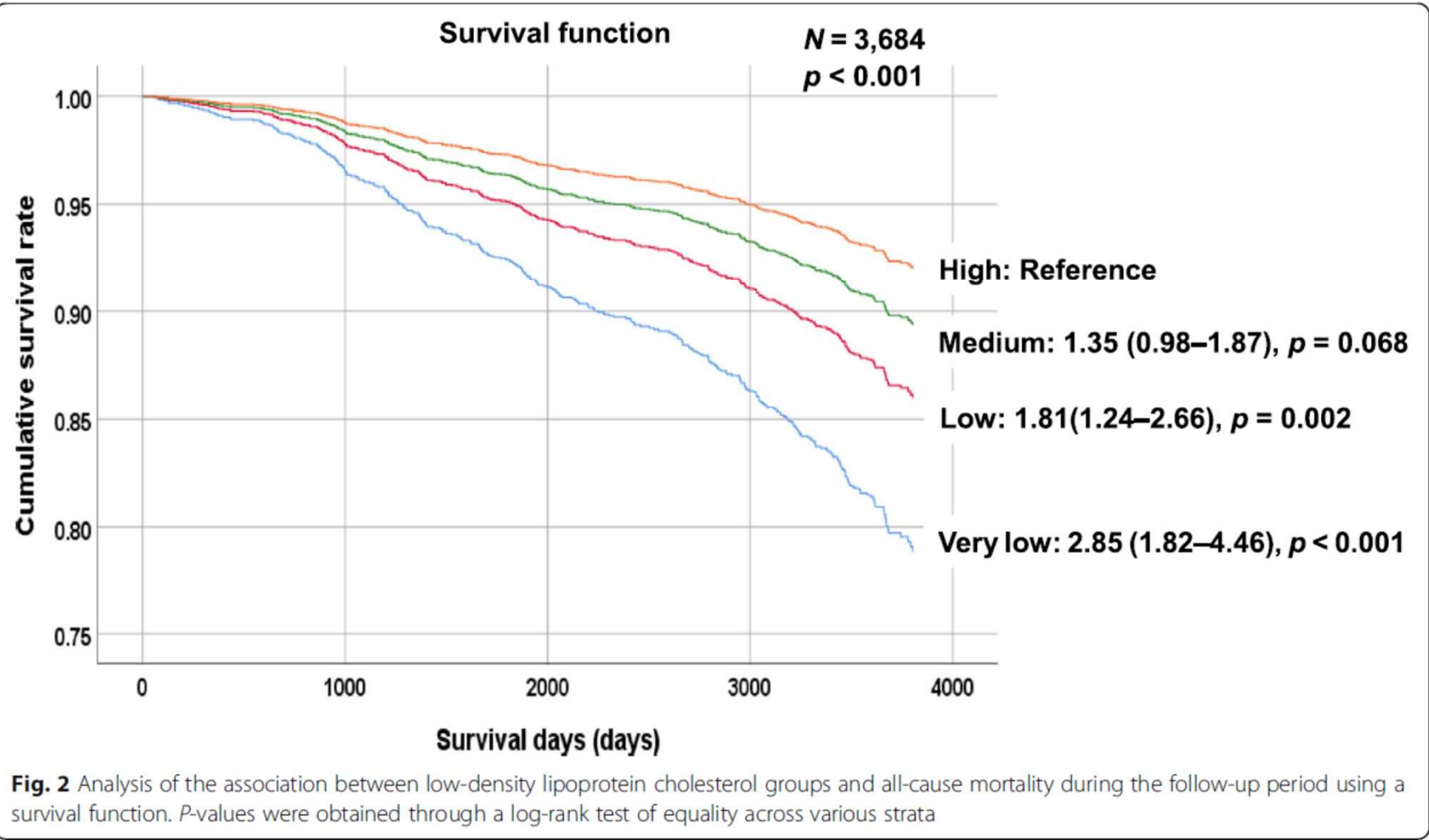
Results: Of the 3684 participants, 326 (8.8%) were confirmed to be deceased. Of these, 180 were men (11.2% of all men) and 146 were women (7.0% of all women). Lower LDL-C levels, gender (male), older age, BMI under 18.5 kg/m^2 , and the presence of diabetes were significant predictors for all-cause mortality. Compared with individuals with LDL-C levels of 144 mg/dL or higher, the multivariable-adjusted Hazard ratio (and 95% confidence interval) for all-cause mortality was 2.54 (1.58–4.07) for those with LDL-C levels below 70 mg/dL, 1.71 (1.15–2.54) for those with LDL-C levels between 70 mg/dL and 92 mg/dL, and 1.21 (0.87–1.68) for those with LDL-C levels between 93 mg/dL and 143 mg/dL. This association was particularly significant among participants who were male (P for interaction = 0.039) and had CKD (P for interaction = 0.015).

Conclusions: There is an inverse relationship between LDL-C levels and the risk of all-cause mortality, and this association is statistically significant.

Keywords: Low-density lipoprotein cholesterol, All-cause mortality, Community-dwelling persons, Cohort study

Supplement 1: Inverse association between cholesterol and all-cause deaths.

1-C (2): Data from ref. 16) Kawamoto et al. . doi: 10.1186/s12944-021-01533-6

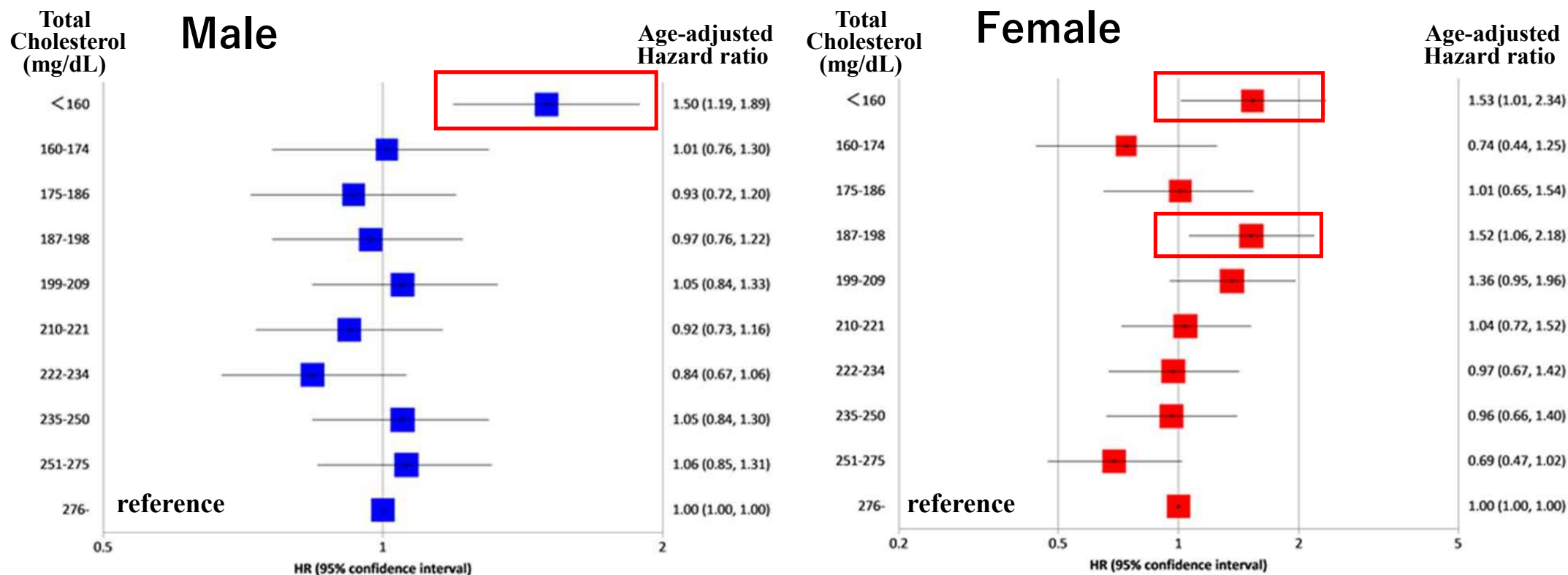


	LDL-C level
High	≥ 144 mg/dL
Medium	93-143
Low	70-92
Very low	<70

Supplement 1: Inverse association between cholesterol and all-cause deaths.

1-D: Data from the Table 3 in ref. 17) Taravatmanesh S et al. doi: 10.31557/APJCP.2019.20.5.1361

Table 3: Age-adjusted and Multivariate-adjusted Hazard Ratio for All Causes of death and total non-CVD Mortality of Different Cholesterol Levels for Males and Females



Adapted from Table 3 in ref. 17

17) Taravatmanesh S et al. The Association Between Low Serum Cholesterol and Non-Cardiovascular Mortality among Italian Males and Females: A Nine- Year Prospective Cohort Study, Asian Pac J Cancer Prev. 2019 May 25;20(5):1361-1368. doi: 10.31557/APJCP.2019.20.5.1361

Supplement 1: Inverse association between cholesterol and all-cause deaths.

1-E: 19) Bassole Epse Brou MAM et al. Liver diseases and low serum albumin as potential confounders in the association between low total cholesterol and elevated all-cause and cancer mortality: J-MICC study. J Clin Lipidol. 2026 Feb;20(2):357-367.

