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LDL-C/HDL-C ratio as a predictor of atherosclerosis in the Japanese population: insights from a cross-sectional study

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Abstract

Background Atherosclerosis is a major contributor to cardiovascular disease, and dyslipidemia, particularly low-density lipoprotein cholesterol (LDL-C)/ high-density lipoprotein cholesterol (HDL-C) ratio, plays a critical role in its pathogenesis. Although extensive research has been conducted in Western populations, the relationship between LDL-C/HDL-C ratio and atherosclerosis in the Japanese population remains underexplored. The aim of this study was to investigate the association between LDL-C/HDL-C ratio and atherosclerosis, as measured by brachial-ankle pulse wave velocity (baPWV), in a Japanese cohort.

Methods This secondary analysis used data from a cross-sectional study involving 912 participants. LDL-C/HDL-C ratio was calculated from fasting blood samples and baPWV was used to assess atherosclerosis. Univariate and multivariate analyses were performed to evaluate the association between LDL-C/HDL-C ratio and baPWV, adjusting for age, sex, body mass index (BMI), and other potential confounders. Subgroup analyses were performed to explore variations by demographic and clinical factors.

Results The mean age of the study population was 51.1 years, and 64.9% were male. Significant differences were observed across LDL-C/HDL-C ratio tertiles for age, sex, BMI, blood pressure, liver enzymes, lipid profiles and lifestyle factors ($p < 0.001$ for most). Univariate analyses showed strong associations between atherosclerosis and age, sex, BMI, blood pressure, liver function markers, metabolic factors and lifestyle behaviours ($p < 0.001$ for most). Multivariate linear regression models were used to examine the association between LDL-C/HDL-C ratio and baPWV, adjusting for factors such as age, sex, BMI, and other metabolic variables. Subgroup analyses showed significant associations between LDL-C/HDL-C ratio and baPWV in women ($p = 0.036$), participants aged < 55 years ($p = 0.009$), and those with BMI < 25 kg/m^2 ($p = 0.044$). No significant interactions were observed between subgroups (p for interaction > 0.05).

Conclusions LDL-C/HDL-C ratio is significantly associated with atherosclerosis in the Japanese population, with varying strength in different demographic and clinical subgroups. These findings highlight the importance of LDL-C/HDL-C ratio as a predictor of atherosclerosis and underscore the need for targeted interventions to manage cardiovascular risk in this population.

Clinical trial number Not applicable.

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Keywords LDL-C/HDL-C ratio, Atherosclerosis, Brachial-ankle pulse wave velocity (baPWV), Japanese population, Arterial stiffness, Cardiovascular risk

Introduction

Atherosclerosis (AS), a chronic inflammatory arterial disease, is the leading cause of cardiovascular disease (CVD) and ischemic stroke, accounting for a significant global burden of morbidity and mortality [1, 2]. Arterial stiffness, frequently evaluated through pulse wave velocity (PWV), serves as a pivotal indicator of AS and CVD risk [3]. Carotid-femoral PWV (cfPWV) is a measure of central arterial stiffness, whereas brachial-ankle PWV (baPWV) provides a more comprehensive assessment of peripheral artery health. This makes it a valuable tool for CVD risk stratification [4]. Despite extensive research into AS pathogenesis, emerging risk factors continue to be identified.

Clinically, some individuals exhibit elevated CVD risk even with normal low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) levels. Research findings indicate a robust correlation between lipid ratios, particularly LDL-C/HDL-C, and arterial stiffness [5]. For instance, a TC/HDL-C ratio of 4 or more has been associated with increased arterial stiffness, independent of age, sex, and lifestyle factors [6]. In a large cross-sectional analysis of prehypertensive subjects, an abnormal LDL-C/HDL-C ratio was found to be associated with a significant increase in baPWV ($P < 0.001$) [7]. The investigation revealed that the LDL-C/HDL-C ratio has been identified in previous research as a significant risk factor for CVD [7–9]. LDL-C/HDL-C ratio has been identified as a reliable predictor of cardiovascular risk. This is due to the fact that it reflects the balance between atherogenic and atheroprotective lipid particles [10]. The relationship between LDL-C/HDL-C ratio and the severity of coronary atherosclerosis remains to be fully elucidated. Moreover, research examining the association between LDL-C/HDL-C ratio and baPWV remains limited.

To bridge this gap, a cross-sectional study investigated the association between LDL-C/HDL-C ratio and baPWV in a Japanese cohort undergoing routine health screenings. The results could inform personalized preventive strategies to mitigate AS and CVD in this population.

