Low density Lipoprotein Cholesterol and all-Cause Mortality rate Findings from a Study on Japanese Community-Dwelling Persons

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Research

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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 1,610 men (63 ± 14 years old) and 2,074 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 age as the time variable 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 3,684 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). The univariate Cox regression analysis revealed that the hazard ratios (HRs) for all-cause mortality significantly increased with a decrease in LDL-C level ($P < 0.001$). The multivariate Cox regression analysis with adjustment variables showed that LDL-C grouping (HR: 0.71; 95% confidence interval [CI]: 0.62–0.82), gender (HR: 0.69, 95% CI: 0.51–0.93), age (HR: 1.09; 95% CI: 1.08–1.11), BMI (HR: 0.68; 95% CI: 0.54–0.86), history of CVD (HR: 1.38; 95% CI: 1.03–1.82), and presence of diabetes (HR: 1.65; 95% CI: 1.23–2.22) were significantly associated with all-cause mortality. Compared with individuals with LDL-C levels of 144 mg/dL or higher, the multivariate-adjusted HRs (95% CI) for all-cause mortality were 2.68 (1.67–4.28) for those with LDL-C levels under 70 mg/dL and 1.74 (1.17–2.59) for those with LDL-C levels between 70 and 92 mg/dL.

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

Introduction

Numerous researchers have highlighted that low-density lipoprotein cholesterol (LDL-C) is a key risk factor associated with cardiovascular diseases (CVDs) [1]. Randomized controlled trials on the impact of lipid-lowering therapies have elucidated that reducing LDL-C levels lowers the risk of developing atherosclerotic CVD [2] [3] [4] [5].

Research has offered contrasting findings on the association between LDL-C levels and CVD-related mortality. While some studies have shown a positive association [6], others present U-shaped associations [7]. Similarly, findings on the association between LDL-C levels and the risk of all-cause mortality remain contradictory. Whereas some research indicates a counterintuitive reverse association (increased levels of LDL-C reduce mortality) [8] [9] [10] [11], others conclude that LDL-C levels are irrelevant [12] [13]. The varying results can be attributed to differences in the race, age, and gender of the targeted participants.

To address these inconsistencies, this study aimed to investigate whether LDL-C is related to survival prognosis based on 7 or 10 years of follow-up among Japanese community-dwelling persons.

Methods

Study Design And Participants

This prospective cohort analysis is part of the Nomura studies [14] initiated in 2002 (first cohort) and 2014 (second cohort). Participants were recruited from the rural areas of Ehime Prefecture, Japan, with a focus on those who had undergone a community-based annual health check at the Nomura Health and Welfare Center. The first cohort included a total of 3,164

people and the second cohort had 1,832 people, all of whom were between the ages of 22 and 95 years. All procedures were carried out in accordance with relevant guidelines and regulations. A self-administered questionnaire was used to obtain data on participants' physical activity, medical history, current condition, and medication. Figure 1 shows the flowchart for the inclusion and exclusion of participants. Follow-up assessments were conducted after a 10-year interval for the first cohort and a 7-year interval for the second cohort. Participants' living status was confirmed using Japan's Basic Resident Register. This study examined evaluation data for the first and second cohorts (N = 3,684). The study protocol was reviewed and approved by the Ehime University Hospital Institutional Review Board (IRB) (1903018). All participants provided written informed consent.

Evaluation Of Risk Factors

Demographic and risk factor data were obtained from clinical files. Body mass index (BMI) was estimated as weight (kg) divided by height (m^2). Smoking status (packs-year) was calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked. Accordingly, participants were categorized as non-smokers, ex-smokers, mild smokers (< 20 packs-year), or heavy smokers (≥ 20 packs-year). The Japanese liquor unit (22.9 g ethanol) was referenced to measure daily alcohol consumption. Participants were categorized as non-drinkers, occasional drinkers (< 1 unit/day), light daily drinkers (1–2 units/day), and heavy daily drinkers (2–3 units/day). None of the participants consumed more than 3 units/day. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were estimated by an automatic sphygmomanometer. To record both types of blood pressure, participants were asked to rest for at least five minutes, after which an appropriately sized cuff was placed on the participant's right upper arm while seated. The average of two consecutive measurements was used for the analysis. Triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), LDL-C, serum uric acid (SUA), and blood glucose (BG) levels were measured during overnight fasting. The glomerular filtration ratio (eGFR) was estimated by modifying the chronic kidney disease epidemiology collaboration (CKD-EPI) equation with a Japanese coefficient: Male, Cr ≤ 0.9 mg/dl, $141 \times (Cr/0.9)^{-0.411} \times 0.993^{age} \times 0.813$; Cr > 0.9 mg/dl, $141 \times (Cr/0.9)^{-1.209} \times 0.993^{age} \times 0.813$; Female, Cr ≤ 0.7 mg/dl, $144 \times (Cr/0.7)^{-0.329} \times 0.993^{age} \times 0.813$; Cr > 0.7 mg/dl, $144 \times (Cr/0.7)^{-1.209} \times 0.993^{age} \times 0.813$ [15].

