Association between LDL-C/HDL-C Ratio and Carotid Atherosclerosis in an Asymptomatic Japanese Population: A Cross-Sectional Study

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Research

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Abstract

Background and aims LDL-C/HDL-C ratio predicted atherosclerosis progression better than LDL-C or HDL-C alone. However, the association between LDL-C/HDL-C ratio and Carotid Atherosclerosis (CA) is still controversial. There is a lack of research on this topic in the Asymptomatic Japanese Population. This study aims to provide further results.

Methods The study population was a cross-sectional study of 1904 subjects free of cardio-cerebrovascular disease at baseline (mean age 57±11.9 years, 51.9% male). All participants underwent ultrasonography of the carotid artery. The presence of carotid plaque score (PS) and plaque number (PN) were evaluated by ultrasonography. Multivariate logistic regression models to estimate the LDL-C/HDL-C ratio and PS relationship. Participants were stratified into three groups based on LDL-C/HDL-C ratio tertiles. Interaction and stratified analyses were conducted according to age, sex, smoking status, drinking status, fatty, and histories of diabetes. Results In regression models and after multiple adjustments, the risk of PS was significantly associated with serum LDL-C/HDL-C ratio levels in which LDL-C/HDL-C ratio was included as a categorical variable. It remained significant for the highest vs the first tertile of the LDL-C/HDL-C ratio (OR=1.50, 95% CI 1.04–2.17). Stratified analysis, we found that the association was more significant aged <65 years old, female and non-diabetes subgroups. Interaction analysis showed no interaction between LDL-C/HDL-C ratio and PS in the fatty, smoking, and drinking subgroups. Conclusions In conclusion, LDL-C/HDL-C ratio is an independent risk factor for CA in the Japanese population. A prospective and randomized clinical trial of LDL-C/HDL-C ratio lowering therapy in the Japanese population is needed to assess the causal nature of the relationship.

Introduction

Atherosclerosis is well known to contribute to the occurrence and development of ischaemic cardiovascular disease (CVD) and acute ischemic stroke (AIS) [1–3]. In 2020, the prevalence, prevalence and risk factors of carotid atherosclerosis in populations in 21 countries and regions were assessed, atherosclerosis is a global public health problem affecting nearly two billion people [4]. The early detection of atherosclerosis in asymptomatic population mainly focuses on peripheral arteries and carotid arteries; the carotid artery is shallow because of its position and a 'window' for systemic arterial disease [5]. Studies suggest that Carotid Plaques are reliable markers of carotid atherosclerosis [6]. Zhao et al. [7] found that approximately 30% of first acute cardiovascular events without any clinical symptoms are fatal. Therefore, it is necessary to identify the risk factors for the silent preclinical stage of atherosclerosis to prevent CVD and AIS.

Previous studies have shown that LDL-C and HDL-C have been widely used to monitor lipid-lowering indexes in almost all CVD patients [8]. However, some clinical trials have shown that despite this, 60-70% of CVD events continue to occur [9–11]. Increasing evidence points to the LDL-C/HDL-C ratio as a novel indicator of the risks of both atherosclerotic cardiovascular and cerebrovascular diseases, as it simultaneously takes into account both LDL-C and HDL-C ratio levels [12–14]. Some studies have suggested that the LDL-C/HDL-C ratio is positively associated with CVD [14–16], while others have found a negative correlation between the LDL-C/HDL-C ratio and all-cause mortality [17–19]. However, previous studies on the LDL-C/HDL-C ratio have drawn inconsistent conclusions.

In the present study, PS is assessed as indicators of CA to investigate the association between LDL-C/HDL-C ratio and CA in an Asymptomatic Japanese Population. It also was attempted to indicate how vascular risk factors may influence the mentioned association with the assistance of stratified analysis.

Materials And Methods

2.1 Design and participants

The original clinical data were derived from a public dataset (https://datadryad.org) offered by Drs, which was described in detail previously [20]. It conformed to the guidelines of the Declaration of Helsinki and was approved by the approval of the ethical review committee of Shin Takeo Hospital. We also made an effort to cite the Dryad data package following protocols released in the Dryad Digital Repository (Tokyo, Japan). Briefly, the study was a Cross-Sectional study of the individual who
participated in the medical examination program at Shin Takeo Hospital from April 1st, 2016 to Oct 31st, 2017[20]. Some patients underwent blood tests and carotid ultrasonography, and completed standard questionnaires all within this period. Eventually, 1904 asymptomatic participants, including 988 males and 916 females were included in this study[20].