Clear inverse association

**Clear inverse association again after exclusion of liver disease:
Pooled HRs of both sex are statistically significant;
1.63(1.35-1.97) for TC<160 and 0.84(0.72-0.99) for TC $\geq$ 240**

MedCheck's Comments:
While low albumin is an indicator of malnutrition, low total cholesterol also serves as an indicator of malnutrition and is associated with increased all-cause mortality. If adjusted for albumin, excluded liver death and cancers, coagulation status and inflammatory responses must be adjusted (See also slide 16)

Moreover, Pooled HR of both sexes for TC $\geq$ 240 is 0.98 (0.78-1.22) indicating no signs of increased all cause mortality among those with high total cholesterol level.

Table 2. Hazard ratios for all-cause mortality by total cholesterol categories.

		Analysis 1		Analysis 2		Analysis 3	
TC levels (mg/dL)		Deaths (n/N)	HR (95% CI)	Deaths (n/N)	HR (95% CI)	Deaths (n/N)	HR (95% CI)
All-cause deaths	Men						
	TC < 160	142/1812	1.78 (1.46-2.16)	121/1703	1.70 (1.38-2.09)	51/1033	1.37 (0.998-1.87)
	TC 160 to < 200	359/9356	Ref	338/9101	Ref	178/5731	Ref
	TC 200 to < 240	364/10302	0.94 (0.81-1.09)	354/10128	0.96 (0.82-1.11)	181/6407	1.00 (0.81-1.23)
	TC $\geq$ 240	118/3661	0.90 (0.73-1.11)	114/3617	0.91 (0.73-1.12)	68/2243	1.19 (0.90-1.58)
	Total	983/25131		927/24549		478/15414	
	Women						
	TC < 160	32/1414	1.93 (1.31-2.85)	19/1360	1.29 (0.79-2.10)	8/792	0.96 (0.46-2.02)
	TC 160 to < 200	126/8830	Ref	119/8667	Ref	63/4937	Ref
	TC 200 to < 240	214/12950	0.83 (0.67-1.04)	209/12758	0.85 (0.68-1.07)	109/7259	0.90 (0.66-1.24)
	TC $\geq$ 240	121/7352	0.73 (0.57-0.94)	120/7277	0.76 (0.59-0.98)	60/4089	0.82 (0.57-1.18)
	Total	493/30546		467/30062		240/17077	

Abbreviations: HR, hazard ratio; n, number of deaths; N, number of participants; Ref, reference; TC, total cholesterol.

All the hazard ratios were obtained using Cox model stratified by cohort, with adjustment for age, body mass index (kg/m²), smoking status (current, past, never, unknown), drinking status (current, past, never, unknown), hypertension (yes/no), and diabetes (yes/no).

Analysis 1: exclusion of baseline cancer and cardiovascular diseases; Analysis 2: further exclusion of baseline liver diseases (hepatitis B and C, cirrhosis); Analysis 3: further adjustment for serum albumin (mg/dL).

Supplement 2: Evidence bases of the JAS Guidelines for prevention of atherosclerotic diseases:

2-A: BQ1 Does LDL cholesterol predict the onset of and mortality from atherosclerotic disease in the Japanese population?

LDL cholesterol predicts the onset of and mortality from atherosclerotic disease in the Japanese population. Furthermore, while a positive association has been shown with cerebral infarction (a type of stroke) and a negative association with hemorrhagic stroke, it cannot be said that there is sufficient evidence for this in the Japanese population compared to the evidence available for total cholesterol.

References (reference numbers are those of the Guidelines)	Comments by MedCheck		
	Primary Outcome	Association	All-cause mortality
1) Imamura T, Doi Y, Arima H, et al. LDL cholesterol and the development of stroke subtypes and coronary heart disease in a general Japanese population: the Hisayama study. <i>Stroke</i> 2009;40:382-8.	Stroke, CHD	POS	Not shown
2) Imano H, Noda H, Kitamura A, et al. Low-density lipoprotein cholesterol and risk of coronary heart disease among Japanese men and women: the Circulatory Risk in Communities Study (CIRCS). <i>Prev Med</i> 2011;52:381-6.	CHD CHD death	POS NO	Not shown
3) Noda H, Iso H, Irie F, et al. Gender difference of association between LDL cholesterol concentrations and mortality from coronary heart disease amongst Japanese: the Ibaraki Prefectural Health Study. <i>J Intern Med</i> 2010;267:576-87.	Death from CHD	POS	Inverse
4) Yokokawa H, Yasumura S, Tanno K, et al. Serum low-density lipoprotein to high-density lipoprotein ratio as a predictor of future acute myocardial infarction among men in a 2.7-year cohort study of a Japanese northern rural population. [<i>Atheroscler Thromb</i> 2011; 18:89-98.	Myocardial Infarction	POS	Not shown
5) Noda H, Iso H, Irie F, et al. Low-density lipoprotein cholesterol concentrations and death due to intraparenchymal hemorrhage: the Ibaraki Prefectural Health Study. <i>Circulation</i> 2009;119:2136-45. See Supplement 2-B (1~3)	Hemorrhagic S CHD	INV	Inverse
6) Okamura T, Kokubo Y, Watanabe M, et al. Low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol and the incidence of cardiovascular disease in an urban Japanese cohort study: the Suita study. <i>Atherosclerosis</i> 2009;203 :587-92.	CHD Stroke	POS NO	Not shown

CHD: coronary heart disease, Hemorrhagic S: hemorrhagic stroke, POS: positive association, NO: no association, INV: inverse association

Supplement 2-B: Evidence bases of the JAS-Guidelines

2-B(1): An example showing inverse association except coronary heart disease (CHD) death.

11) Noda H, Iso H, et al. Low-density lipoprotein cholesterol concentrations and death due to intraparenchymal hemorrhage: the Ibaraki Prefectural Health Study (Same as JAS Guidelines ref. 5)

Circulation 2009;119:2136-45. doi: 10.1161/CIRCULATIONAHA.108.795666. PMID: 19364982

Abstract

Background: Few studies have examined the association between low levels of low-density lipoprotein (LDL) cholesterol and risk of intraparenchymal hemorrhage.

Methods and results: A total of 30 802 men and 60 417 women, 40 to 79 years of age with no history of stroke or coronary heart disease, completed a baseline risk factor survey in 1993 under the auspices of the Ibaraki Prefectural Health Study. Systematic mortality surveillance was performed through 2003, and 264 intraparenchymal hemorrhage deaths were identified. LDL cholesterol levels were calculated with the Friedewald formula. Persons with LDL cholesterol $\geq$ 140 mg/dL had half the sex- and age-adjusted risk of death due to intraparenchymal hemorrhage of those with LDL cholesterol $<$ 80 mg/dL. After adjustment for cardiovascular risk factors, the multivariable hazard ratio compared with persons with LDL cholesterol $<$ 80 mg/dL was 0.65 (95% CI 0.44 to 0.96) for those with LDL cholesterol 80 to 99 mg/dL, 0.48 (0.32 to 0.71) for 100 to 119 mg/dL, 0.50 (0.33 to 0.75) for 120 to 139 mg/dL, and 0.45 (0.30 to 0.69) for $\geq$ 140 mg/dL. These inverse associations were not altered substantially after the exclusion of persons with hypertriglyceridemia, after analysis with a Cox proportional hazard model with time-dependent covariates, or in sensitivity analysis for the potential effect of competing risks.

Conclusions: Low LDL cholesterol levels are associated with elevated risk of death due to intraparenchymal hemorrhage.

Supplement 2-B(2): Data for Figure 1 from [11]

Table 5. Crude Mortality Rate (per 100 000 Person-Years) and Multivariable HR and 95% CI of Intracerebral Hemorrhage and Other Cardiovascular Disease According to LDL Cholesterol Categories