Participants were said to have hypertension if their SBP was 140 mmHg or higher, their DBP was 90 mmHg or higher, or they were on antihypertensive medication. Further, participants were classified as having hypertriglyceridemia if their TG levels were 150 mg/dL or higher and hypo-HDL cholesterolemia if HDL-C levels were above 40 mg/dL. Those on antidiabetic medication and with BG levels of 126 mg/dL or higher were categorized as diabetic. Use of an SUA-lowering medication or SUA levels of 7.0 mg/dL or higher were indicators of hyperuricemia. Chronic kidney disease (CKD) was defined as an eGFR under 60 mL/min/1.73 m^2. Ischemic heart disease, ischemic stroke, and peripheral vascular disease were classified as CVD.

Statistical analysis

All data were analyzed using IBM SPSS Statistics (version 26.0; SPSS Inc., Chicago, IL, United States). Normally distributed data are presented as the mean ± standard deviation and non-normally distributed data are expressed as median values (interquartile range) (e.g., for TG and BG levels). Parameters with non-normal distributions were log-transformed, and the transformed values were used in all analyses. Participants were divided into four groups on the basis of LDL-C level (very low: ≤ 69; low: 70–92; medium: 93–143; high: ≥ 144 mg/dL). Student's t-test or an analysis of variance (ANOVA) was conducted on continuous data and a χ^2 test was used on categorical data to analyze for differences in means and prevalence among the groups. Next, a Cox proportional hazard regression was performed to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Age was used as the primary time variable. The age at the time of recruitment (days) of participants was treated as admission time, and the age of death or censoring (at the end of the follow-up period) was treated as exit time. Analyses were adjusted for gender; age; BMI; smoking and drinking habits; history of CVD, hypertension, hypertriglyceridemia, low HDL-cholesterolemia, diabetes, and CKD; use of @lipid-lowering medication; and LDL-C group. Subgroup analyses were performed to determine if the observed association between LDL-C levels and all-cause mortality was consistent. Next, a

likelihood ratio test was conducted to determine the interaction between LDL-C grouping and subgroup variables. All confounding variables, except the effect variable, were adjusted in the interaction test performed to analyze the effect variable. All *P*-values less than 0.05 were considered statistically significant.

Results

The sample comprised 3,684 participants. The mean age was 64 ± 13 years old and 43.7% were male. The median follow-up time (interquartile range) was 3,160 (2,330–3,693) days. A total of 326 (8.8%) participants were confirmed to have died, and of these, 180 were men (11.2% of all men) and 146 were women (7.0% of all women) (Table 1).

Table 1
Baseline characteristics of participants

Characteristics *N* = 3,684	Value
Gender (male), %	43.7
Age (years)	64 ± 13
Body mass index categories[†], %	5.0/67.8/27.2
Body mass index (kg/m^2)	23.3 ± 3.2
Smoking habits (neve/past/light/heavy), %	66.4/25.6/2.7/5.2
Drinking habits (never/occasional/light/heavy), %	51.7/25.8/13.6/9.0
History of cardiovascular disease, %	8.0
Hypertension, %	57.0
Systolic blood pressure (mmHg)	138 ± 21
Diastolic blood pressure (mmHg)	80 ± 11
Hypertriglyceridemia, %	18.0
Triglyceridemia (mg/dL)	93 (70–131)
Low HDL-cholesterolemia, %	4.4
HDL cholesterol (mg/dL)	63 ± 16
Lipid-lowering medication, %	9.7
LDL cholesterol (mg/dL)	118 ± 31
LDL cholesterol categories[‡], %	4.9/15.1/60.0/20.0
Diabetes, %	9.5
Blood glucose (mg/dL)	100 (91–114)
Chronic kidney disease, %	10.2
eGFR (mL/min/1.73 m^2)	78.0 ± 16.4
Hyperuricemia, %	13.5
Serum uric acid (mg/dL)	5.1 ± 1.4
HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration ratio.	
[†] Body mass index categories: < 18.5 kg/m^2, 18.5–25.0 kg/m^2, ≥ 25 kg/m^2.	
[‡] LDL cholesterol categories: very low, < 70 mg/dL; low, 70–92 mg/dL; medium, 93–143 mg/dL; high, ≥ 144 mg/dL.	
Data are presented as means ± standard deviation except for the data for triglycerides and hemoglobin A1c, which were skewed and are thus presented as median (interquartile range) values.	