2.2 Data Collection And Measurements

Data collection and measurement has been described previously[20]. The general inspection (age, sex, body mass index, diastolic blood pressure [DBP], systolic blood pressure [SBP]), medical history, longterm medication use (antihypertensive medicine, antidiabetic medicine, and cholesterol-lowering medications), and lifestyle (including smoking and drinking habits), of participants were obtained by using a standardized self-administered questionnaire. Blood samples were drawn from the antecubital vein of seated participants after 8h of fasting. Fasting blood samples were analyzed for LDL-C, HDL-C, LDL-C/HDL-C ratio, triglyceride, fasting plasma glucose, and HBA1c. The smoking status was categorized into two groups: Non-smokers and smokers. Non-smokers were referred to the participants who never smoked cigarettes. Smokers were defined as individuals who had smoked in the past but quit smoking until baseline or as participants who smoked at baseline. Drinking status (rarely, sometimes, and daily), and drinking volume (with respect to quantify the consumption of alcoholic beverage/day) in form of <180, 180-360, 360-540 or >540mL. Hypertension was defined as a history of hypertension or SBP ≥ 140 or DBP ≥ 90 mmHg (or both) or oral hypotensive agents. Diabetes was defined either by fasting plasma glucose (FPG) ≥ 7.00 mmol/L, and/or self-reported history of diabetes, and/or treatment with insulin or oral hypoglycemic agents during the follow-up period.

2.3 Carotid Artery Color Doppler Ultrasound

The ultrasonic testing was conducted with ultrasonic diagnostic equipments, LOGIQ S7 Expert (GE Healthcare Japan, Tokyo) and Aplio 400 (Canon Medical systems, Tochigi, Japan). Two characteristics were recorded: carotid plaque score (PS)[21] and plaque number (n-plaque). The PS was calculated as follows. The carotid artery was divided into four 15 mm long sections: the central side of the common CA, the peripheral side of the CA, the bifurcation of the CA and the central side of the internal carotid artery. Then, the sum of the maximum values of intima-media thickness exceeding 1.0 mm was calculated[22]. To measure both the left and right carotid arteries by experienced radiologists blinded to the clinical data.

Statistical analysis

Baseline characteristics of the study population were divided into three groups based on LDL-C/HDL-C ratio tertiles (T1-3): 0.3≤T1<1.6, 1.7≤T2<2.3, 2.4≤T3<5.5. Continuous variables are presented as the mean (standard deviation (SD)) or median (range) if non-normally distributed, categorical variables were presented as frequency (percentage). The association of LDL-C/HDL-C ratio and PS was assessed with the use of multivariable logistic regression models. In another separate analysis, LDL-C/HDL-C ratio was included as a continuous variable in the model. Four different models were constructed in this study and results were presented as both crude and adjusted hazard ratios (OR) estimates with 95% CI. The potential confounders included in this study was selected based on their associations with the outcome or a change in effect estimate of more than 10%. Model 1 was adjusted for age, sex, history of diabetes, and history of hypertension at baseline. Model 2 was adjusted for covariates included in Model 1, plus BMI, smoking habits, medication to reduce a level of cholesterol at baseline. Model 3 was adjusted for covariates included in Model 2 and HBA1C, TG, BS. Interaction and stratified analyses were conducted according to age (≥45, ≥45and< 65, ≥65), sex, fatty, diabetes mellitus, smoking habits, drinking habits. All subgroup analyses adjusted TG, blood glucose level, systolic blood pressure, diastole blood pressure, medication to reduce a level of cholesterol except the stratification factor itself. All the analyses were performed with the statistical software packages R (http://www.R-project.org, The R Foundation) and Free Statistics software versions 1.3. A two-tailed test was performed and p <0.05 was considered statistically significant.
Results