	LDL-Cholesterol categories, mg/dL				
mg/dL	<80	80-99	100-119	120-139	≥ 140
All-cause mortality					
No. of events	1049	1490	1727	1422	1456
Crude mortality rate	1233	904	765	706	657
Multivariable HR	1.0	0.81 (0.74–0.87)	0.72 (0.66–0.78)	0.67 (0.62–0.73)	0.66 (0.61–0.72)
P		<0.001	<0.001	<0.001	<0.001
Total cardiovascular disease					
No. of events	261	384	478	407	484
Crude mortality rate	307	233	212	202	218
Multivariable HR	1.0	0.80 (0.68–0.94)	0.76 (0.65–0.89)	0.72 (0.62–0.85)	0.82 (0.70–0.96)
P		<0.001	<0.001	<0.001	0.07
Total stroke					
No. of events	141	195	235	203	218
Crude mortality rate	166	118	104	101	98
Multivariable HR	1.0	0.73 (0.59–0.91)	0.67 (0.54–0.83)	0.65 (0.52–0.81)	0.67 (0.54–0.84)
P		<0.001	<0.001	<0.001	<0.001
Hemorrhagic stroke					
No. of events	70	93	103	92	96
Crude mortality rate	82	56	46	46	43
Multivariable HR	1.0	0.70 (0.51–0.95)	0.56 (0.41–0.77)	0.54 (0.39–0.75)	0.51 (0.37–0.71)
P		0.02	<0.001	<0.001	<0.001
Subarachnoid hemorrhage					
No. of events	24	37	47	39	43
Crude mortality rate	28	22	21	19	19
Multivariable HR	1.0	0.79 (0.47–1.33)	0.73 (0.44–1.20)	0.64 (0.38–1.08)	0.62 (0.37–1.05)
P		0.38	0.22	0.10	0.07
Intracerebral hemorrhage					
No. of events	46	56	56	53	53
Crude mortality rate	54	34	25	26	24
Multivariable HR	1.0	0.65 (0.44–0.96)	0.48 (0.32–0.71)	0.50 (0.33–0.75)	0.45 (0.30–0.69)
P		0.03	<0.001	<0.001	<0.001
Ischemic stroke					
No. of events	71	102	132	111	122
Crude mortality rate	83	62	59	55	55
Multivariable HR	1.0	0.75 (0.55–1.02)	0.77 (0.58–1.04)	0.75 (0.55–1.02)	0.85 (0.62–1.15)
P		0.07	0.09	0.07	0.29
Coronary heart disease					
No. of events	48	96	130	109	156
Crude mortality rate	56	58	58	54	70
Multivariable HR	1.0	1.14 (0.81–1.62)	1.19 (0.85–1.67)	1.11 (0.78–1.57)	1.50 (1.07–2.10)
P		0.45	0.31	0.57	0.02
Intracerebral hemorrhage and coronary heart disease					
No. of events	94	152	186	162	209
Crude mortality rate	110	92	82	80	94
Multivariable HR	1.0	0.90 (0.70–1.17)	0.84 (0.65–1.08)	0.81 (0.62–1.05)	0.97 (0.75–1.26)
P		0.43	0.17	0.11	0.83

Crude mortality rate was described as number of deaths per 100 000 person-years.
Multivariable HR (95% CI) was adjusted for age, sex, and other cardiovascular risk factors. For cause-specific analyses, persons who died of other causes were treated as censored.

Figure 1: Only CHD death is positively associated with high LDL-Cholesterol among many causes of death

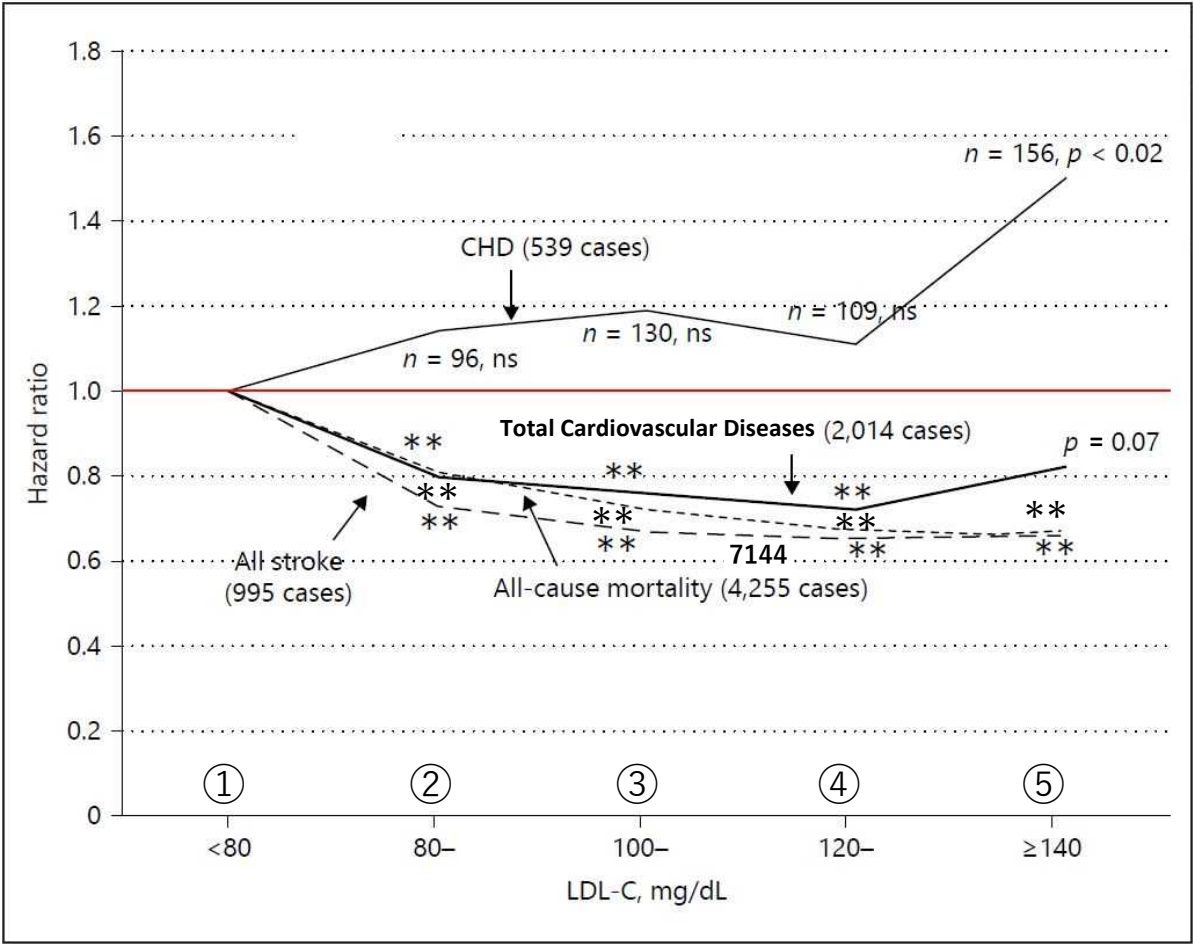


Figure is from ref. 11 with some correction of data according to the original data by Noda et al. Meta-analysis of Hazard ratios (HRs) of group ②, ③ and ④ of the mortality from CHD yielded 1.15(95%CI : 0.94-1.40, p=0.176, I²=0%). Only the group ⑤ of the mortality from CHD is significantly higher than the group ① among many causes of death.

Supplement 2-B(3): Data for Figure 2 from [11]

Table 5. Crude Mortality Rate (per 100 000 Person-Years) and Multivariable HR and 95% CI of Intracerebral Hemorrhage and Other Cardiovascular Disease According to LDL Cholesterol Categories

mg/dL	LDL-Cholesterol categories, mg/dL				
	<80	80-99	100-119	120-139	≥140
All-cause mortality					
No. of events	1049	1490	1727	1422	1456
Crude mortality rate	1233	904	765	706	657
Multivariable HR	1.0	0.81 (0.74–0.87)	0.72 (0.66–0.78)	0.67 (0.62–0.73)	0.66 (0.61–0.72)
P		<0.001	<0.001	<0.001	<0.001
Total cardiovascular disease					
No. of events	261	384	478	407	484
Crude mortality rate	307	233	212	202	218
Multivariable HR	1.0	0.80 (0.68–0.94)	0.76 (0.65–0.89)	0.72 (0.62–0.85)	0.82 (0.70–0.96)
P		<0.001	<0.001	<0.001	0.07
Total stroke					
No. of events	141	195	235	203	218
Crude mortality rate	166	118	104	101	98
Multivariable HR	1.0	0.73 (0.59–0.91)	0.67 (0.54–0.83)	0.65 (0.52–0.81)	0.67 (0.54–0.84)
P		<0.001	<0.001	<0.001	<0.001
Hemorrhagic stroke					
No. of events	70	93	103	92	96
Crude mortality rate	82	56	46	46	43
Multivariable HR	1.0	0.70 (0.51–0.95)	0.56 (0.41–0.77)	0.54 (0.39–0.75)	0.51 (0.37–0.71)
P		0.02	<0.001	<0.001	<0.001
Subarachnoid hemorrhage					
No. of events	24	37	47	39	43
Crude mortality rate	28	22	21	19	19
Multivariable HR	1.0	0.79 (0.47–1.33)	0.73 (0.44–1.20)	0.64 (0.38–1.08)	0.62 (0.37–1.05)
P		0.38	0.22	0.10	0.07
Intraparenchymal hemorrhage					
No. of events	46	56	56	53	53
Crude mortality rate	54	34	25	26	24
Multivariable HR	1.0	0.65 (0.44–0.96)	0.48 (0.32–0.71)	0.50 (0.33–0.75)	0.45 (0.30–0.69)
P		0.03	<0.001	<0.001	<0.001
Ischemic stroke					
No. of events	71	102	132	111	122
Crude mortality rate	83	62	59	55	55
Multivariable HR	1.0	0.75 (0.55–1.02)	0.77 (0.58–1.04)	0.75 (0.55–1.02)	0.85 (0.62–1.15)
P		0.07	0.09	0.07	0.29
Coronary heart disease					
No. of events	48	96	130	109	156
Crude mortality rate	56	58	58	54	70
Multivariable HR	1.0	1.14 (0.81–1.62)	1.19 (0.85–1.67)	1.11 (0.78–1.57)	1.50 (1.07–2.10)
P		0.45	0.31	0.57	0.02
Intraparenchymal hemorrhage and coronary heart disease					
No. of events	94	152	186	162	209
Crude mortality rate	110	92	82	80	94
Multivariable HR	1.0	0.90 (0.70–1.17)	0.84 (0.65–1.08)	0.81 (0.62–1.05)	0.97 (0.75–1.26)
P		0.43	0.17	0.11	0.83