Table 2 shows the baseline characteristics of the study participants according to LDL-C concentration at baseline. The age of participants in the lowest LDL-C group was younger than the other groups, though age was significantly higher in the highest LDL-C group. BMI, TG levels, and BG levels were significantly higher as LDL-C levels increased. eGFR and SUA levels were significantly lower among male participants. The proportion of smokers and drinkers significantly decreased across the LDL-C groups. Blood pressure was also similar across each LDL-C group, albeit with a small significant increase in SBP from the

lowest to highest LDL-C group. The proportion of participants with hypertriglyceridemia, low HDL-cholesterolemia, and hyperuricemia was significantly lower in the very low LDL-C group.

Table 2
Baseline characteristics of participants by low-density lipoprotein cholesterol categories

	LDL cholesterol categories (mg/dL)				
	Very Low (< 5%)	**Low (5–19%)**	**Medium (20–79%)**	**High (≥ 80%)**	
	< 70	**70–92**	**93–143**	**≥ 144**	
Characteristics N = **3,684**	N = **181**	N = **555**	N = **2,212**	N = **736**	P-**value** *
Gender (male), %	78.5	59.1	41.6	29.9	**< 0.001**
Age (years)	59 ± 17	61 ± 15	65 ± 12	65 ± 11	**< 0.001**
Body mass index categories †, %	10.5/70.7/18.8	7.4/69.9/22.7	4.5/68.4/27.0	3.3/63.5/33.3	**< 0.001**
Body mass index (kg/m^2)	22.3 ± 3.3	22.7 ± 3.2	23.3 ± 3.1	23.9 ± 3.3	**< 0.001**
Smoking habits (never = 1, past = 2, light = 3, heavy = 4), %	43.6/50.3/1.7/4.4	55.1/35.3/2.5/7.0	68.8/22.7/3.0/5.5	73.6/20.9/2.2/3.3	**< 0.001**
Drinking habits (never = 1, occasional = 2, light = 3, heavy = 4), %	23.2/22.7/24.9/29.3	37.8/29.5/20.5/12.1	53.3/26.1/12.5/8.0	64.1/22.6/8.7/4.6	**< 0.001**
History of cardiovascular disease, %	6.1	8.6	8.5	6.7	0.303
Hypertension, %	53.6	52.3	58.1	58.3	0.057
Systolic blood pressure (mmHg)	136 ± 20	135 ± 21	138 ± 21	139 ± 22	**0.001**
Diastolic blood pressure (mmHg)	80 ± 12	79 ± 12	80 ± 11	81 ± 12	**0.001**
Hypertriglyceridemia, %	32.0	12.1	16.7	23.0	**< 0.001**
Triglyceridemia (mg/dL)	100 (60–179)	81 (61–114)	91 (69–127)	105 (81–145)	**< 0.001**
Low HDL-cholesterolemia, %	9.4	4.9	3.8	4.9	**0.004**
HDL cholesterol (mg/dL)	60 ± 19	63 ± 18	63 ± 15	61 ± 15	**< 0.001**
Lipid-lowering medication, %	6.6	11.0	10.5	6.9	**0.011**

† Body mass index categories: < 18.5 kg/m^2, 18.5–25.0 kg/m^2, ≥ 25 kg/m^2. Data presented are means ± standard deviation. Data for triglycerides and Hemoglobin A1c were skewed and are thus presented as median (interquartile range) values, and were log-transformed for analysis. **P*-values are from ANOVA for continuous variables or from the χ^2-test for categorical variables. Significant values ($P < 0.05$) are presented in bold.