3.1. Participants’ characteristics

The current study enrolled 988 men and 916 women. Baseline characteristics of participants by the tertile of the LDL-C/HDL-C ratio are shown in Table 1. In the general inspection, significant differences in sex, BMI, as well as drinking habits, and smoking habits, and the presence of metabolic syndrome, medications to reduce a level of cholesterol were found between groups. In the blood tests, significant differences were seen in HDL, LDL, HbA1c, BS, SBP and DBP. In the ultrasonic tests, significant differences were found in PS.
Table 1 Baseline characteristics of the study populations by the baseline LDL-C/HDL-C ratio

| Baseline characteristics | Total n=1904 | LDL-C/HDL-C ratio |   |   |   |   |
|--------------------------|-------------|-------------------|---|---|---|---|
|                          |             | Tertile 1 (n = 579) | Tertile 2 (n = 687) | Tertile 3 (n = 638) | p  |
| General                  |             |                   |               |               |   |   |
| Age (years, SD)          | 57.0 ± 11.9 | 56.9 ± 12.5       | 57.7 ± 11.7   | 56.4 ± 11.7   | 0.164 |
| Male, n (%)              | 988 (51.9)  | 240 (41.5)        | 334 (48.6)    | 414 (64.9)    | < 0.001 |
| BMI (Kg/m2)              | 23.2 ± 3.4  | 21.8 ± 3.3        | 22.9 ± 3.1    | 24.7 ± 3.2    | < 0.001 |
| HT, n (%)                | 715 (37.6)  | 208 (35.9)        | 267 (38.9)    | 240 (37.6)    | 0.56 |
| DM, n (%)                | 183 (9.6)   | 45 (7.8)          | 69 (10)       | 69 (10.8)     | 0.177 |
| Smoking habit, n (%)     | 336 (17.6)  | 71 (12.3)         | 113 (16.4)    | 152 (23.8)    | < 0.001 |
| Drinking habit, n (%)    |             |                   |               |               | 0.001 |
| rarely drink             | 798 (41.9)  | 208 (35.9)        | 304 (44.3)    | 286 (44.8)    |   |
| sometimes                | 563 (29.6)  | 172 (29.7)        | 196 (28.5)    | 195 (30.6)    |   |
| everyday                 | 543 (28.5)  | 199 (34.4)        | 187 (27.2)    | 157 (24.6)    |   |
| Amount of drinking per day, n (%) |   |                   |               |               | 0.747 |
| Less than 180mL          | 1224 (64.3) | 359 (62)         | 457 (66.5)    | 408 (63.9)    |   |
| 180–360mL                | 467 (24.5)  | 151 (26.1)       | 158 (23)      | 158 (24.8)    |   |
| 360–540mL                | 158 (8.3)   | 52 (9)           | 51 (7.4)      | 55 (8.6)      |   |
| More than 540mL          | 55 (2.9)    | 17 (2.9)         | 21 (3.1)      | 17 (2.7)      |   |
| Metabolic syndrome, n (%)|             |                   |               |               | < 0.001 |
| No                       | 1429 (75.1) | 493 (85.1)       | 551 (80.2)    | 385 (60.3)    |   |
| Reserve                  | 196 (10.3)  | 30 (5.2)         | 55 (8)        | 111 (17.4)    |   |
| Yes                      | 279 (14.7)  | 56 (9.7)         | 81 (11.8)     | 142 (22.3)    |   |
| medication to reduce a level of cholesterol, n (%) |   |                   |               |               | < 0.001 |
| No                       | 1589 (83.5) | 469 (81)        | 552 (80.3)    | 568 (89)      |   |
| Yes                      | 315 (16.5)  | 110 (19)        | 135 (19.7)    | 70 (11)       |   |
| Biochemical data         |             |                   |               |               |   |
| LDL (mg/dl)              | 120.9 ± 30.4 | 95.2 ± 21.3 | 120.1 ± 20.6 | 144.9 ± 26.8 | < 0.001 |
| HDL (mg/dl)              | 61.1 ± 15.4 | 74.6 ± 14.9 | 60.7 ± 10.7 | 49.4 ± 9.0 | < 0.001 |
| TG (mg/dl)               | 89.0 (64.0, 129.0) | 67.0 (51.0, 87.0) | 87.0 (64.0, 119.0) | 121.0(90.0,172.0) | < 0.001 |
| HbA1c (%)                | 5.8 ± 0.6 | 5.6 ± 0.5 | 5.8 ± 0.6 | 5.9 ± 0.7 | < 0.001 |
| BS (mg/dl)               | 101.0 (95.0, 107.0) | 99.0(93.0, 105.0) | 100.0(95.0, 107.0) | 103.0(97.0,110.0) | < 0.001 |
| SBP (mmHg)               | 123.9 ± 18.4 | 121.8 ± 18.7 | 123.8 ± 18.9 | 125.9 ± 17.6 | < 0.001 |
| DBP(mmHg) | 73.9 ± 12.2 | 71.7 ± 11.9 | 73.8 ± 12.1 | 76.0 ± 12.1 | < 0.001 |
|-----------|-------------|-------------|-------------|-------------|---------|
| Carotid data | | | | | |
| The number of plaque, n (%) | 0.281 | | | | |
| 0 | 1241 (65.2) | 405 (69.9) | 437 (63.6) | 399 (62.5) | |
| 1 | 337 (17.7) | 83 (14.3) | 129 (18.8) | 125 (19.6) | |
| 2 | 203 (10.7) | 60 (10.4) | 72 (10.5) | 71 (11.1) | |
| 3 | 79 (4.1) | 19 (3.3) | 31 (4.5) | 29 (4.5) | |
| 4 | 33 (1.7) | 9 (1.6) | 13 (1.9) | 11 (1.7) | |
| 5 | 6 (0.3) | 3 (0.5) | 1 (0.1) | 2 (0.3) | |
| 6 | 4 (0.2) | 0 (0) | 3 (0.4) | 1 (0.2) | |
| 8 | 1 (0.1) | 0 (0) | 1 (0.1) | 0 (0) | |
| PS, n (%) | 663 (34.8) | 174 (30.1) | 250 (36.4) | 239 (37.5) | 0.014 |