Methods

Data source

The dataset used in this study was obtained from the 'DATADRYAD' repository (www.datadryad.org), an open access platform that allows users to freely download raw data. The authors of the original study have waived all copyright and ownership claims associated with the data, allowing us to conduct secondary analyses without violating any intellectual property rights, and we have ensured proper citation of the Dryad data package when using the data: Fukuda T, Hamaguchi M, Kojima T, Ohshima Y, Ohbora A, Kato T, Nakamura N, Fukui M (2014) Data from: Association between serum γ-glutamyltranspeptidase and atherosclerosis: a population-based cross-sectional study. Dryad Digital Repository. https://doi.org/10.5061/dryad.m484p.

The database provided a comprehensive set of variables, including sex, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), uric acid (UA), estimated glomerular filtration rate (eGFR), fasting plasma glucose (FPG), total cholesterol (TC), triglycerides (TG), LDL-C, high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), fasting plasma glucose (FPG), HDL-C, and triglycerides (TG). (FPG), total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), brachial-ankle pulse wave velocity (baPWV), ankle-brachial index (ABI), menopausal status, smoking status, alcohol consumption, exercise habits and fatty liver disease.

Study population

The research process is summarised here for clarity, with detailed descriptions available in the original report by Takuya Fukuda et al. This cross-sectional study was conducted at the Medical Health Checkup Centre of Murakami Memorial Hospital in Gifu City, Japan, and the study period spanned from March 2004 to December 2012. Participants underwent a comprehensive health check-up programme that included pulse wave velocity measurement and abdominal ultrasound.A total of 1,445 participants were recruited, with selection based on exclusion criteria: (1) those taking hormone replacement therapy, (2) those with a positive hepatitis B or C virus antigen test result, (3) users of oral contraceptives, (4) pregnant individuals, and (5) those with an ankle brachial index (ABI) below 0.95.The Murakami Memorial Hospital Ethics Committee approved the study in accordance with the tenets of the Declaration of Helsinki, and all participants provided informed consent before enrolment. The study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines [11].

Measurement of BaPWV, LDL-C/HDL-C ratio and additional covariants

An automated waveform analyser (Colin Medical Technology, Komaki, Japan) was used to measure baPWV and ABI. Participants were asked to rest in the supine position for five minutes in a quiet, temperature-controlled room before ECG electrodes were placed on both wrists and a heart sound microphone positioned at the left sternal border. Cuffs connected to a plethysmographic sensor and an oscillometric pressure sensor were then placed around the branchiae and ankles. Takuya Fukuda et al. then calculated the path lengths from the suprasternal notch to the brachium (Lb) and to the ankle (La), and automatically determined the delay time from the peak of the brachial waveform to each ankle waveform (DTba). Finally, baPWV was determined using the formula (La-Lb)/DTba. The coefficients of variation were 10% for intraobserver ($r = 0.87$, $p < 0.01$) and 8.4% for interobserver ($r = 0.98$, $p < 0.01$).The original study provides a comprehensive description of the measurement and assessment of LDL-C/HDL and other covariates.

Statistical analysis

A descriptive analysis was performed on all participants. The distribution of continuous variables was described with the use of the mean and the standard deviation (SD) or the median and the interquartile range [IQR]. Categorical variables were presented as proportions and percentages of the total. Chi-squared tests were used for categorical variables, one-way ANOVA for normally distributed data, and the Kruskal-Wallis test for skewed data. Three regression models were developed: Model 1 was adjusted for age, sex, and BMI; Model 2 included these variables plus AST, GGT, and ABI; Model 3 incorporated the variables from Model 1 along with smoking status, alcohol consumption, and exercise habits. Penalized splines were employed for smooth curve fitting to evaluate the association between LDL-C/HDL-C ratio and baPWV. Sensitivity analyses were conducted to verify the robustness of the findings, and the trend significance was assessed by categorizing LDL-C/HDL-C ratio. Subgroup analyses were performed by stratifying relevant covariates to explore potential effect modification. Statistical analyses were conducted using R software (The R Foundation) and Free Statistics software version 1.9.2.A bilateral P value below 0.05 was deemed statistically significant.

Results

Baseline characteristics

The study population consisted of 912 participants divided into tertiles based on LDL/HDL ratio (Q1, Q2, Q3). Significant differences between groups were observed for most variables ($p < 0.001$). Males were more common in the groups with higher LDL/HDL ratios (Q3: 81.6% vs. Q1: 48.7%, $p < 0.001$). Age did not differ significantly between groups ($p = 0.199$), but BMI, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were higher in Q3 compared to Q1 ($p < 0.001$ for all). Liver enzymes (AST, ALT, GGT) and fasting plasma glucose (FPG) also increased with higher LDL/HDL ratios ($p < 0.001$), as did uric acid (UA) and lipid profiles (TC, TG, LDL-c), while HDL-c decreased significantly ($p < 0.001$). Estimated glomerular filtration rate (eGFR) was lower in Q3 ($p < 0.001$) and brachial-ankle pulse wave velocity (baPWV) was higher ($p < 0.001$), indicating greater arterial stiffness.