	LDL cholesterol categories (mg/dL)				
LDL cholesterol (mg/dL)	58 ± 9	82 ± 6	118 ± 14	162 ± 18	**< 0.001**
Diabetes, %	11.0	8.5	9.7	9.4	0.733
Blood glucose (mg/dL)	97 (89–111)	98 (89–114)	100 (91–114)	103 (92–117)	**0.002**
Chronic kidney disease, %	11.6	9.0	10.2	10.6	0.712
eGFR (mL/min/1.73 m^2)	82.9 ± 20.0	80.7 ± 17.4	77.6 ± 16.1	76.2 ± 15.1	**< 0.001**
Hyperuricemia, %	26.5	15.0	12.5	12.2	**< 0.001**
Serum uric acid (mg/dL)	5.8 ± 1.6	5.2 ± 1.5	5.1 ± 1.4	5.1 ± 1.4	**< 0.001**

† Body mass index categories: < 18.5 kg/m^2, 18.5–25.0 kg/m^2, ≥ 25 kg/m^2. Data presented are means ± standard deviation. Data for triglycerides and Hemoglobin A1c were skewed and are thus presented as median (interquartile range) values, and were log-transformed for analysis. **P*-values are from ANOVA for continuous variables or from the χ^2-test for categorical variables. Significant values ($P < 0.05$) are presented in bold.

Table 3 reveals that the risk (HR; 95% CI) for all-cause mortality was significantly associated with LDL-C grouping (0.71; 0.62–0.82) as well as gender (0.69; 0.51–0.93), age (1.09; 1.08–1.11), BMI (0.68; 0.54–0.86), and history of CVD (1.38; 1.03–1.85) and diabetes (1.65; 1.23–2.22).

Table 3
Adjusted hazard ratios and 95% confidence intervals of baseline characteristics for all-cause mortality

Characteristics N = 3,684	HR (95% CI)	*P*-value
Gender (male = 1, female = 2)	0.69 (0.51–0.93)	**0.016**
Age (per 1 year)	1.09 (1.08–1.11)	**< 0.001**
Body mass index categories †	0.68 (0.54–0.86)	**0.001**
Smoking habits (never = 1, past = 2, light = 3, heavy = 4)	1.00 (0.84–1.19)	0.985
Drinking habits (never = 1, occasional = 2, light = 3, heavy = 4)	0.99 (0.86–1.14)	0.882
History of cardiovascular disease (no = 0, yes = 1)	1.38 (1.03–1.85)	**0.033**
Hypertension (no = 0, yes = 1)	1.06 (0.83–1.37)	0.643
Hypertriglyceridemia (no = 0, yes = 1)	0.94 (0.69–1.29)	0.695
Low HDL-cholesterolemia (no = 0, yes = 1)	0.57 (0.30–1.06)	0.074
LDL cholesterol categories ‡	0.71 (0.62–0.82)	**< 0.001**
Lipid-lowering medication (no = 0, yes = 1)	0.90 (0.61–1.32)	0.577
Diabetes (no = 0, yes = 1)	1.65 (1.23–2.22)	**0.001**
Chronic kidney disease (no = 0, yes = 1)	0.95 (0.70–1.28)	0.713
Hyperuricemia (no = 0, yes = 1)	1.18 (0.86–1.62)	0.313
HR, hazard ratio; CI, confidence interval.		
† Body mass index categories: < 18.5 kg/m^2 = 1, 18.5–25.0 kg/m^2 = 2, ≥ 25.0 kg/m^2 = 3.		
‡ LDL cholesterol categories: very low, < 70 mg/dL = 1; low, 70–92 mg/dL = 2; medium, 93–143 mg/dL = 3; high, ≥ 144 mg/dL = 4.		
Significant values (*P* < 0.05) are presented in bold.		

Kaplan–Meier survival curves were charted for survival days and cumulative survival rates to identify patterns in the relationships between the four LDL-C groups and all-cause mortality (Fig. 2). The cumulative survival rate was significantly lower for individuals with very low and low LDL-C levels compared with those with high LDL-C levels (HR: $P < 0.001$ and $P = 0.002$).

Table 4 shows a higher risk of all-cause mortality in the very low (< 70 mg/dL) and low (70–92 mg/dL) LDL-C groups compared with the high LDL-C group (≥ 144 mg/dL). Next, the analysis was adjusted for gender; age; BMI; smoking and drinking status; use of lipid-lowering medication; and history of CVD, hypertension, hypertriglyceridemia, low HDL-cholesterolemia, CKD, and hyperuricemia. The results indicate that the association between the very low and low LDL-C groups and the higher risk of all-cause mortality remained significant. Such associations were also observed in the four LDL-C groups when participants were divided by age (< 65, 65–74, and ≥ 75 years old).