Values are given as mean ± standard deviation, medians with interquartile range or number (%). BMI, body mass index. HT, hypertension. DM, diabetes mellitus. LDL-C, low-density lipoprotein cholesterol. HDL-C, high-density lipoprotein cholesterol. LDL-C/HDL-C ratio, quotient of LDL-C and HDL-C. TG, Triglyceride. HbA1c, hemoglobin A1c. BS, blood glucose level. SBP, systolic blood pressure. DBP, diastole blood pressure. PS, carotid plaque score. PN, plaque number.

3.2 The relationship between LDL-C/HDL-C ratio and PS in multiple regression model in Table 2

After adjustment in multivariable analyses, LDL-C/HDL-C ratio was significantly associated with PS. When included as a continuous variable, LDL-C/HDL-C ratio was also associated with an increased risk of PS (adjusted OR per 1-unit increase in LDL-C/HDL-C ratio, 1.20 (95%CI, 1.06-1.36). It could be interpreted that a unit increase of LDL-C/HDL-C ratio exhibited a correlation with a 20% increase of incidence of PS. In the unadjusted model, compared with people in the bottom tertiles, the OR for PS risk was 1.33 (95%CI 1.05-1.69) and 1.39 (95%CI 1.1-1.77) for individuals with LDL-C/HDL-C ratio in the second, third, respectively. In the model 3, compared with people in the first tertiles, the OR for PS risk was 1.35 (95%CI: 1~1.82) and 1.5 (95%CI: 1.04~2.17) for individuals with LDL-C/HDL-C ratio in the second, third, respectively. The restricted cubic splines (Fig. 1) showed a significant linear association between LDL-C/HDL-C ratio and risk of high PS (p for non-linearity = 0.805).
Table 2: Association between baseline LDL-C/HDL-C ratio and PS hyperintensity in multiple regression model.

| Variable                  | Non-adjusted Model | Model-1 | Model-2 | Model-3 |
|---------------------------|--------------------|---------|---------|---------|
|                           | OR(95%CI)          | P-value | OR(95%CI) | P-value | OR(95%CI) | P-value | OR(95%CI) | P-value |
| LDL-C/HDL-C ratio per 1 mg/dL | 1.2 (1.06~1.36) | 0.004   | 1.23 (1.07~1.42) | 0.004   | 1.31 (1.12~1.52) | 0.001   | 1.37 (1.12~1.68) | 0.002   |
| LDL-C/HDL-C ratio Tertiles |                    |         |         |         |         |         |         |         |
| LDL-C/HDL-C ratio1(≥0.3, <1.6) | 1                  | 1       | 1       | 1       |
| LDL-C/HDL-C ratio2(1.7, 2.3) | 1.33 (1.05~1.69) | 0.017   | 1.29 (0.99~1.69) | 0.059   | 1.32 (1~1.72) | 0.046   | 1.35 (1~1.82) | 0.053   |
| LDL-C/HDL-C ratio3(2.4, 5.5) | 1.39 (1.1~1.77) | 0.006   | 1.34 (1.02~1.76) | 0.034   | 1.47 (1.1~1.96) | 0.009   | 1.5 (1.04~2.17) | 0.031   |
| P for trend                | 0.008              | 0.038   | 0.01    | 0.035   |

Non-adjusted Model.