Crude mortality rate was described as number of deaths per 100 000 person-years.
Multivariable HR (95% CI) was adjusted for age, sex, and other cardiovascular risk factors. For cause-specific analyses, persons who died of other causes were treated as censored

Figure 2: Not only total stroke but also ischemic stroke is inversely associated with LDL-Cholesterol level

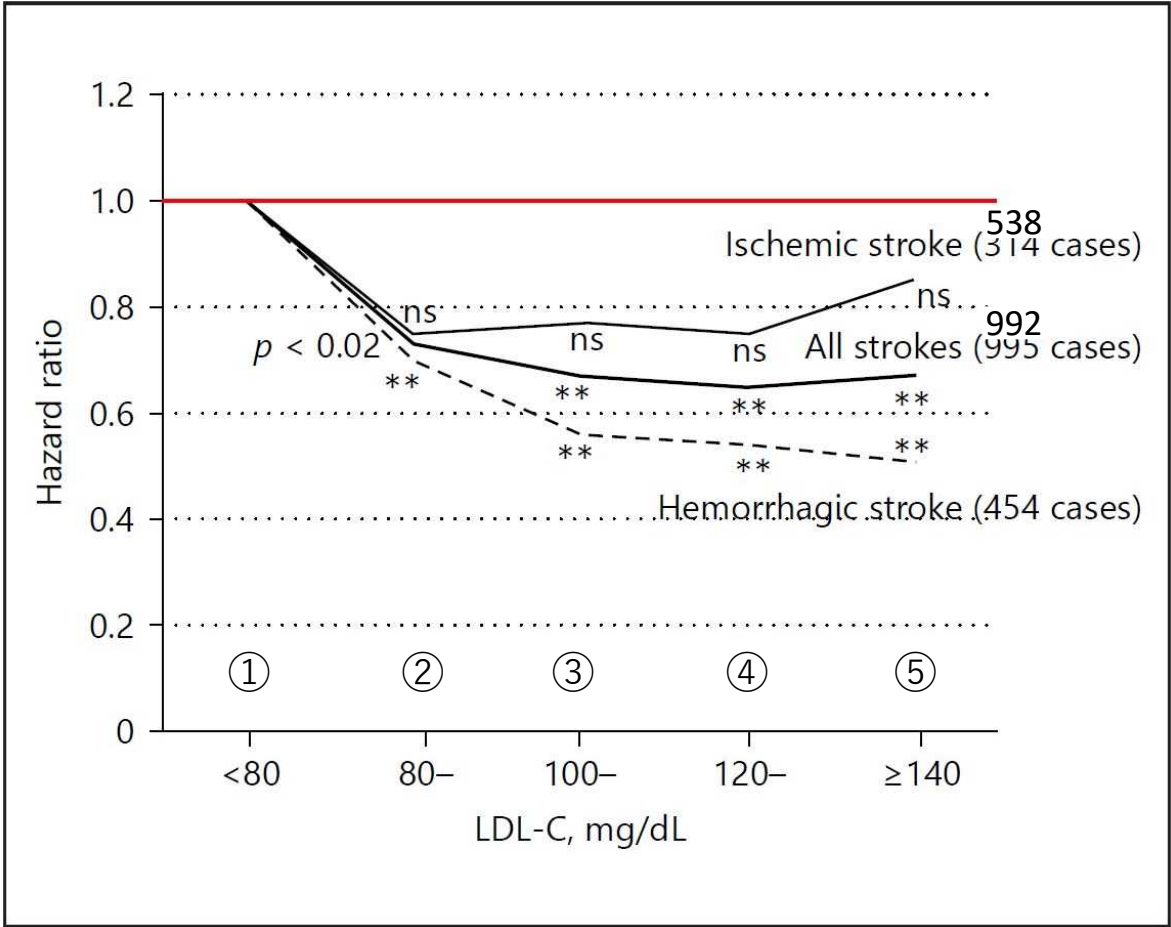
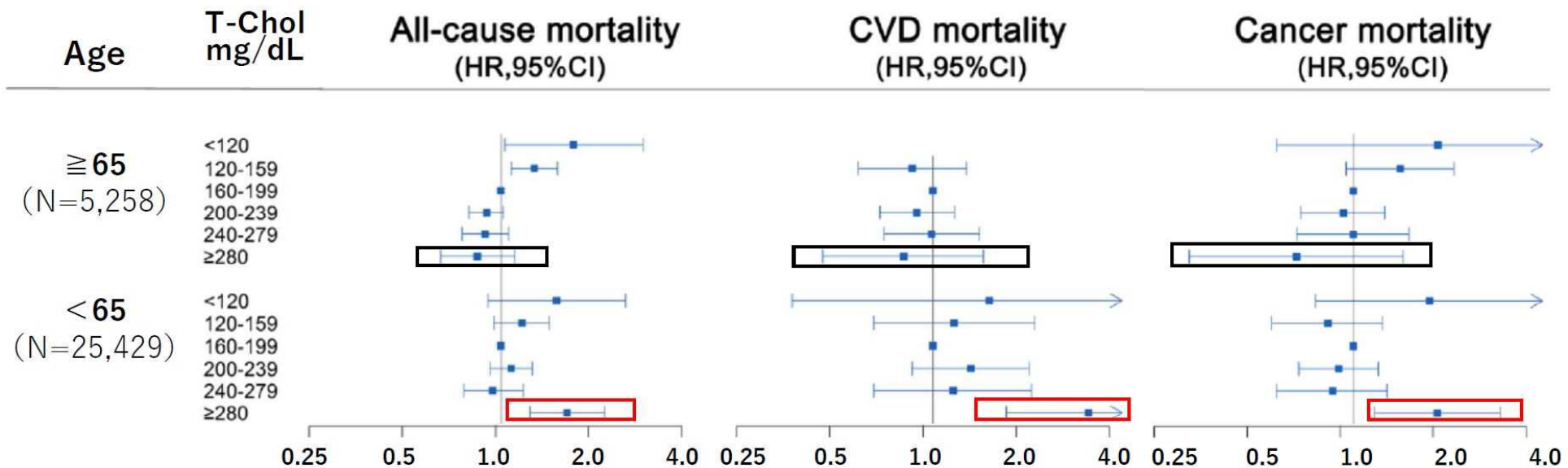


Figure is from ref. 11 with some correction of data according to the original data by Noda et al. Meta-analysis of Hazard ratios (HRs) of group ② and ③ of ischemic stroke yielded 0.76(95%CI: 0.62-0.94, p=0.011, I²=0%) and Group ④ and ⑤ 0.80 (0.64-0.99, P=0.043, I²=0%). All combined HR of group ② through ⑤ is 0.78(0.67-0.91, p=0.0013, I²=0%).

Figure 3: Association of Total Cholesterol with All-cause and Cardiovascular Mortality by age [15]