Table 4
Hazard ratios and 95% confidence intervals of baseline low density lipoprotein cholesterol categories for all-cause mortality by age group

LDL cholesterol	Prevalence of death/total (%)	Non-adjusted HR (95% CI)	Gender and age-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI) [a]
Overall (n = 3,684)				
Very low	33/181 (18.2)	**2.85 (1.82–4.46)**	**2.93 (1.85–4.64)**	**2.68 (1.67–4.28)**
Low	62/555 (11.2)	**1.81 (1.24–2.66)**	**1.88 (1.27–2.77)**	**1.74 (1.17–2.59)**
Medium	185/2212 (8.4)	1.35 (0.98–1.87)	1.27 (0.92–1.75)	1.20 (0.86–1.66)
High	46/736 (6.3)	1.00	1.00	1.00
P for trend	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**
< 65 years of age (n = 1,571)				
Very low	8/93 (8.6)	**6.12 (1.84–20.3)**	**6.57 (1.91–22.7)**	**5.66 (1.58–20.3)**
Low	10/267 (3.7)	2.80 (0.88–8.92)	2.96 (0.91–9.62)	2.62 (0.80–8.62)
Medium	32/899 (3.6)	2.73 (0.97–7.41)	2.76 (0.97–7.82)	2.56 (0.90–7.31)
High	4/312 (1.3)	1.00	1.00	1.00
P for trend	**0.002**	**0.028**	**0.027**	0.064
≥ 65 and < 75 years of age (n = 1,395)				
Very low	9/52 (17.3)	**2.76 (1.24–6.15)**	**2.34 (1.02–5.39)**	**2.52 (1.08–5.93)**
Low	18/179 (10.1)	1.62 (0.84–3.11)	1.43 (0.73–2.79)	1.37 (0.70–2.69)
Medium	60/872 (6.9)	1.12 (0.66–1.89)	1.02 (0.60–1.74)	0.93 (0.54–1.59)
High	18/292 (6.2)	1.00	1.00	1.00
P for trend	**0.007**	**0.037**	0.109	**0.044**
≥ 75 years of age (n = 718)				
Very low	16/36 (44.4)	**3.03 (1.61–5.71)**	**2.53 (1.33–4.84)**	**2.13 (1.09–4.16)**

HR, hazard ratio; CI, confidence interval. LDL cholesterol categories: very low, < 70 mg/dL = 1; low, 70–92 mg/dL = 2; medium, 93–143 mg/dL = 3; high, ≥ 144 mg/dL = 4.

[a] Multivariate-adjusted HR: adjusted for gender, age, body mass index categories, smoking status, drinking status, history of cardiovascular disease, hypertension, hypertriglyceridemia, low HDL-cholesterolemia, lipid-lowering medication, chronic kidney disease, and hyperuricemia.

Significant values (*P* < 0.05) are presented in bold.

LDL cholesterol	Prevalence of death/total (%)	Non-adjusted HR (95% CI)	Gender and age-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI) [a]
Low	34/109 (31.2)	**2.27 (1.35–3.84)**	**1.99 (1.17–3.39)**	**1.75 (1.01–3.05)**
Medium	93/441 (21.1)	1.27 (0.81–1.98)	1.22 (0.78–1.92)	1.09 (0.68–1.73)
High	24/132 (18.2)	1.00	1.00	1.00
P for trend	**< 0.001**	**< 0.001**	**0.004**	**0.021**

HR, hazard ratio; CI, confidence interval. LDL cholesterol categories: very low, < 70 mg/dL = 1; low, 70–92 mg/dL = 2; medium, 93–143 mg/dL = 3; high, ≥ 144 mg/dL = 4.

[a] Multivariate-adjusted HR: adjusted for gender, age, body mass index categories, smoking status, drinking status, history of cardiovascular disease, hypertension, hypertriglyceridemia, low HDL-cholesterolemia, lipid-lowering medication, chronic kidney disease, and hyperuricemia.

Significant values ($P < 0.05$) are presented in bold.

Finally, Table 5 stratifies participants by gender; BMI (< 25 and ≥ 25 kg/m^2); history of CVD, hypertension, diabetes, and CKD; use of lipid-lowering medication; and time to death (< 1,095 or ≥ 1,095 days). The results similarly show that the higher LDL-C level groups were associated with a lower risk of all-cause mortality, and this association was particularly significant among participants who were male and had CKD.

