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Original Article

Non-HDL Cholesterol is a More Superior Predictor of Small-Dense LDL Cholesterol than LDL Cholesterol in Japanese Subjects with TG Levels <400 mg/dL

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***Aim*: The Japan Atherosclerosis Society (JAS) guidelines for the diagnosis and treatment of hyperlipidemia in Japanese adults recommend using low-density lipoprotein cholesterol (LDL-C) calculated by Friedewald formula (F_LDL-C) for subjects with triglyceride (TG) levels <400 mg/dL and non-high-density lipoprotein cholesterol (non-HDL-C) levels for subjects with TG levels ≥400 mg/dL. Because small-dense LDL particles are more atherogenic than large LDL particles, we sought the better lipid parameter which was more reflective of the high small-dense LDL-C (sdLDL-C) levels in subjects with TG levels <400 mg/dL.**

***Methods*: This study included 769 Japanese subjects who met our inclusion criteria and underwent an annual health examination, including sdLDL-C analyses.**

***Results*: The correlation coefficient of non-HDL-C for sdLDL-C (r=0.760) was significantly higher than that of F_LDL-C (r=0.601). The area under the curve (95% confidence interval) was 0.771 (0.731, 0.811) for F_LDL-C and 0.871 (0.842, 0.901) for non HDL-C, which showed significantly higher predictive value for more than fourth quartile value of sdLDL-C (46 mg/dL). The optimal cut-off point of non-HDL-C was 158 mg/dL. Even in subjects stratified by waist circumstance, homeostasis model assessment of insulin resistance, TG, and F_LDL-C levels and non-HDL-C showed stronger relationships with sdLDL-C than F_LDL-C. Moreover, non-HDL-C showed a better relationship with sdLDL-C than total cholesterol (TC), TC/HDL-C, and non-HDL-C/HDL-C.**

***Conclusion*: Our data suggested that non-HDL-C is superior to F_LDL-C and one of the reliable surrogate lipid markers of sdLDL-C in Japanese subjects with TG levels <400 mg/dL.**

Key words: Small-dense LDL, Non-HDL cholesterol, LDL cholesterol calculated by Friedewald formula, Annual health examination

Introduction

The correlation between hypercholesterolemia and the risk of coronary heart disease (CHD) indicates that reduced levels of serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) results in a reduced risk of CHD[1-5]. LDL-C comprises multiple distinct subclasses that differ in size, density, physicochemical composition, metabolic behavior, and atherogenicity[6]. Clinical atherosclerotic events are reported to be uncommon in humans with very low plasma cholesterol levels throughout their lives[7]. Despite these facts, LDL-C levels are not always elevated in patients with CHD[8]. Earlier evidence strongly suggests that in addition to lipoprotein levels, the specific natures of these lipoproteins are associated with the development and progression of coronary atherosclerosis[9]. Clinical studies strongly suggest that a predominance of small-dense LDL-C (sdLDL-C) is associated with a risk of CHD[9-12]. Therefore, an evaluation of serum lipid levels is a very important step toward reducing the incidence of atherosclerotic events.

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Table 1. Characteristics of study subjects

	Men ($n=493$)	Women ($n=276$)	P
Age (years)	57.6 ± 12.4	58.8 ± 11.5	0.18
BMI (kg/m^2)	23.9 ± 3.0	21.8 ± 3.1	0.63
Waist circumference (cm)	84.7 ± 8.3	78.8 ± 8.7	0.33
Systolic BP (mmHg)	124.0 ± 16.6	118.3 ± 18.2	0.08
Diastolic BP (mmHg)	79.7 ± 12.6	72.1 ± 11.7	0.16
FPG (mg/dL)	103.1 ± 12.7	98.3 ± 15.3	<.001
HOMA-IR	1.65 ± 1.50	1.33 ± 1.20	<.001
TG (mg/dL)	114.7 ± 56.4	90.6 ± 45.6	<.001
HDL-C (mg/dL)	59.8 ± 14.6	75.8 ± 16.6	0.02
F_LDL-C (mg/dL)	122.8 ± 27.8	130.1 ± 32.9	0.001
Non HDL-C (mg/dL)	145.7 ± 31.5	148.2 ± 35.3	0.31
SdLDL-C (mg/dL)	39.2 ± 15.8	34.1 ± 13.5	0.005
HMW-Ad (μg/mL)	2.92 ± 1.97	5.90 ± 3.41	<.001