Model 1: adjusted for age, sex, hypertension, diabetes mellitus at baseline.

Model 2: adjusted for Model 1 + BMI, smoking habits, medication to reduce a level of cholesterol.

Model 3: adjusted for Model 2 + blood glucose level, triglyceride, HbA1c.

In order to assess the robustness of our results, following subgroup stratified analyses were performed. We further conducted subgroup analyses stratified by age, sex, fatty, diabetes, smoking habits, drinking habits to estimate the association between LDL-C/HDL-C ratio and risk of PS are presented in Table 3 and Fig 2. The interaction analysis revealed that age, sex, Diabetes could make a link between LDL-C/HDL-C ratio and incidence of PS. Firstly, there was a significant interaction between LDL-C/HDL-C ratio and age (P = 0.002), No significant correlation was found between LDL-C/HDL-C ratio and PS in subjects aged ≥ 65 years old (adjusted OR, 0.97; 95%CI, 0.77-1.21). However, the results for female and diabetes subgroups were showing a positive relationship between elevated LDL-C/HDL-C ratio and higher risk of without diabetes, and this association appeared to be more substantial in participants with female. Interaction analysis showed no interaction between LDL-C/HDL-C ratio and PS in the fatty, smoking and drinking subgroups. The stratified analysis demonstrated a statistically significant association between LDL-C/HDL-C ratio and PS in without fatty subjects (adjusted OR, 1.32; 95%CI, 1.08-1.6), subjects without smoking habits (adjusted OR, 1.23; 95%CI, 1.04-1.45). It was illuminated that a high LDL-C/HDL-C ratio was positively associated with PS incidence in subjects rarely and sometimes drink, rather than in everyday drink subjects.

Table 3: Association between baseline LDL-C/HDL-C ratio and the risk of Carotid Atherosclerosis in the subgroup analyses
| Subgroup       | Total n(%) | PS n(%) | OR(95% CI) No adjusted | OR(95% CI) adjusted | P value | P value for interaction |
|----------------|------------|---------|------------------------|---------------------|---------|-------------------------|
| Age            |            |         |                        |                     |         |                         |
| ≥45            | 343        | 23 (6.7)| 2.2 (1.41~3.43)        | 1.97 (1.21~3.2)     | 0.006   |                         |
| ≥45, ≥65       | 707        | 200 (28.3)| 1.64 (1.33~2.02)      | 1.53 (1.21~1.93)    | <0.001  |                         |
| ≥65            | 854        | 440 (51.5)| 0.98 (0.81~1.19)      | 0.97 (0.77~1.21)    | 0.775   |                         |
| Sex            |            |         |                        |                     |         |                         |
| male           | 988        | 413 (41.8)| 0.92 (0.78~1.07)      | 0.99 (0.83~1.18)    | 0.88    |                         |
| female         | 916        | 250 (27.3)| 1.6 (1.29~1.99)       | 1.33 (1.03~1.73)    | 0.031   |                         |
| Fatty          |            |         |                        |                     |         |                         |
| No             | 1190       | 392 (32.9)| 1.39 (1.17~1.65)      | 1.32 (1.08~1.6)     | 0.007   |                         |
| Yes            | 714        | 271 (38)| 0.94 (0.78~1.15)      | 1.1 (0.88~1.37)     | 0.409   |                         |
| Diabetes       |            |         |                        |                     |         |                         |
| No             | 1721       | 554 (32.2)| 1.25 (1.09~1.42)      | 1.24 (1.07~1.44)    | 0.004   |                         |
| Yes            | 183        | 109 (59.6)| 0.77 (0.52~1.14)      | 0.73 (0.45~1.18)    | 0.192   |                         |
| Smoking habits |            |         |                        |                     |         |                         |
| No             | 1568       | 541 (34.5)| 1.27 (1.1~1.47)       | 1.23 (1.04~1.45)    | 0.018   |                         |
| Yes            | 336        | 122 (36.3)| 1.01 (0.78~1.29)      | 1.03 (0.77~1.39)    | 0.826   |                         |
| Drinking habits|            |         |                        |                     |         |                         |
| rarely drink   | 798        | 259 (32.5)| 1.32 (1.08~1.6)       | 1.35 (1.06~1.72)    | 0.013   |                         |
| sometimes      | 563        | 177 (31.4)| 1.39 (1.1~1.76)       | 1.32 (1~1.73)       | 0.048   |                         |
| everyday       | 543        | 227 (41.8)| 1.01 (0.81~1.26)      | 1.13 (0.88~1.46)    | 0.351   |                         |