Table 5
Hazard ratios and 95% confidence intervals of baseline low density lipoprotein cholesterol categories for all-cause mortality by sub-analysis

Characteristics N = 3,684	Multivariable-adjusted HR (95% CI)	*P*-value	*P* for interaction
Gender			
Men (n = 1,610)	0.64 (0.53–0.76)	**< 0.001**	**0.039**
Women (n = 2,074)	0.84 (0.66–1.09)	0.185	
Body mass index			
< 25 kg/m^2 (n = 2,681)	0.71 (0.60–0.83)	**< 0.001**	0.261
≥ 25 kg/m^2 (n = 1,003)	0.80 (0.57–1.14)	0.216	
History of cardiovascular disease			
No (n = 3,389)	0.72 (0.62–0.85)	**< 0.001**	0.908
Yes (n = 295)	0.72 (0.50–1.05)	0.086	
Hypertension			
No (n = 1,583)	0.69 (0.53–0.91)	**0.008**	0.705
Yes (n = 2,101)	0.73 (0.61–0.87)	**< 0.001**	
Lipid-lowering medication			
No (n = 3,327)	0.70 (0.60–0.81)	**< 0.001**	0.379
Yes (n = 357)	0.93 (0.54–1.61)	0.794	
Diabetes			
No (n = 3,334)	0.73 (0.61–0.87)	**< 0.001**	0.059
Yes (n = 350)	1.01 (0.69–1.47)	0.962	
Chronic kidney disease			
No (n = 3,310)	0.79 (0.66–0.93)	**0.005**	**0.015**
Yes (n = 374)	0.51 (0.37–0.69)	**< 0.001**	
Time to death			
< 1,095 days (n = 73)	Not examined	------	Not examined
≥ 1,095 days (n = 3,611)	0.72 (0.61–0.85)	**< 0.001**	
HR, hazard ratio; CI, confidence interval.			

[a] Multivariate-adjusted HR: adjusted for gender, age, body mass index categories, smoking status, drinking status, history of cardiovascular disease, hypertension, hypertriglyceridemia, low HDL-cholesterolemia, lipid-lowering medication, chronic kidney disease, and hyperuricemia. Significant values ($p < 0.05$) are presented in bold.

Discussion

The main finding of this cohort study is that LDL-C is a significant and independent predictor of all-cause mortality in community-dwelling adults. After adjustment for possible confounding factors, the results showed that participants with the

lowest LDL-C levels (< 70 mg/dL) were at a significantly higher risk for all-cause mortality than those with high LDL-C levels (≥ 144 mg/dL). Participants who died within three years of the follow-up were excluded to avoid the possibility of reverse causality, although the results remain largely unchanged. Further, LDL-C levels were significantly associated with death among those aged 75 years or older. To the best of our knowledge, few studies have demonstrated the relationship between LDL-C level and all-cause mortality in Japanese community-dwelling persons.

The results of this study, especially that low LDL-C levels are significantly associated with an increased risk of all-cause mortality, are consistent with the results of several existing studies. The Kangbuk Samsung Health Study on 347,971 individuals (mean age: 39.6 years old; male: 57.4%; mean follow-up: 5.64 ± 3.27 years) highlighted that the lowest LDL-C group (< 70 mg/dL) was at a higher risk of all-cause mortality (HR: 1.81; 95% CI: 1.44–2.28) compared with the reference group (120–139 mg/dL) [7]. Further, it reported 2,028 deaths among the total number of participants and 11,376 (10.5%) deaths during the study among the 108,243 individuals aged 20–100 years (male: 45.0%; median follow-up: 9.4 years). The study also showed a U-shaped relationship between LDL-C levels and the risk of all-cause mortality: that is, low levels (< 70 mg/dL; HR: 1.25, 95% CI: 1.15–1.36) and high levels (> 189 mg/dL; HR: 1.15, 95% CI: 1.05–1.27) were associated with an increased risk of all-cause mortality compared with the reference group (132–154 mg/L) [16]. The China Health and Retirement Longitudinal Study (follow-up: four years) recorded a total of 305 deaths out of 4,981 male participants. Compared with the LDL-C baseline group (117–137 mg/dL), a lower LDL-C level (≤ 84 mg/dL) was associated with an increased risk of four-year all-cause mortality in middle-aged and older adult Chinese male participants [17]. According to a recent systematic review of 19 cohort studies with more than 68,094 older adults, all-cause mortality was highest in the lowest LDL-C quartile group. Study participants' risk for all-cause mortality can be ascribed to their consumption of lipid-lowering agents and co-morbidities [18]. However, a population-based register study on 118,160 individuals aged 50 years or older without baseline statin use showed an association between high LDL-C levels and lower mortality among older adults [10]. The present study also reports that low LDL-C levels at baseline, as well as being male, older, having lower BMI, and having a history of CVD and diabetes, were linked with an increase in all-cause mortality. This finding was significant for male participants and those who did not have CKD.