Variables are given as means ± standard deviations.
BMI, body mass index; BP, blood pressure; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment-insulin resistance; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; F_LDL-C, low-density lipoprotein cholesterol calculated by Friedewald formula; non-HDL-C, non-high-density lipoprotein cholesterol; sdLDL-C, small-dense low-density lipoprotein cholesterol; HMW-Ad, high-molecular-weight adiponectin

guidelines for the diagnosis and treatment of hyperlipidemia in Japanese adults in 1997[13]. The JAS later revised these guidelines in 2002, 2007, and 2012[14-16]. In 2007, JAS recommended using LDL-C calculated by Friedewald formula (F_LDL-C) for subjects with triglyceride (TG) levels <400 mg/dL and directly measured LDL-C (D_LDL-C) for subjects with TG levels ≥400 mg/dL to evaluate the cholesterol levels and predict the risk of atherosclerotic disease. A comparison of the 2012 and 2007 JAS guidelines indicates that the F_LDL-C level was recommended for subjects with TG levels <400 mg/dL. In contrast, the non-high-density lipoprotein cholesterol (non-HDL-C) level was promoted for dyslipidemia evaluation in subjects with TG levels ≥400 mg/dL. Direct assays for LDL-C measurement include the traditional ultracentrifugation-based and detergent-based methods. The reported error for one detergent-based assay was 41.6%, suggesting uncertain quality control[17]. The JAS recommended using F_LDL-C levels in subjects with TG levels <400 mg/dL. However, F_LDL-C values are known to be less accurate not only as TG levels increase but also as LDL-C levels decrease below 100 mg/dL[18, 19]. The D_LDL-C level was no longer recommended for dyslipidemia evaluation because of quality control concerns.

Accumulating evidence indicates that despite the nature of LDL-C as a strong risk factor for CHD, LDL-C levels are not always elevated in patients with CHD. Hirano *et al.* reported that patients with CHD had increased sdLDL-C levels, irrespective of the presence of diabetes, despite having LDL-C levels comparable to those of normolipidemic controls[20]. Furthermore, another report stated that estimated cholesterol levels in the large LDL subfraction were not associated with an increased risk of CHD in men and that the cardiovascular risk attributable to variations in LDL size was largely related to markers indicating a preferential accumulation of sdLDL particles[21]. Unfortunately, sdLDL-C is not a widely accepted parameter because of the limited availability of the special equipment, techniques, and kits required for its measurement. Therefore, it is very important to use commonly measured lipid parameters, such as LDL-C and non-HDL-C, for evaluations of atherogenicity intended to include sdLDL-C.

This study aimed to identify the better surrogate lipid parameter reflective of high sdLDL-C levels in subjects with TG <400mg/dL.

Methods

Subjects

A total of 994 subjects underwent annual health examinations at the Health Evaluation and Promotion Center at Tokai University Hachioji Hospital between April 2011 and March 2014. These examinations included sdLDL-C analyses. After excluding subjects with TG levels ≥400 mg/dL and subjects who were under treatment for diabetes and dyslipidemia, 769