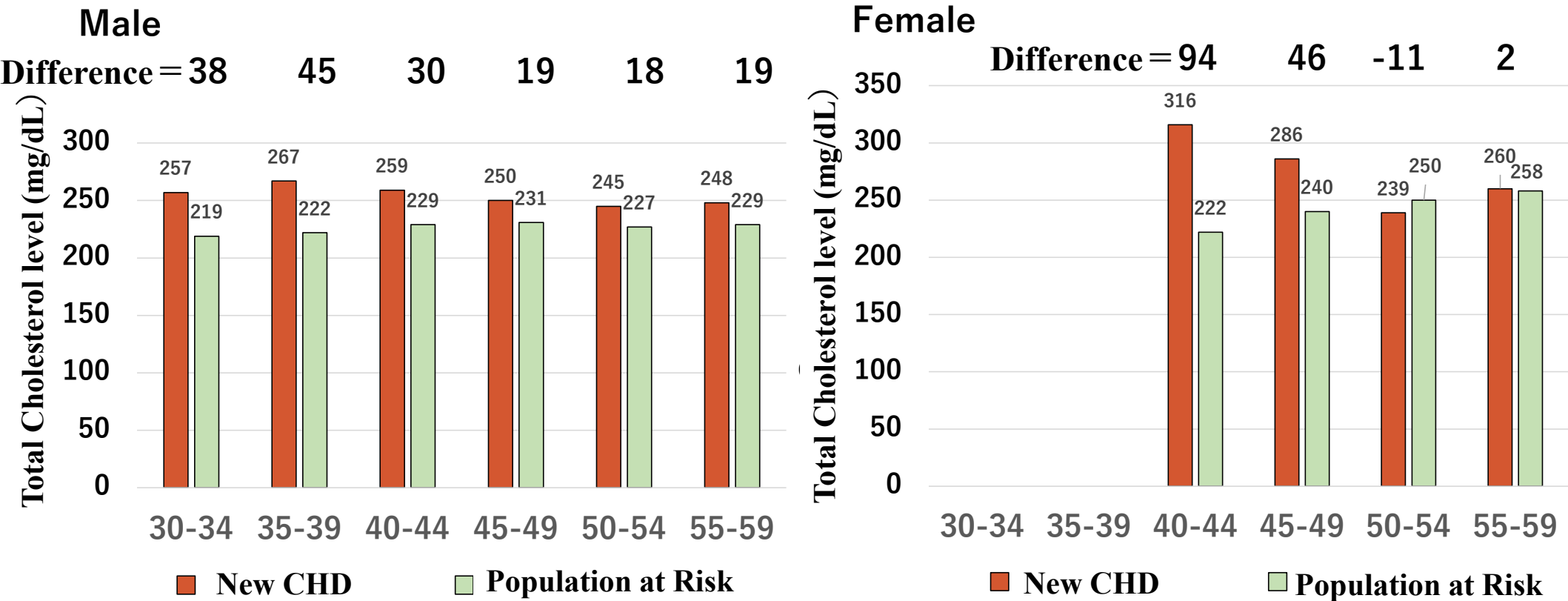


Adapted from Reference [15]. Forest plots of subgroups analyses by age (age, gender, race, education level, married, smoking, body mass index, systolic blood pressure, estimated glomerular filtration rate, high density lipoprotein cholesterol, energy intake, hypertension, diabetes, antihypertensive drugs, hypoglycemic agents, and lipid-lowering drugs were all adjusted except the variable itself)

The most notable difference between the age groups of 65 and older and those less than 65 is observed in the group with levels of 280 mg/dL or higher. Among those aged 65 and older, the hazard ratio for death from any disease is lowest in the ≥280 mg/dL group; in contrast, among those under 65, the hazard ratios for all disease categories are high in this range—particularly for cardiovascular disease (CVD) mortality, which is markedly elevated. This is likely because individuals with familial hypercholesterolemia (FH)—who face a high risk of fatal myocardial infarction at a young age due to coagulation abnormalities and elevated TNF- α levels—experience high mortality before age 65, resulting in a drastically lower prevalence of the condition in the population aged 65 and older.

Supplement 3: Age-related difference appeared in the Framingham Study

3-A: Figure 4: Mean Serum Cholesterol at Initial Examination: Comparison New CHD and Population at Risk
(Based on the data in the Table 5 in the Framingham Study published in 1961 [26])



Among women, there are no coronary disease events in the 30s, whereas total cholesterol levels are markedly high in those who experience new coronary heart disease (CHD) in their early 40s. However, at age 50 and older, cholesterol levels can no longer be considered a risk factor for CHD. Similarly, among men, the difference in cholesterol levels between those who experience a new CHD and the general population exceeds 30 mg/dL up to age 44, but narrows to less than 20 mg/dL at age 45 and older.

Supplement 3: Age-related difference appeared in the Framingham Study

3-B: Data for Figure 4 based on the data on the Table 5 in the Framingham Study 1961 [26]

TABLE 5. Mean Serum Cholesterol at Initial Examination: Comparison New CHD and Population at Risk

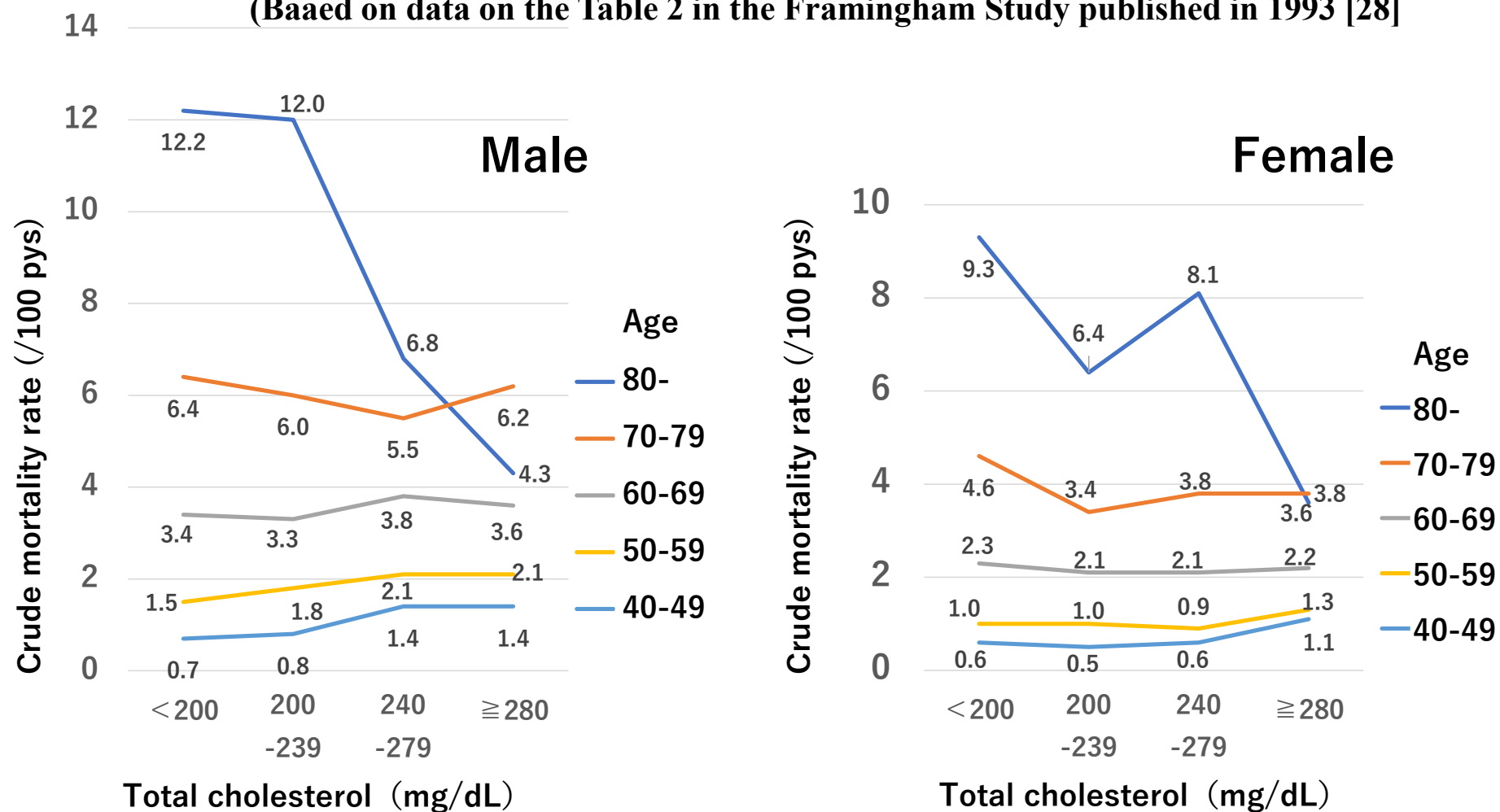
Age at Entry	Number		Total Cholesterol Mean		Standard Deviation of Population
	New CHD	Population at Risk	New CHD	Population at Risk	
Men					
30-34	5	375	257*	219	45
35-39	11	419	267*	222	42
40-44	14	402	259*	229	46
45-49	14	341	250*	231	37
50-54	27	338	245*	227	40
55-59	41	252	248*	229	43
Women					
40-44	3	480	316*	222	39
45-49	14	423	286*	240	48
50-54	13	403	239	250	46
55-59	24	355	260	258	48

* Significantly elevated (at the 5% level) compared with population at risk.

Supplement 3: Age-related difference appeared in the Framingham Study

3-C: Figure 5: Crude mortality within age categories by sex and total cholesterol

(Based on data on the Table 2 in the Framingham Study published in 1993 [28])



In both men and women up to their 50s, an increase in total cholesterol levels is associated with a slight rise in all-cause mortality. In the 60s, there is no correlation between total cholesterol levels and all-cause mortality. Among those aged 70 and older—and particularly in the 80s—an inverse correlation is evident.

Supplement 4: Age-related difference appeared in the Japanese Study: mortality risk in men with highest total cholesterol. Data from ref [29] by Ueshima et al.