Lifestyle factors also differed significantly. Current smoking was more common in Q3 (28% vs. 13.5% in Q1, $p < 0.001$), and alcohol consumption patterns showed a trend towards higher consumption in the lower LDL/HDL ratio groups ($p = 0.032$). Physical inactivity was more common in Q3 (86% vs. 74.5% in Q1, $p = 0.002$) and fatty liver was significantly more common in Q3 (51% vs. 11.5% in Q1, $p < 0.001$). (Table 1)

Association between LDL/HDL ratio and BaPWV

Univariate analyses, as shown in Table 2, revealed several significant associations between risk factors and atherosclerosis. Age, sex and body mass index (BMI) were strongly correlated with atherosclerosis, with older age ($p < 0.001$), male sex ($p < 0.001$) and higher BMI ($p < 0.001$) showing positive associations. Both systolic and diastolic blood pressure (SBP and DBP) were significantly associated with atherosclerosis ($p < 0.001$ for both), emphasising the role of hypertension in atherosclerosis. Liver function markers, including AST, ALT and GGT, also showed significant positive associations ($p < 0.001$ for all), suggesting a potential link between liver health and cardiovascular risk.

Metabolic factors such as fasting plasma glucose (FPG), uric acid (UA) and lipid profiles (TC, TG, LDL-c and HDL-c) were significantly associated with atherosclerosis ($p < 0.001$ for all). In particular, higher LDL-c and lower HDL-c levels were strongly associated with atherosclerosis. Lifestyle factors, including smoking status ($p < 0.001$) and alcohol consumption ($p = 0.032$) were also significant, with current smokers and heavy drinkers at higher risk. Physical inactivity ($p = 0.002$) and the presence of fatty liver ($p < 0.001$) also contributed to the risk of atherosclerosis.

As demonstrated in Table 3, the multivariable-adjusted analysis indicated a significant association between the LDL/HDL ratio and brachial-ankle pulse wave velocity (baPWV) across various models. In the unadjusted model, the LDL/HDL ratio exhibited a robust positive correlation with baPWV (β = 31.67, 95% CI: 15.16-48.17, $P < 0.001$). Following adjustment for age, sex and BMI

Table 1 Baseline characteristic of the study population according to LDL/HDL ratio

Variables	Total (*n* = 912)	Q1 (*n* = 304)	Q2 (*n* = 304)	Q3 (*n* = 304)	*P* valve
Sex, n (%)					< 0.001
Male	592 (64.9)	148 (48.7)	196 (64.5)	248 (81.6)	
Female	320 (35.1)	156 (51.3)	108 (35.5)	56 (18.4)	
Age, (years)	51.1 ± 9.6	50.5 ± 10.1	51.9 ± 9.4	51.0 ± 9.2	0.199
BMI, (kg/m2)	23.1 ± 3.1	21.8 ± 2.7	23.2 ± 2.8	24.3 ± 3.3	< 0.001
SBP, (mmHg)	120.2 ± 15.0	116.8 ± 14.3	121.2 ± 14.7	122.7 ± 15.3	< 0.001
DBP, (mmHg)	76.1 ± 10.0	73.6 ± 9.8	76.5 ± 10.0	78.3 ± 9.7	< 0.001
AST, (IU/L)	20.9 ± 8.1	20.0 ± 7.0	20.5 ± 8.4	22.1 ± 8.6	< 0.001
ALT, (IU/L)	19.0 (14.0, 26.0)	16.0 (13.0, 20.0)	19.0 (14.0, 25.0)	22.5 (16.0, 34.0)	0.004
GGT, (IU/L)	4.4 ± 0.8	4.1 ± 0.8	4.4 ± 0.9	4.6 ± 0.8	< 0.001
FPG, (mg/dl)	98.1 ± 14.1	95.0 ± 9.2	97.6 ± 17.7	101.6 ± 13.3	< 0.001
UA, (mg/dl)	5.3 ± 1.4	4.8 ± 1.3	5.2 ± 1.4	5.8 ± 1.3	< 0.001
TC, (mg/dl)	209.8 ± 36.0	193.5 ± 32.0	209.3 ± 33.9	226.8 ± 34.1	< 0.001
TG, (mg/dl)	81.0 (53.0, 124.0)	53.0 (39.8, 76.2)	77.5 (58.0, 108.5)	121.5 (88.0, 175.2)	< 0.001
HDL-c, (mg/dl)	53.5 ± 14.6	66.2 ± 13.5	52.8 ± 9.9	41.6 ± 7.4	< 0.001
LDL-c, (mg/dl)	128.1 ± 31.7	102.9 ± 23.0	130.4 ± 24.1	150.9 ± 27.2	< 0.001
eGFR, (mL/min/1.73 m2)	70.4 ± 12.0	73.2 ± 12.6	69.5 ± 12.0	68.5 ± 11.0	< 0.001
ABI	56.0 ± 277.6	37.6 ± 222.5	64.3 ± 290.6	66.2 ± 312.0	0.365
baPWV (cm/s)	1415.8 ± 246.3	1370.1 ± 214.4	1427.3 ± 252.5	1449.8 ± 263.1	< 0.001
Smoking status, n (%)					< 0.001
None or Past	715 (78.4)	263 (86.5)	233 (76.6)	219 (72)	
Current	197 (21.6)	41 (13.5)	71 (23.4)	85 (28)	
Alcohol consumption, n (%)					0.032
None or minimal	595 (65.2)	185 (60.9)	193 (63.5)	217 (71.4)	
Light	149 (16.3)	49 (16.1)	50 (16.4)	50 (16.4)	
Moderate	90 (9.9)	36 (11.8)	35 (11.5)	19 (6.2)	
Heavy	78 (8.6)	34 (11.2)	26 (8.6)	18 (5.9)	
Habit of exercise, n (%)					0.002
No	719 (80.2)	222 (74.5)	238 (80.1)	259 (86)	
Yes	177 (19.8)	76 (25.5)	59 (19.9)	42 (14)	
Fatty liver, n (%)					< 0.001
No	646 (70.9)	269 (88.5)	228 (75.2)	149 (49)	
Yes	265 (29.1)	35 (11.5)	75 (24.8)	155 (51)	