Each stratification adjusted for all the factors (Triglyceride, HbA1c, blood glucose level, systolic blood pressure, diastolic blood pressure, medication to reduce a level of cholesterol) except the stratification factor itself.
Discussion

To the best of our knowledge, this is the first study to describe a cross-sectional relationship between LDL-C/HDL-C ratio and risk of incident carotid atherosclerosis in a population with asymptomatic in Japan. In the present study, the LDL-C/HDL-C ratio was identified as a significant and independent risk factor of PS in the asymptomatic population. Indeed, a unit increase in LDL-C/HDL-C ratio level was associated with a 20% higher risk of ps, further confirming the relationship between LDL-C/HDL-C ratio and PS. Moreover, we found that both age and sex and DM significantly influenced this relationship, suggesting that these three factors may interact with the ps biological pathway to stimulate the development of LDL-C/HDL-C ratio.

LDL-C is considered a primary target of lipid-lowering therapy in almost all patients with CVD. However, even LDL-lowering therapy using statin agents still leaves considerable residual risk of CVD events, which may be due to residual risks associated with lipid abnormalities[23, 24]. A prospective community-based cohort study demonstrated that LDL-C/HDL-C was a better predictor of CIMT progression than either HDL-C or LDL-C levels alone 2020[25, 26]. Enomoto M et al.[27]found LDL-C:HDL-C ratio was a better marker in predicting IMT progression than HDL-C or LDL-C alone during an 8-year follow-up survey.

Previous studies indicated that LDL-C:HDL-C ratio is recognised as a new biometric that has clinical relevance in AS diseases[28–30]. Our results were consistent with those of most studies and further showed a positive association of LDL-C/HDL-C with presence of carotid plaque in Japanese. In the Helsinki Heart Study analyses, LDL-C:HDL-C ratio was shown to be the best single predictor of cardiac events[31]. Katakami et al.[32]explored the relationships between various lipid parameters including lipid ratios and carotid AS in 934 patients with T2DM having no obvious atherosclerotic diseases in Japan. They concluded that LDL-C:HDL-C ratio was positively associated with carotid atherosclerotic plaques. Wu et al[33]surveyed the impact of LDL-C:HDL-C ratio on CIMT among 1579 residents aged 40–74 years in northern Taiwan. The results demonstrated that LDL-C:HDL-C ratio was an important determinant of increased CIMT. A series of studies have found that LDL-C/HDL-C may provide greater predictive power for atherosclerotic change by concurrently reflecting both cholesterol entering and leaving the arterial intima. However, in some studies, association was not observed between LDL-C/HDL-C with carotid plaque failed to identify any associations between LDL-C:HDL-C ratio and carotid AS CIMT carotid plaques as well as carotid plaque type[34]. The small sample of the study may possibly explain the discrepancy.

Although the association between LDL-C/HDL-C ratio and PS in the stratified analysis was consistent with that in the multivariable logistic regression analysis. We found that it was not statistically significant in subjects older than 65 years, smokers, drinkers and in subjects who were diagnosed with fatty, diabetes. While aging, smoking, drinking, diabetes and fatty are risk factors for ps subjects with these risk factors are also supposed to have higher LDL-C/HDL-C ratio levels in the group. Consequently, residual confoundings were inevitable when we analyzed association of LDL-C/HDL-C ratio and prevalence of PS in subjects with these factors. Additionally, the sample size decreased after stratification, there was no significant association between LDL-C/HDL-C ratio and high CIMT in the subgroup of T2DM, which was similar to the significant association between LDL-C/HDL-C ratio and CIMT in a Cohort-sectional study of 13612 Chiese T2DM patients[35]. T2DM is characterized by a clustering of CVD risk factors including dyslipidemia. Different study design and method of statistical analysis, and a smaller sample size of T2DM (n = 183) in our study may explain the discrepancy.