Table 2-1 Cumulative age-adjusted mortality rates by sex, age, and total cholesterol level
Analysis excluding deaths during the first 5 years of follow-up (14-year follow-up starting in 1980)

Sex	Serum total cholesterol level (mg/dL)							
Age (year)	<159	160-179	180-199	200-219	220-239	240-259	260-	Total
Male								
Cumulative deaths								
30-40	4	4	4	1	2	0	0	15
41-50	16	7	6	7	4	2	4	46
51-60	25	20	35	14	6	3	3	106
61-70	43	47	42	27	14	9	0	182
71-	45	45	44	33	9	3	2	181
Cumulative mortality rate (/1000 person)								
30-40	18.5	14.2	13.7	5.1	19.8	0.0	0.0	13.1
41-50	70.8	26.5	24.8	38.0	38.5	38.5	133.3	41.7
51-60	147.1	92.2	170.7	95.2	74.1	85.7	125.0	120.6
61-70	341.3	317.6	293.7	333.3	291.7	321.4	0.0	312.2
71-	600.0	608.1	733.3	733.3	450.0	375.0	666.7	635.1
Age-adjusted cumulative mortality rates based on Japanese standard population (/1000 person)								
30-60	73.2	40.4	61.7	42.1	41.7	37.7	82.5	53.4
61-	456.7	447.2	489.9	511.9	362.3	345.3	297.5	456.3
31-	174.4	147.8	174.7	166.1	126.3	118.9	139.3	159.7
Relative risk and 95% confidence interval (reference: total cholesterol 160–179 mg/dL group)								
30-60	1.81 (1.17-2.80)	1.00 ---	1.53 (0.98-2.37)	1.04 (0.61-1.77)	1.03 (0.54-1.98)	0.93 (0.37-2.37)	2.04 (0.88-4.75)	---
61-	1.02 (0.84-1.24)	1.00 ---	1.10 (0.91-1.32)	1.14 (0.93-1.42)	0.81 (0.59-1.12)	0.77 (1.18-0.51)	0.67 (0.31-1.41)	---
30- (All ages)	1.18 (0.96-1.45)	1.00 ---	1.18 (0.97-1.44)	1.12 (0.90-1.41)	0.85 (0.63-1.16)	0.80 (0.52-1.24)	0.94 (0.54-1.63)	---

MedCheck Comments:

For individuals aged 60 or younger, the risk of all-cause mortality decreases fairly consistently as total cholesterol levels rise up to 259 mg/dL; an upward trend is observed only when levels reach 260 mg/dL or higher.

In contrast, among those aged 61 and older, there is a fairly consistent inverse correlation (with all-cause mortality tending to decrease as total cholesterol levels rise).

Supplement 5: Decreasing cholesterol is associated with overall and CVD death

11% overall Death rate increase per 1 mg/dL per year drop in cholesterol levels

Cholesterol and Mortality -30 Years of Follow-up From the Framingham Study

27) Anderson KM et al. JAMA. 1987 Apr 24;257(16):2176-80. doi: 10.1001/jama.257.16.2176.

Abstract:

From 1951 to 1955 serum cholesterol levels were measured in 1959 men and 2415 women aged between 31 and 65 years who were free of cardiovascular disease (CVD) and cancer; **Under age 50 years**, cholesterol levels are directly related with 30-year overall and CVD mortality; overall death increases 5% and CVD death 9% for each 10 mg/dL. After age 50 years there is no increased overall mortality with either high or low serum cholesterol levels. There is a direct association between **falling cholesterol levels over the first 14 years and mortality over the following 18 years (11% overall and 14% CVD death rate increase per 1 mg/dL per year drop in cholesterol levels)**. Under age 50 years these data suggest that having a very low cholesterol level improves longevity. After age 50 years the association of mortality with cholesterol values is confounded by people whose cholesterol levels are falling—perhaps due to diseases predisposing to death.

Change in Cholesterol and Subsequent Mortality

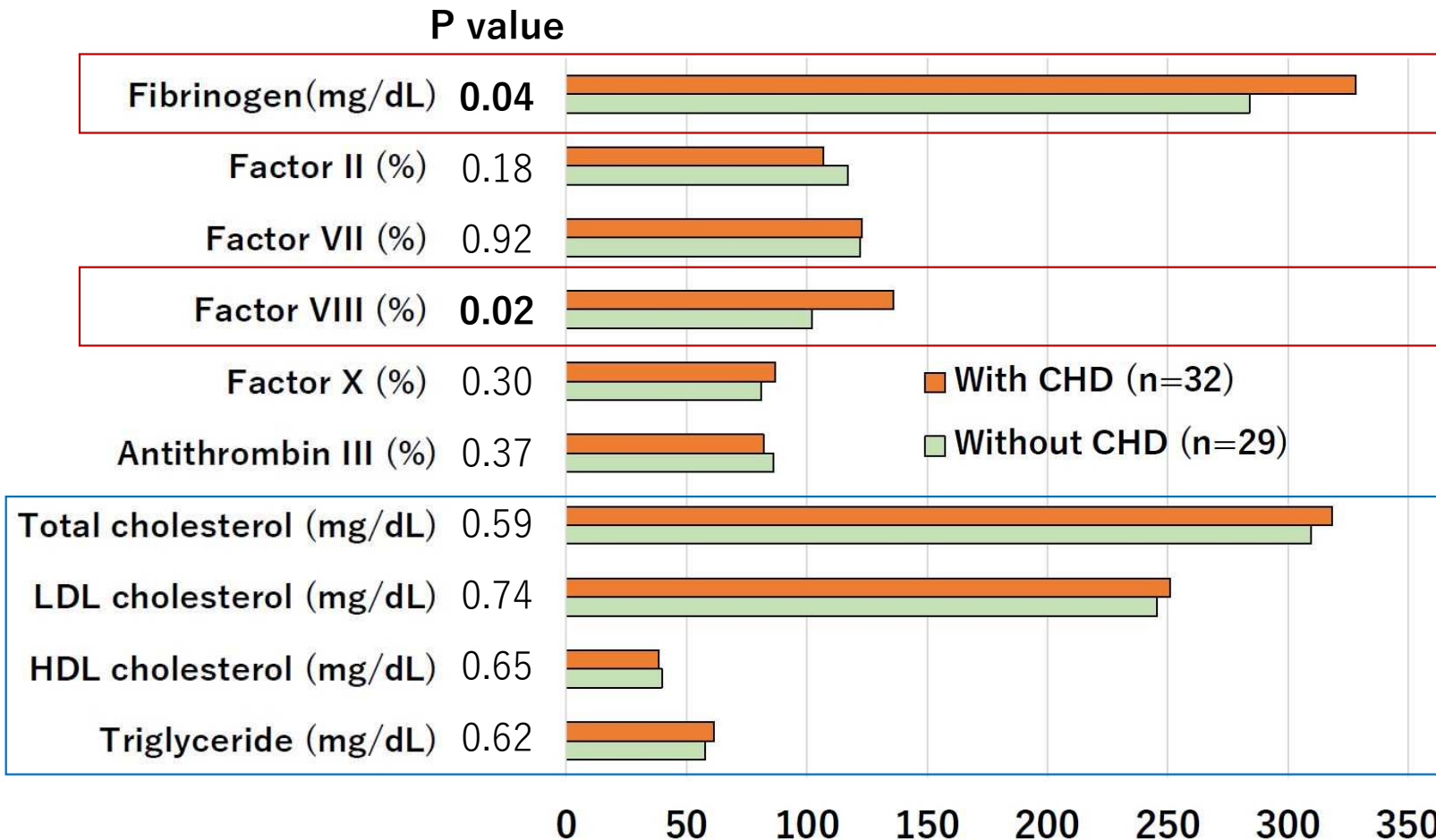
Falling cholesterol levels—the negative slope variable—were associated with elevated overall mortality and CVD mortality in both men and women (Table 4). Fourteen percent of the men and 20% of the women had cholesterol slopes that were negative. Combining men and women free of CVD and cancer, stratifying by sex and age groups, a model fitting only negative slope estimates that for each 1 mg/dL per year drop in serum cholesterol values over the 14-year period of cholesterol measurement, there is an 11% increase in both the overall death rate ($\beta = .103$; $P < .01$) and the CVD death rate ($\beta = .105$; $P < .01$) during the following 18 years. That is, persons whose cholesterol levels dropped 14 mg/dL during 14 years would be expected to have an 11% higher death rate than persons whose cholesterol levels remained constant or rose during the same period.

MedCheck's Comments:

Given that as many as 14% of men and 20% of women showed a negative cholesterol slope, it is highly unlikely that they were already suffering from a condition causing such a decline—one that would eventually lead to death—as early as 4 to 18 years prior. Therefore, it may not be denied that the drop in cholesterol levels actually triggered the onset of infectious diseases, cancer, or other fatal conditions.

Supplement 6: Evidence showing association between CHD and coagulation

More comments on Figure 6: Hemostatic variables in patients with familial hypercholesterolemia with and without CHD.



Data based on Sugrue et al. [38].

CHD was associated with significantly increased levels of fibrinogen and coagulation factor VIII

but not with increased levels of classical risk factors such as total cholesterol, LDL-C, HDL-C, and TG.

38) Sugrue DD, et al. Coronary artery disease and haemostatic variables in heterozygous familial hypercholesterolaemia. *Br Heart J.* 1985;53(3):265–268. doi:10.1136/hrt.53.3.265. PMID: 3970784.

Supplement 7: Evidence bases of JAS Guidelines 2022:

7-A: BQ2: Does Total cholesterol predict the onset of and mortality from atherosclerotic disease in the Japanese population?