Data were mean ± SD or median (IQR) for skewed variables or numbers (proportions) for categorical variables

LDL/HDL ratio, low-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio; Q1, Q2, and Q3 are quartiles of the LDL/HDL ratio. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, g-glutamyltranspeptidase; FPG, fasting plasma glucose; UA, uric acid; TC, total cholesterol; TG, triglyceride; eGFR, estimated glomerular filtration rate; ABI, ankle-brachial index; baPWV, brachial-ankle pulse wave velocity

(model 1), this association remained significant, although the β decreased to 18.47 (95% CI: 3.18-33.76, P = 0.018). Subsequent modification of the model to incorporate additional factors (AST, GGT, ABI in model 2 and smoking, alcohol consumption and exercise habits in model 3) resulted in a modest decline in effect size, yet the association remained statistically significant, with the final β in model 3 measuring 16.77 (95% CI: 0.65-32.89, P = 0.042).

When the data were analysed by quartiles, it was demonstrated that higher quartiles of the LDL/HDL ratio were associated with increased baPWV. In the second and third quartiles, the associations were found to be significant, with β values of 23.13 (P = 0.185) and 42.67 (P = 0.021) in model 1, and the trend test remained significant across models (P < 0.05 for all). The findings indicate that an elevated LDL/HDL ratio is consistently associated with increased atherosclerosis, even after adjustment for multiple confounders.

Figure 1 shows the relationship between the LDL/HDL ratio and brachial-ankle pulse wave velocity (baPWV), a marker of atherosclerosis. The analysis revealed a non-linear relationship between the LDL/HDL ratio and baPWV, with the curve showing a gradual increase in baPWV as the LDL/HDL ratio increases. The solid line represents the predicted values, while the dashed lines indicate the 95% confidence intervals. Of note, the p-value for non-linearity was 0.639, indicating that the relationship was not significantly out of line. However, the visual trend indicates that higher LDL/HDL ratios are associated with increased arterial stiffness, as reflected

Table 2 Results of univariate analysis of BaPWV

Variable	β (95%CI)	*p* value
LDL/HDL ratio	31.67 (15.14,48.19)	< 0.001
Sex, n (%)	-49.44 (-82.84,-16.05)	0.004
Age, (years)	12.95 (11.5,14.39)	< 0.001
BMI, (kg/m2)	4.95 (-0.17,10.07)	0.058
SBP, (mmHg)	8.43 (7.51,9.35)	< 0.001
DBP, (mmHg)	11.29 (9.87,12.71)	< 0.001
AST, (IU/L)	3.4 (1.43,5.37)	< 0.001
ALT, (IU/L)	1.5 (0.38,2.61)	0.009
GGT, (IU/L)	55.95 (37.36,74.54)	< 0.001
FPG, (mg/dl)	4.21 (3.1,5.31)	< 0.001
UA, (mg/dl)	22.77 (11.23,34.31)	< 0.001
TC, (mg/dl)	0.71 (0.27,1.16)	0.002
TG, (mg/dl)	0.44 (0.23,0.65)	< 0.001
HDL-c, (mg/dl)	-1.33 (-2.42,-0.23)	0.018
LDL-c, (mg/dl)	0.66 (0.16,1.17)	0.01
eGFR, (mL/min/1.73 m2)	-6.39 (-7.65,-5.12)	< 0.001
ABI	0.04 (-0.02,0.1)	0.19
Smoking status	-0.16 (-39.07,38.75)	0.994
Alcohol consumption	0.07 (-0.06,0.19)	0.284
Habit of exercise, n (%)	16.65 (-23.27,56.57)	0.413
Fatty liver, n (%)	93.74 (58.98,128.51)	< 0.001