This study examined the real-world association between low LDL-C levels and mortality outcomes among individuals undergoing lipid-lowering therapy and with a baseline history of CVD, hypertension, and diabetes. However, the sub-analysis shows similar notable findings for those who were not undergoing lipid-lowering therapy or had no other diseases. This result could alleviate concerns that serious illnesses may lower cholesterol shortly before death occurs. Further, the findings suggest that considerably lower LDL-C levels do not necessarily protect against all-cause mortality among community-dwelling persons who are not on lipid-lowering medication, thus supporting the lipid paradox [7]. In addition, the difference in results between male and female participants can be attributed to fewer deaths among women than men, which results in insufficient association power [17].

The mechanisms leading to increased all-cause mortality in individuals with very low LDL-C levels are not completely understood. Several explanations can be offered for these findings. Low LDL-C levels increase susceptibility to serious diseases [19]. Conversely, it has been hypothesized that frailty and illnesses lower cholesterol levels [20]. LDL-C may protect against viruses and cancers caused by viruses, and is therefore a component of innate immunity [21]. In addition, exotoxins produced by Gram-positive bacteria are absorbed by LDL-C [22] Thus, higher LDL-C levels have been associated with reduced infection-related mortality and other non-CVD mortality, which explains the inverse relationship with all-cause mortality [23]. In this study, comorbidities such as hypertriglyceridemia, low HDL cholesterolemia, and hyperuricemia were more frequently observed in individuals with the lowest LDL-C levels.

Strength And Limitations

This study has the following strengths and limitations. First, the sample consisted mainly of middle-aged and elderly people (mean age: 64 ± 13 years) living in a rural area in Japan. Therefore, it cannot be considered representative of the general population. Second, the survey covered people whose deaths were registered in the basic resident register. Those who moved

out of the region during the survey period are not included. Third, the possible effects of medication (e.g., antihypertensive, lipid-lowering, and antidiabetic medication), underlying diseases, and lifestyle modifications at the baseline and during the follow-up period on the present findings cannot be overlooked. Fourth, this study did not measure certain specific lipoproteins (e.g., small dense LDL), which could be a possible explanation for this phenomenon. Finally, the relatively low number of participants and deaths may weaken the causal relationship between LDL-C levels and all-cause mortality. A large-scale cohort study with a long-term follow-up period is warranted to evaluate the relationship between low LDL-C levels and mortality outcomes.

Conclusions

The current results, based on a follow-up study of people aged 22 years and older, show that lower LDL-C levels (< 70 mg/dL) are not only associated with a preventive effect, but are also predictive of higher all-cause mortality, after adjustment for potential confounders such as body composition indices and metabolic factors. Therefore, further attention to individuals for whom lower LDL-C levels are not induced by lipid-lowering medication may be necessary.

Declarations

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Authors ' contributions

RK and AK participated in the design of the study, performed the statistical

analysis and drafted the manuscript. RK, AK, DN, TA, and TK

contributed to the acquisition and interpretation of data. RK and AK contributed to the conception and design of the statistical analysis. RK conceived of the study, participated in its design, coordination and helped to draft the manuscript. All authors read and approved the manuscript.

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Availability of data and materials

The participant survey data supporting the conclusions of this manuscript

are not publicly available due to protection of the privacy of the participants.

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of the Ehime University Graduate School of Medicine (IRB: no. 1903018) and informed consent was obtained from all subjects participating in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