Total cholesterol predicts the onset of and mortality from atherosclerotic disease in the Japanese population. A positive association has been shown with cerebral infarction and a negative association has been shown with hemorrhagic stroke,

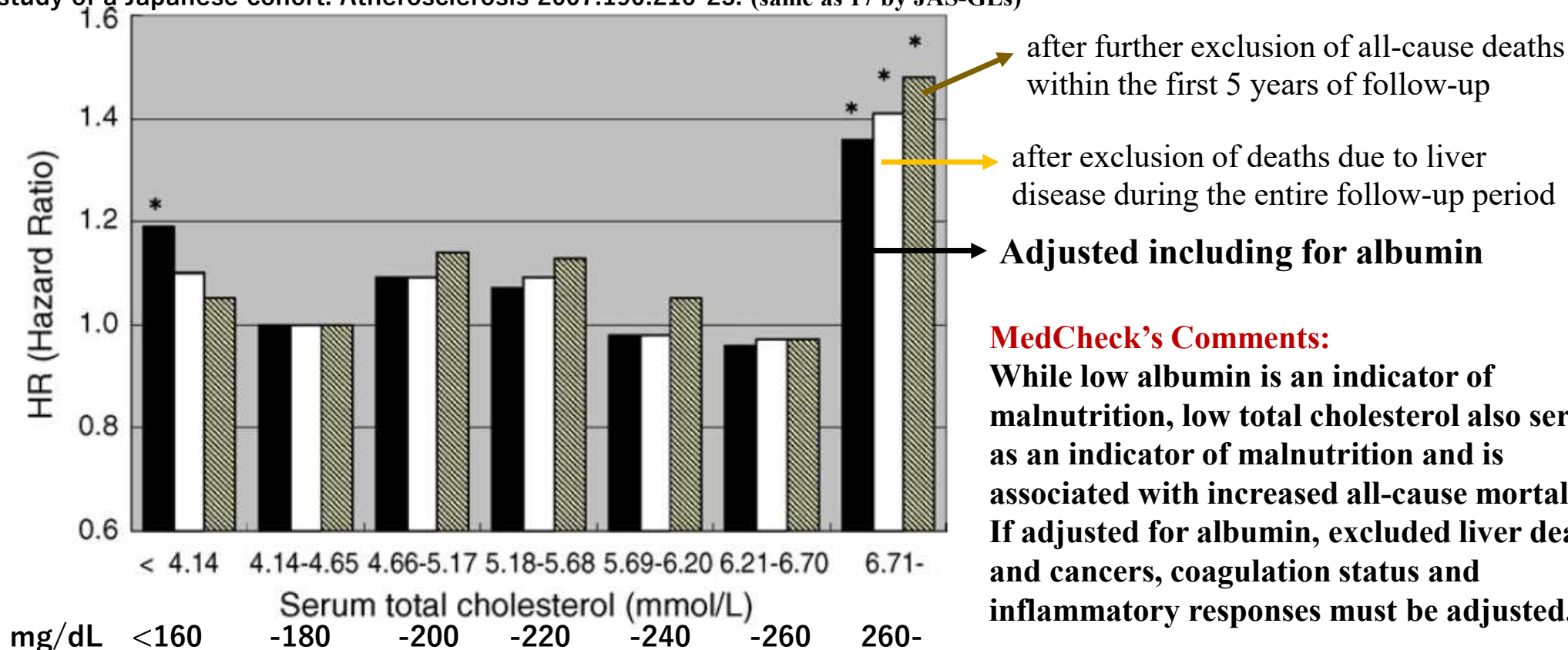
GL No	References	Primary Outcome	Association	All-cause mortality
15	Kodama K, Sasaki H, Shimizu Y. Trend of coronary heart disease and its relationship to risk factors in a Japanese population: a 26-year follow-up. Hiroshima/Nagasaki study. Jpn Circ J 1990;54:414-21.	AMI Ischemic and hemorrhagic stroke	POS INV	Not shown
16	Konishi M, Iso H, Iida M, et al. Trends for coronary heart disease and its risk factors in Japan: epidemiologic and pathologic studies. Jpn Circ J 1990; 54: 428-35.	CHD death at urban area at rural area	POS INV	Not shown
17	Okamura T, Tanaka H, Miyamatsu N, et al. The relationship between serum total cholesterol and all-cause or causespecific mortality in a 17.3-year study of a Japanese cohort. Atherosclerosis 2007;190:216-23.	All cause death after excluding all liver death, cancer death within 5 years of observation and adjusted for albumin	POS	over-adjustment
18	Tanabe N, Iso H, Okada K et al. Serum total and non-highdensity lipoprotein cholesterol and the risk prediction of cardiovascular events - the JALS-ECC-. Circ J 2010;74:1346-56.	AMI incidence vs TC/non-HDL-C	POS	Not shown
19	Wakugami K, Iseki K, Kimura Y, et al. Relationship between serum cholesterol and the risk of acute myocardial infarction in a screened cohort in Okinawa, Japan. Jpn Circ J 1998;62:7-14.	AMI incidence	POS	Not shown
20	Kitamura A, Iso H, Naito Y, et al. High-density lipoprotein cholesterol and premature coronary heart disease in urban Japanese men. Circulation 1994;89:2533-9.	CHD incidence is inversely related to HDL-C in urban Japanese middle-aged men, whose mean total cholesterol is relatively low (5.10 mmol/L= 197mg/dL).		Not shown
21	Sugiyama D et al. Risk of hyper-cholesterolemia for cardiovascular disease and the population attributable fraction in a 24-year Japanese cohort study. J Atheroscler Thromb 2015;22: 95-107. doi: 10.5551/jat.25908. Epub 2014 Sep 3. PMID: 25185893	CHD incidence Death from CHD and HF	POS POS	Not shown
22	Nagasawa SY, Iso H, et al. Relation between serum total cholesterol level and cardiovascular disease stratified by sex and age group: a pooled analysis of 65,594 individuals from 10 cohort studies in Japan. J Am Heart Assoc 2012;1:e001974.	AMI incidence except older female (No) Hemorrhagic and Total stroke incidence Ischemic stroke incidence	POS INV No	Not shown
23	Okumura K, Iseki K, Wakugami K, et al. Low serum cholesterol as a risk factor for hemorrhagic stroke in men: a community-based mass screening in Okinawa, Japan. Jpn Circ J 1999;63:53-8.	Hemorrhagic stroke incidence	INV	Not shown
24	Cui R, Iso H, Toyoshima H, et al. Serum total cholesterol levels and risk of mortality from stroke and coronary heart disease in Japanese: the JACC study. Atherosclerosis 2007;194:415-20.	AMI incidence Hemorrhagic stroke incidence	POS INV	Not shown
25	Tanizaki Y, Kiyohara Y, Kato I, et al. Incidence and risk factors for subtypes of cerebral infarction in a general population: the Hisayama study. Stroke 2000;31:2616-22.	Cardiogenic thrombotic ischemic stroke	INV	Not shown
26	Cui R, Iso H, Yamagishi K, et al. High serum total cholesterol levels is a risk factor of ischemic stroke for general Japanese population: the JPHC study. Atherosclerosis 2012 ;22 1:565-9.	Ischemic stroke incidence (male)	POS	Not shown

AMI: acute myocardial infarction, CHD: coronary heart disease, Hemorrhagic S: hemorrhagic stroke, POS: positive correlation, NO: no correlation, NEG: negative correlation

Supplement 7: Evidence bases of JAS Guidelines 2022:

7-B(1) : Only one paper claims positive association between total cholesterol and total mortality

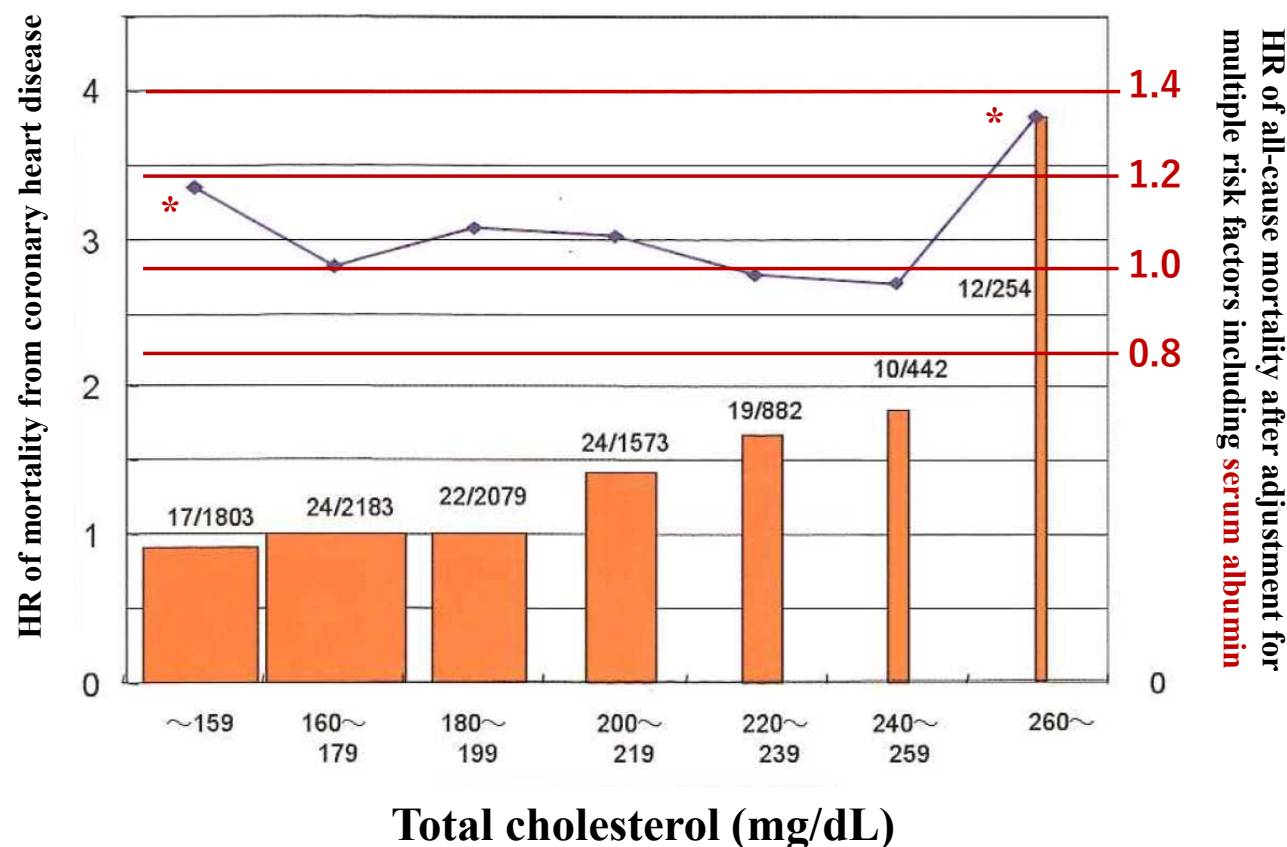
57) Okamura et al. The relationship between serum total cholesterol and all-cause or cause-specific mortality in a 17.3-year study of a Japanese cohort. *Atherosclerosis* 2007;190:216-23. (same as 17 by JAS-GLs)