BaPWV, brachial-ankle pulse wave velocity; 95% CI, 95% confidence interval; LDL/HDL ratio, low-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, g-glutamyltranspeptidase; FPG, fasting plasma glucose; UA, uric.acid; TC, total cholesterol; TG, triglyceride; eGFR, estimated glomerular filtration rate; ABI, ankle-brachial index

by higher baPWV values. This finding highlights the potential role of the LDL/HDL ratio in the assessment of cardiovascular risk, particularly in the context of atherosclerosis and arterial health. Only 98% of the data are shown in the graph to ensure clarity and focus on the central trend.

Subgroup analysis of LDL/HDL ratio and BaPWV

The subgroup analysis of the association between LDL/HDL ratio and brachial-ankle pulse wave velocity (baPWV) is shown in Fig. 2. After adjustment for age, sex, and body mass index, significant positive associations were observed in women (adjusted coefficient: 29.67, 95% CI: 2.11–57.23, $P = 0.036$), participants aged < 55 years (adjusted coefficient: 19.15, 95% CI: 4.74–33.56, $P = 0.009$), and those with a BMI < 25 kg/m² (adjusted coefficient: 18.93, 95% CI: 0.58–37.29, $P = 0.044$). In addition, non-smokers and those with minimal or no alcohol consumption showed significant associations ($P = 0.003$ for both). No significant interactions were found between subgroups (P for interaction > 0.05), indicating consistent relationships between LDL/HDL ratio and baPWV across different demographic and clinical characteristics. These findings suggest that the LDL/HDL ratio is a robust predictor of atherosclerosis, with varying strength in specific subgroups. (Fig. 2)

Disscusion

This study investigated the association between LDL-C/HDL-C ratio and atherosclerosis, as measured by brachial-ankle pulse wave velocity (baPWV), in a Japanese population. The results showed a significant positive association between LDL-C/HDL-C ratio and baPWV, suggesting that higher ratios are associated with increased atherosclerosis. Subgroup analyses showed that this association was particularly pronounced in women, those aged < 55 years and those with a BMI < 25 kg/m². In addition, univariate analyses identified several significant risk factors for atherosclerosis, including age, sex, BMI, blood pressure, lipid profiles and lifestyle behaviours. Multivariate linear regression models were utilised to investigate the correlation between the LDL-C/HDL-C ratio and baPWV, with adjustments made for confounding factors such as age, sex, BMI, and additional metabolic variables. These findings underscore the importance of LDL-C/HDL-C ratio as a predictor of atherosclerosis and highlight the multifactorial nature of cardiovascular risk in the Japanese population.

CVD has become the foremost cause of mortality in China. The country's ageing population has resulted in a marked increase in the associated health and economic

Table 3 Multivariable-adjust β and 95%CI of LDL/HDL ratio associated with BaPWV

Variable	unadjusted		model 1		model 2		model 3	
	β(95%CI)	*P* value	β(95%CI)	*P* value	β(95%CI)	*P* value	β(95%CI)	*P* value
LDL/HDL ratio	31.67 (15.16 ~ 48.17)	< 0.001	18.47 (3.18 ~ 33.76)	0.018	17.32 (2.09 ~ 32.54)	0.026	16.77 (0.65 ~ 32.89)	0.042
Q1	0(Ref)		0(Ref)		0(Ref)		0(Ref)	
Q2	57.13 (18.3 ~ 95.95)	0.004	23.13 (-11.01 ~ 57.26)	0.185	21.46 (-12.56 ~ 55.47)	0.217	20.92 (-13.5 ~ 55.34)	0.234
Q3	79.71 (40.88 ~ 118.53)	< 0.001	42.67 (6.56 ~ 78.78)	0.021	38.56 (2.55 ~ 74.56)	0.036	37.91 (0.41 ~ 75.41)	0.048
Trend.test		< 0.001		0.021		0.036		0.048

Model 1 adjust for age, sex, and BMI

Model 2 adjust for Model 1 + AST + GGT + ABI

Model 3 adjust for Model 1 + smoking status, alcohol consumption, habit of exercise