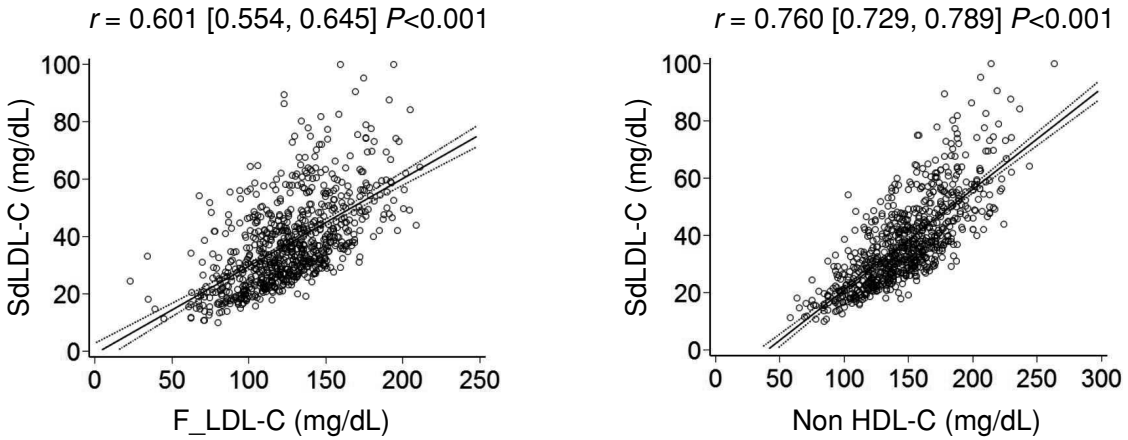

Fig. 1. Scatter plots and regression lines with 95% CIs for comparisons of sdLDL-C and lipid parameters in subjects with TG levels < 400 mg/dL

Pearson's correlation coefficient with 95% CIs is indicated on the graph.
sdLDL-C, small-dense low-density lipoprotein cholesterol; TG, triglyceride; F_LDL-C, low-density lipoprotein cholesterol calculated using the Friedewald formula; non-HDL-C, non-high-density lipoprotein cholesterol; CIs, confidence intervals

subjects were ultimately included in this study. Medical history information was obtained through self-administered questionnaires and interviews conducted by nurses. Among the 769 subjects, 142 were using antihypertensive drugs.

Measurements

Waist circumference (WC) was measured at the level of the umbilicus while the subject was standing and during slight expiration. Blood pressure (BP) was measured on the upper right arm using an automatic blood pressure monitor (TM-2655P; A&D, Tokyo, Japan) while the subject was seated. Blood samples were collected early in the morning after fasting overnight. Fasting immunoreactive insulin (FIRI) levels were measured using a fluorescence enzyme immunoassay (ST AIA-PACK IRI; Toso, Tokyo, Japan). The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as follows: Fasting plasma glucose (FPG; mg/dL) × FIRI (mU/mL)/405[22]. Levels of HDL-C and TG were measured using visible spectrophotometry (Determiner L HDL-C, and Determiner L TG II, respectively; Kyowa Medex, Tokyo, Japan). The serum LDL-C calculated by Friedewald formula (F_LDL-C) levels were calculated using the Friedewald formula[23]: LDL-C = TC − HDL-C − [TG/5]. Non-HDL-C levels were calculated by subtracting the HDL-C from the TC. Furthermore, sdLDL-C levels were measured using a homogeneous method (sd LDL-Ex; DENKA SEIKEN Co., Tokyo, Japan). High-molecular-weight adiponectin (HMW-Ad) was measured using chemiluminescent enzyme immunoassay based on a monoclonal antibody to human HMW-Ad (Fujirebio, Tokyo, Japan). Verbal consent for the analytical use of anonymized health records was obtained from the subjects. The study protocol was approved by the institutional ethics committee of the Tokai University School of Medicine.

Statistical Analyses

The significance of pairwise comparisons was determined using the *t*-test. Relationships between study variables were investigated using Pearson's correlation coefficient. Because the reference range for sdLDL-C was uncertain, the fourth quartile value (46 mg/dL) was determined. A receiver operating characteristic (ROC) curve was prepared to evaluate the discriminatory ability of the variables, and the area under the curve (AUC) with its 95% confidence interval (CI) was calculated. To determine the optimal cut-off point of non-HDL-C, the square root of ([1 − sensitivity]^2 + [1 − specificity]^2) was calculated, which was the point on the ROC curve with the shortest distance from the upper left corner.

Statistical analyses were performed using SAS software, version 9.3 (SAS Institute Inc., Cary, NC, USA). All *P*-values were two-tailed, and a *P*-value < 0.05 was considered statistically significant.