Multivariable-adjusted hazard ratios (HR) for all-cause mortality grouped according to serum total cholesterol **after adjustment** for gender, age, **serum albumin**, body mass index, hypertension, diabetes, cigarette smoking and alcohol intake. Black bars show HR for all-cause mortality among all participants. White bars show HR for all-cause mortality after exclusion of deaths due to liver disease during the entire follow-up period. Hatched bars show HR for all-cause mortality after further exclusion of all-cause deaths within the first 5 years of follow-up. (* $P < 0.05$).

Supplement 7: Evidence bases of JAS Guidelines 2022:

7-B (2): Very few population at risk of high total cholesterol with coronary death and total death
ref. 17 (by 2022 JAS-GL) or ref. 57 (in this MedCheck article)

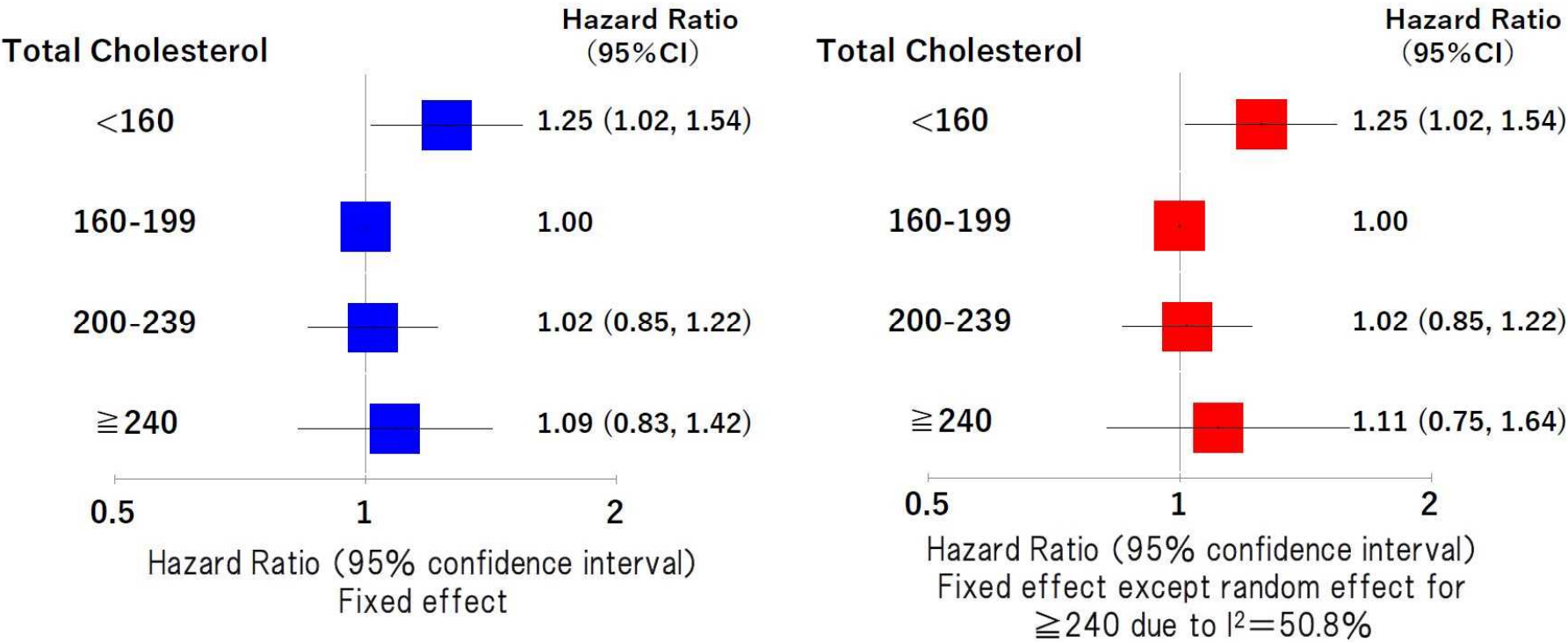


Adapted from the Figure 38 (p69) in the Cholesterol Guidelines for Longevity 2010 Edited by Japan Society for Lipid Nutrition (in Japanese). Figure plotted based on data from Okamura et al. (2007) [57]. The numbers above the bars represent the number of deaths from coronary heart disease divided by the number of subjects. Using the 160–179 mg/dL range as the reference value for total mortality, significant differences (* $P < 0.05$) were observed in the ≤ 159 mg/dL and ≥ 260 mg/dL groups. Please refer to the original publication for the exact mortality figures. The column widths are proportional to the number of subjects. Population with ≥ 260 mg/dL and reference group are 2.8% and 24% of all population respectively.

Supplement 7: Evidence bases of JAS Guidelines 2022:

7-C: The paper which was excluded from the list of evidence of JAS Guidelines even if all liver deaths and deaths within the first 5 years of follow-up were excluded.

Adapted from the data on Table 4b in [18] by Nago et al. J Epidemiol. 2011;21(1):67-74. doi: 10.2188/jea.je20100065.



Even after excluding deaths from liver disease and deaths within the first 5 years, an increased risk of all-cause mortality is observed among individuals with low total cholesterol levels (below 160 mg/dL). No increase in all-cause mortality is observed in the group with levels of 240 or higher. Furthermore, while there is no difference in all-cause mortality risk between men and women in the group with total cholesterol levels below 240 ($I^2 \leq 4\%$), heterogeneity was observed in the group with levels of 240 or higher ($I^2 = 50.8\%$).

Supplement 8: Inverse association between LDL-cholesterol and mortality in the elderly

8-A: 9)Ravnskov U, Diamond DM, Hama R et al. BMJ Open 2016;6: e010401

BMJ Open Lack of an association or an inverse association between low-density-lipoprotein cholesterol and mortality in the elderly: a systematic review

Uffe Ravnskov,¹ David M Diamond,² Rokura Hama,³ Tomohito Hamazaki,⁴ Björn Hammarskjöld,⁵ Niamh Hynes,⁶ Malcolm Kendrick,⁷ Peter H Langsjoen,⁸ Aseem Malhotra,⁹ Luca Mascitelli,¹⁰ Kilmer S McCully,¹¹ Yoichi Ogushi,¹² Harumi Okuyama,¹³ Paul J Rosch,¹⁴ Tore Schersten,¹⁵ Sherif Sultan,⁶ Ralf Sundberg¹⁶

To cite: Ravnskov U, Diamond DM, Hama R, *et al*. Lack of an association or an inverse association between low-density-lipoprotein cholesterol and mortality in the elderly: a systematic review. *BMJ Open* 2016;6:e010401.

ABSTRACT

Objective: It is well known that total cholesterol becomes less of a risk factor or not at all for all-cause and cardiovascular (CV) mortality with increasing age, but as little is known as to whether low-density lipoprotein cholesterol (LDL-C), one component of total cholesterol, is associated with mortality in the elderly, we decided to investigate this issue.

Strengths and limitations of this study

- This is the first systematic review of cohort studies where low-density lipoprotein cholesterol (LDL-C) has been analysed as a risk factor for all-cause and/or cardiovascular mortality in elderly people.

9)Ravnskov U, Diamond DM, Hama R et al. Lack of an association or an inverse association between low-density-lipoprotein cholesterol and mortality in the elderly: a systematic review. *BMJ Open* 2016;6: e010401

Supplement 8: Inverse association between LDL-cholesterol and mortality in the elderly

8-B: Individual data showing inverse association between LDL cholesterol and mortality in the elderly

9)Ravnskov U, Diamond DM, Hama R et al. BMJ Open 2016;6: e010401