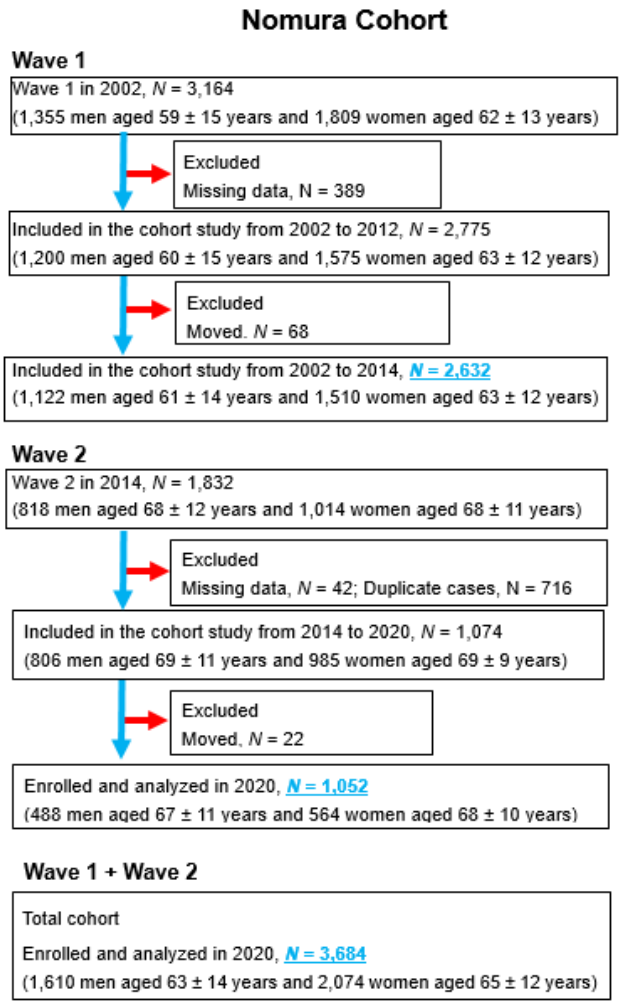

Figure 1

Flowchart of participants.

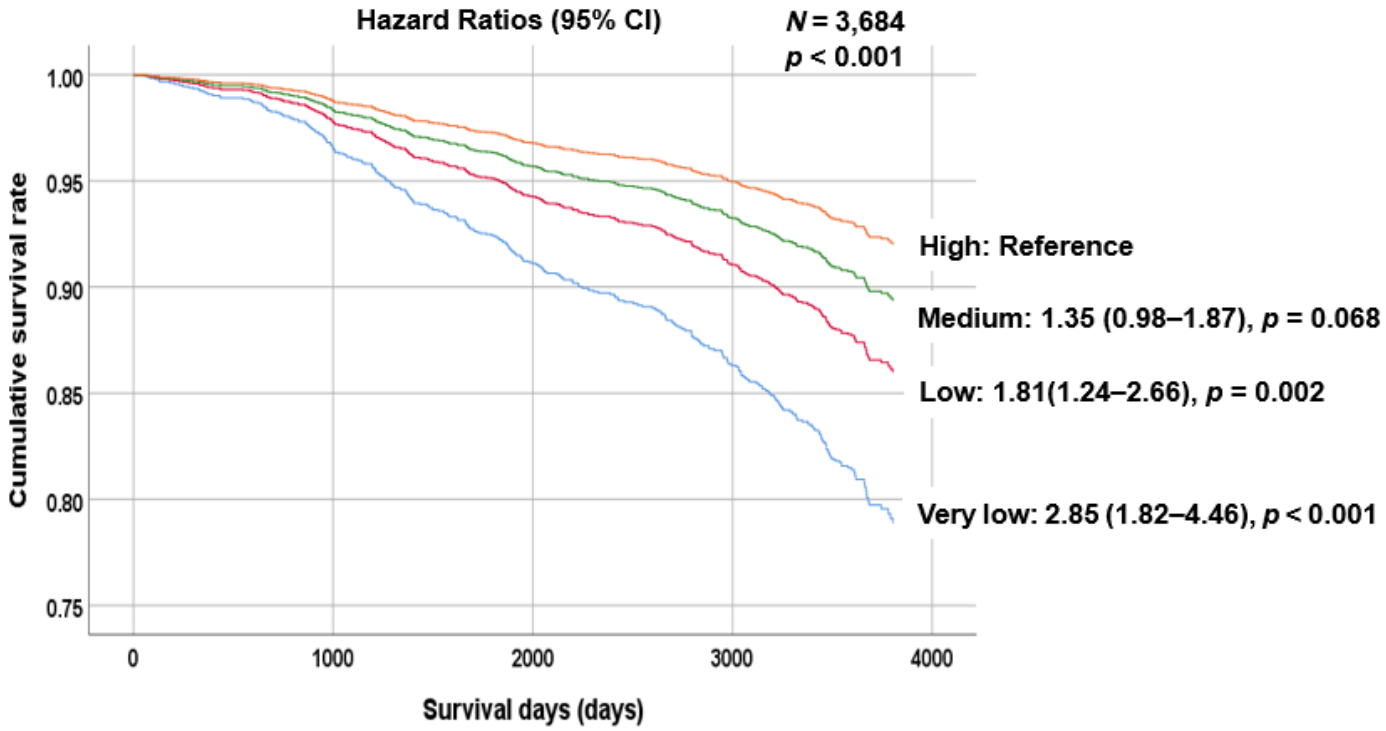

Figure 2

Analysis of the association between low-density lipoprotein cholesterol groups and all-cause mortality during the follow-up period using a survival function. P-values were obtained through a log-rank test of equality across various strata.

Supplementary Files

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- iThenticate.pdf