LDL/HDL ratio, low-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio; baPWV, brachial-ankle pulse wave velocity; 95% CI,95% confidence interval; Ref, reference; BMI, body mass index; AST, aspartate aminotransferase; GGT, g-glutamyltranspeptidase; ABI, ankle-brachial index

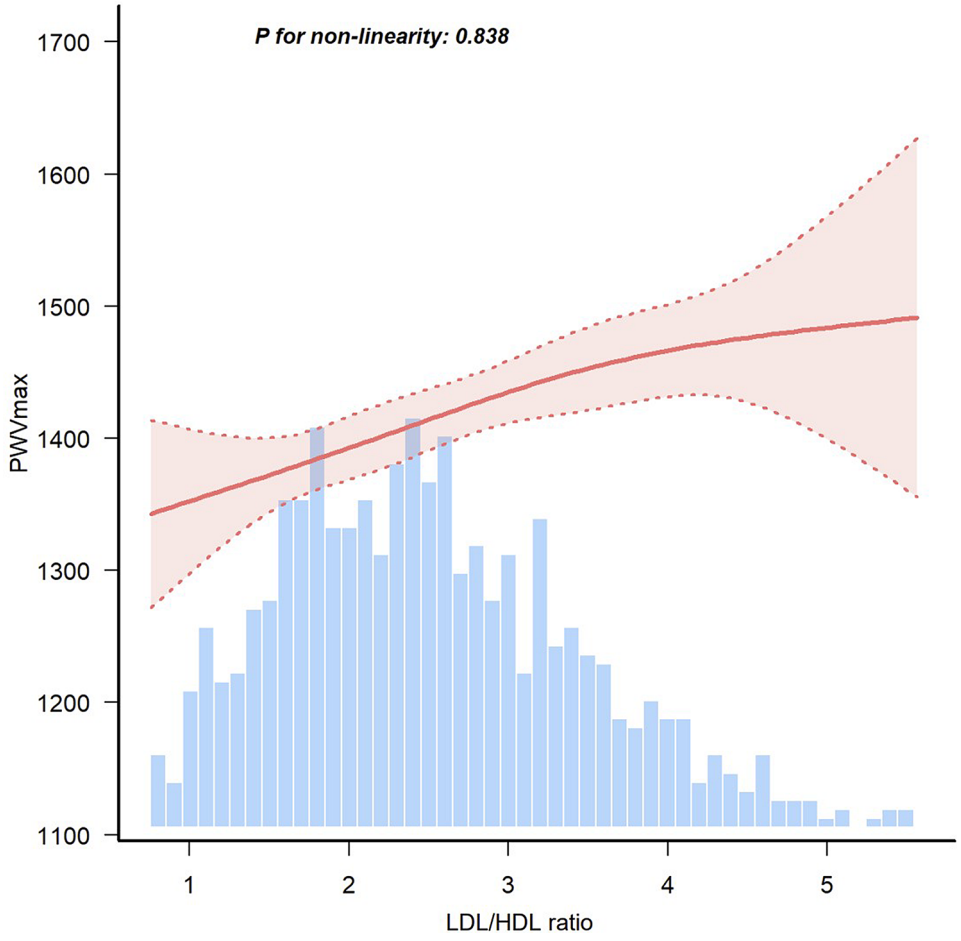

Fig. 1 Association between LDL/HDL ratio and baPWV. LDL/HDL ratio, low-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio; baPWV, brachial-ankle pulse wave velocity. Solid and dashed lines represent the predicted value and 95% confidence intervals. Only 98% of the data is shown

burden [12]. Aging of the blood vessels, characterised by increased stiffness in elastic arteries and impaired endothelial function, is a pivotal factor contributing to cardiovascular disease in the elderly population [13]. Recent studies have indicated that alternative lipid markers, including ratios such as TC/HDL-C, LDL-C/HDL-C, TG/HDL-C, and non-HDL-C/HDL-C, can serve as effective diagnostic tools for assessing atherosclerosis risk, even in cases where traditional lipid parameters such as triglycerides, HDL-C, LDL-C, and total cholesterol are found to be within normal limits [14]. The observed association between the LDL-C/HDL-C ratio and baPWV in our study aligns with previous research that has identified the LDL-C/HDL-C ratio as a robust predictor of cardiovascular risk [15]. Similar to findings in Western populations, our results suggest that a higher LDL-C/HDL-C ratio is associated with increased arterial stiffness, a key marker of atherosclerosis. However, the strength of this association in our Japanese cohort appears to differ from studies conducted in Western populations, where the relationship is often more pronounced in males [16]. In contrast, our study found a stronger association in females, which may reflect differences in hormonal influences, lipid metabolism, or lifestyle factors unique to the Japanese population [17]. One study observed that, in subjects with optimal blood pressure, higher LDL-C/HDL-C ratios corresponded with increased baPWV ($p < 0.001$) [18]. By contrast, other lipid ratios—notably the total cholesterol/HDL-C ratio—showed more consistent positive associations with arterial stiffness [19]. Additionally, the stronger association observed in individuals aged < 55 years suggests that the LDL-C/HDL-C ratio may be a more sensitive marker of early atherosclerosis in younger individuals, consistent with findings from recent studies in Asian populations [20]. Although consistent with broader literature, our study provides population-specific data and granular stratification, refining risk assessment in understudied demographics. These differences highlight the importance of considering population-specific factors when interpreting lipid-related cardiovascular risk.