This study found a linear association between LDL-C/HDL-C ratio and the risk of ps by the restricted cubic spine. The significant Ptrend in the Cox model also indirectly indicated the linear association. Our previous work described the cut-off value of LDL-C:HDL-C ratio for assessing CVD risk factors was 2.5 among Uygur adults[7]. However, we observed less risk between 1.6 and 2.3 but a significant increase for values upper than 2.3, which indicated that keeping the values of LDL-C/HDL-C ratio between 1.6 and 2.3 may be the suggested range of the LDL-C/HDL-C ratio to prevent high ps. The discordance between our results may be due to different characteristics between our population and theirs. Moreover, people with the LDL-C/HDL-C ratio >2.3 had an increased risk of high ps and the risk of high ps increased gradually with the increase
in the LDL-C/HDL-C ratio. The finding suggests that maintaining the LDL-C/HDL-C ratio under a low level may be useful to prevent and control the progression to high PS.

**Limitations**

However, limitations should also be considered in deriving conclusions. First, although we adjusted for numerous confounding factors, there may be potential residual confounding factors as with all Cross-Sectional studies. Second, this study included only Japanese participants, and therefore these findings may not be generalisable to other biogeographic ethnic groups. Third, we were unable to observe the long-term changes in the serum lipid levels.

**Conclusions**

In summary, our results indicate that the LDL-C/HDL-C ratios have a linear association with carotid atherosclerosis in Japanese. These data suggest that LDL-C/HDL-C ratios are recommended as a tool to assess the risk of early stage atherosclerosis in regular clinical practice.

**Declarations**

**Ethics statement**

The studies involving human participants were reviewed and approved by the ethical review committee of Shin Takeo Hospital. The patients/participants provided their written informed consent to participate in this study.

**Authors’ contributions**

Juan Wang and Jiuling Liu contributed equally to this work. Juan Wang participated in the study design, statistical analysis, writing and revising the manuscript. Jiuling Liu participated in the study design and interpretation of data and revising the manuscript. Juan Wang participated in the study design and interpretation of data. Jiuling Liu contributed to statistical analysis and revised the manuscript critically. All authors read and approved the final manuscript.

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**Availability of data and materials**

The data are available at http://www.Datadryad.org/. which allows researchers to freely download the original data.

**Conflict of interest**

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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**Figures**

![Figure 1](image)

**Figure 1**

LDL-C/HDL-C ratio level
### Figure 2

Association between baseline LDL-C/HDL-C ratio and the risk of Carotid Atherosclerosis in the subgroup analyses

| Subgroup       | Total | PS,N(%)  | Adjusted OR(95% CI) | P for interaction |
|----------------|-------|----------|---------------------|-------------------|
| Age            |       |          |                     |                   |
| Age<45         | 343   | 23 (6.7) | 1.97 (1.21,3.2)     | 0.002             |
| 45≤Age<65      | 707   | 200 (28.3)| 1.53 (1.21,1.93)    |                   |
| Age≤65         | 854   | 440 (51.5)| 0.97 (0.77,1.21)    |                   |
| Sex            |       |          |                     | 0.003             |
| male           | 988   | 413 (41.8)| 0.99 (0.83,1.18)    |                   |
| female         | 916   | 250 (27.3)| 1.33 (1.03,1.73)    |                   |
| Fatty          |       |          |                     |                   |
| No             | 1190  | 392 (32.9)| 1.32 (1.08,1.6)     | 0.101             |
| Yes            | 714   | 271 (38)  | 1.11 (0.88,1.37)    |                   |
| Diabetes       |       |          |                     |                   |
| No             | 1721  | 554 (32.2)| 1.24 (1.07,1.44)    | 0.01              |
| Yes            | 183   | 109 (59.6)| 0.73 (0.45,1.18)    |                   |
| Smoking habit  |       |          |                     |                   |
| No             | 1568  | 541 (34.5)| 1.23 (1.04,1.45)    | 0.118             |
| Yes            | 336   | 122 (36.3)| 1.03 (0.77,1.39)    |                   |
| Drinking habits|       |          |                     |                   |
| rarely         | 798   | 259 (32.5)| 1.35 (1.06,1.72)    | 0.194             |
| sometimes      | 563   | 177 (31.4)| 1.32 (1.01,1.73)    |                   |
| everyday       | 543   | 227 (41.8)| 1.13 (0.88,1.46)    |                   |