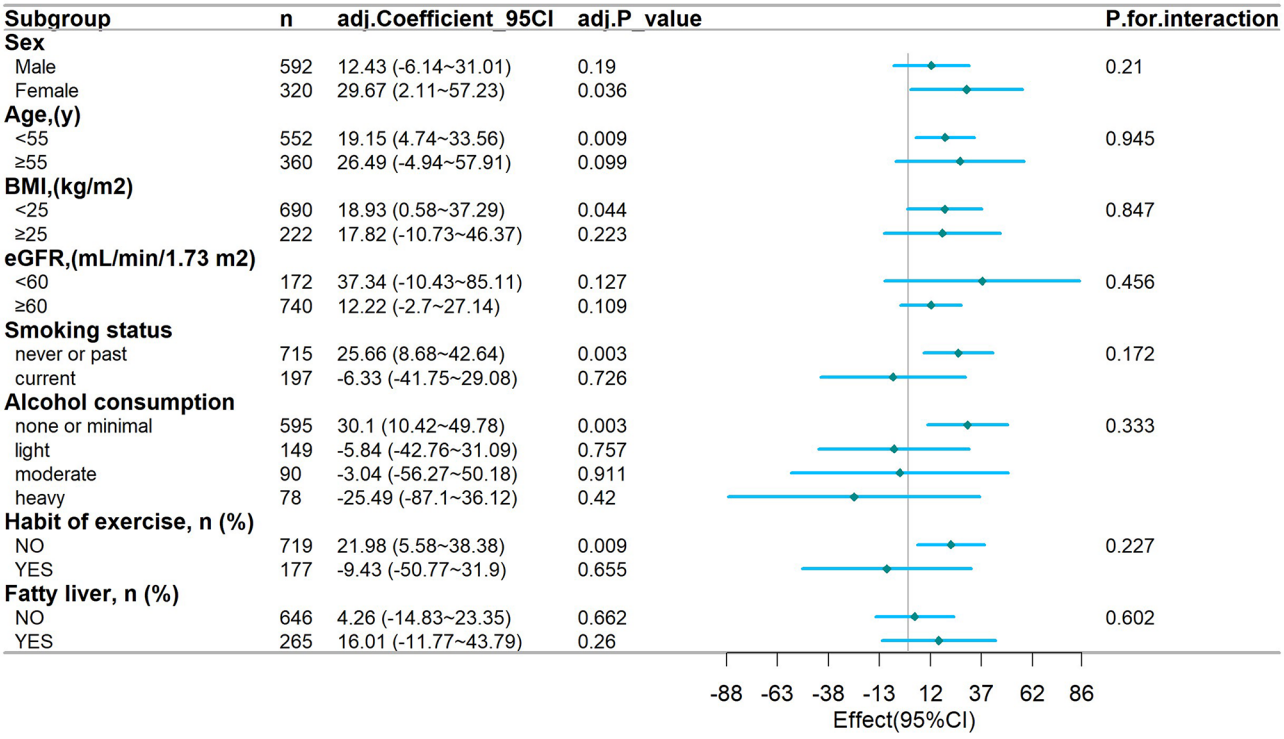

Fig. 2 Subgroup analysis of LDL/HDL ratio and baPWV. LDL/HDL ratio, low-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio; baPWV, brachial-ankle pulse wave velocity; They were adjusted for age, sex, body mass index. Dots represent effect values, with horizontal lines indicating 95% CIs. Diamonds indicate overall effect values, with outer points of the diamonds indicating 95% CIs

Several studies explored the associations between LDL-C/HDL-C ratio and the risk of atherosclerosis. A longitudinal study was conducted that yielded a correlation between elevated LDL-C/HDL-C ratio and accelerated carotid plaque formation [21]. A study of a Chinese cohort has indicated that elevated LDL-C/HDL-C ratio levels have a significant impact on the risk of increased carotid intima-media thickness [22]. It has been hypothesized that LDL-C/HDL-C ratio may serve as a more effective predictor of the severity of coronary atherosclerotic heart disease than LDL-C or HDL-C alone [7]. A meta-analysis indicated that the LDL-C/HDL-C ratio is consistent with individual lipid index results, all of which are based on the analysis of fasting venous blood serum [23]. The LDL-C/HDL-C ratio is regarded as a more sensitive and comprehensive marker than separate blood lipid indices. Due to its unique protein and phospholipid composition, HDL-C has anti-inflammatory properties that help slow the progression of atherosclerosis [24]. Zhixiong Zhong et al. identified a strong link between elevated LDL-C/HDL-C ratios and cardiovascular events in acute coronary syndrome (ACS) patients [8]. The LDL-C/HDL-C ratio serves as a more dependable indicator of lipid levels in ACS compared to using LDL-C or HDL-C individually [25]. A study observed that LDL-C/HDL-C ratio levels were significantly elevated in the ACS experimental group compared to the control group, aligning with findings by Po Gao et al. [26]. The LDL-C/HDL-C ratio has been shown to serve as a predictive marker for identifying high-risk patients, thus allowing for timely and appropriate interventions. It has significant clinical value in the prevention of the onset and progression of atherosclerosis.

A notable strength of this study lies in its methodological approach, particularly the use of brachial-ankle pulse wave velocity (baPWV) as a non-invasive and reliable measure of arterial stiffness. Unlike traditional methods such as carotid intima-media thickness (CIMT), baPWV provides a direct assessment of arterial stiffness, which is a more dynamic marker of atherosclerosis progression [27]. Several studies have reported that baPWV may underestimate atherosclerosis in people with hypertension who have a history of cardiovascular events [28]. Then meta-analyses indicate a significant association between high baPWV levels and a heightened risk of cardiovascular disease [29]. A meta-analysis establishes brachial-ankle pulse wave velocity (baPWV) as an independent predictor of cardiovascular disease risk [30]. Our findings are consistent with recent studies that have validated baPWV as a sensitive tool for evaluating cardiovascular risk in diverse populations [31]. Furthermore, the adjustment for key confounders, including age, sex, and BMI, enhances the reliability of our findings, as these factors are known to influence both lipid profiles

and arterial stiffness [32]. The use of the LDL-C/HDL-C ratio as a composite lipid marker also adds to the study's novelty, as it provides a more comprehensive assessment of cardiovascular risk compared to isolated lipid parameters [10]. In a study of subjects with normal blood pressure, this ratio emerged as an independent risk factor for increased baPWV [33]. These methodological choices strengthen the validity of our results and contribute to the growing body of evidence on lipid-related atherosclerosis risk.

It is imperative to acknowledge the limitations inherent in this study. Frist, the study's design precludes the establishment of causality, as it cannot determine whether the LDL-C/HDL-C ratio directly influences arterial stiffness or if other confounding factors are involved. Second, the study focused exclusively on a Japanese population, which may limit the generalizability of the findings to other ethnic groups with different genetic, dietary, and lifestyle backgrounds. Third, although adjustments were made for key confounders, unmeasured factors such as dietary patterns, genetic predispositions, or environmental influences may still affect the results. Finally, the use of baPWV as a surrogate marker for atherosclerosis, while validated, may not fully capture the complexity of plaque formation and arterial remodeling. Prospective studies with extended follow-up periods would also help clarify the long-term prognostic implications of LDL-C/HDL-C ratio in atherosclerosis patients.

Conclusions

This study highlights the LDL-C/HDL-C ratio as a key predictor of atherosclerosis in the Japanese population, emphasizing its role in cardiovascular risk assessment. Future research should focus on longitudinal studies to establish causality and explore underlying mechanisms. Expanding to multi-ethnic cohorts and incorporating advanced biomarkers and genetic data could enhance risk stratification and inform personalized prevention strategies. These efforts may improve cardiovascular outcomes, particularly in populations with unique lipid profiles and lifestyle patterns.

Abbreviations

ABI	Ankle-brachial index
ACS	Acute coronary syndrome
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
baPWV	Brachial-ankle pulse wave velocity
BMI	Body mass index
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
eGFR	Estimated glomerular filtration rate
FPG	Fasting plasma glucose
GGT	Gamma-glutamyl transferase
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
SBP	Systolic blood pressure
TC	Total cholesterol
TG	Triglycerides
UA	Uric acid

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Author contributions

YJ and LZ contributed to the drafting of the manuscript, analysis and interpretation of the data. ZG contributed to the conception and critical revision of the manuscript, analysis and interpretation of the data and approved the final version of the submitted manuscript. Both authors read and approved the final manuscript.

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Data availability

Extra data can be accessed via the Dryad data repository at http://datadryad.org/ with the https://doi.org/10.5061/dryad.m484p. The datasets used and analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The studies involving humans were approved by The Murakami Memorial Hospital's ethics committee. The studies were conducted in accordance with the local legislation and institutional requirements. All participants were provided informed consent during the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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