Results

Table 1 lists the subjects' characteristics. Men and women did not differ significantly with respect to age, body mass index (BMI), WC, BP, and non-HDL-

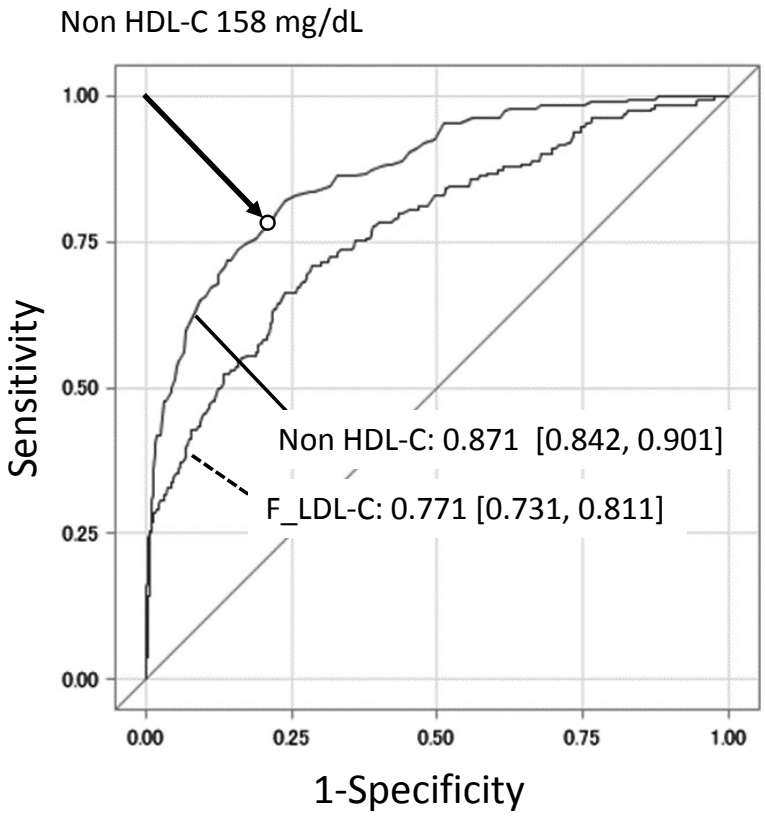

Fig. 2. The ROC curves of F_LDL-C and non-HDL-C for predicting high sdLDL-C level (≥46.0 mg/dL)

AUCs with its 95% CI for F_LDL-C and non-HDL-C, and optimal cut-off point of non-HDL-C (circle) are shown in the graph.
ROC, receiver operator characteristic; F_LDL-C, low-density lipoprotein cholesterol calculated using the Friedewald formula; non-HDL-C, non-high-density lipoprotein cholesterol; sdLDL-C, small-dense low-density lipoprotein cholesterol; AUC, area under the curve; CI, confidence interval

C levels. However, FPG, HOMA-IR, TG, and sdLDL-C values were significantly higher in men than in women. In contrast, the HDL-C, F_LDL-C, and HMW-Ad values were significantly higher in women than in men.

Fig. 1 shows scatter plots and regression lines with 95% CIs for comparisons of sdLDL-C with F_LDL-C and non-HDL-C in subjects with TG levels <400 mg/dL. The correlation coefficient of non-HDL-C for sdLDL-C (r=0.760) was significantly higher than that of F_LDL-C (r=0.601).

Fig. 2 illustrates the ROC curve to evaluate the discriminatory ability for more than fourth quartile value of sdLDL-C (46 mg/dL). The AUC (95% CI) was 0.771 (0.731, 0.811) for F_LDL-C and 0.871 (0.842, 0.901) for non-HDL-C, which showed a significantly higher predictive value for fourth quartile of sdLDL-C. The optimal cut-off point of non-HDL-C yielding the minimum value of the square root of [(1 − sensitivity)^2 + (1 − specificity)^2] was 158 mg/dL. The optimal cut-off point was also the point that maximized the product of sensitivity and specificity, with sensitivity and specificity of 0.772 and 0.793, respectively. The prevalence was 78.8%, and the positive predictive value was 54.9%.

Fig. 3 shows scatter plots and regression lines with 95% CIs for comparisons of sdLDL-C with F_LDL-C and non-HDL-C when subjects were stratified by WC levels. The correlation coefficient of F_LDL-C for sdLDL-C decreases as WC increases. On the contrary, the correlation coefficients of non-HDL-C for sdLDL-C were higher than those of F_LDL-C in all classes and remain high even in subjects with WC ≥90 cm.

Fig. 4 shows scatter plots and regression lines with 95% CIs for comparisons of sdLDL-C with F_LDL-C and non-HDL-C when subjects were stratified by HOMA-IR. The correlation coefficient of F_

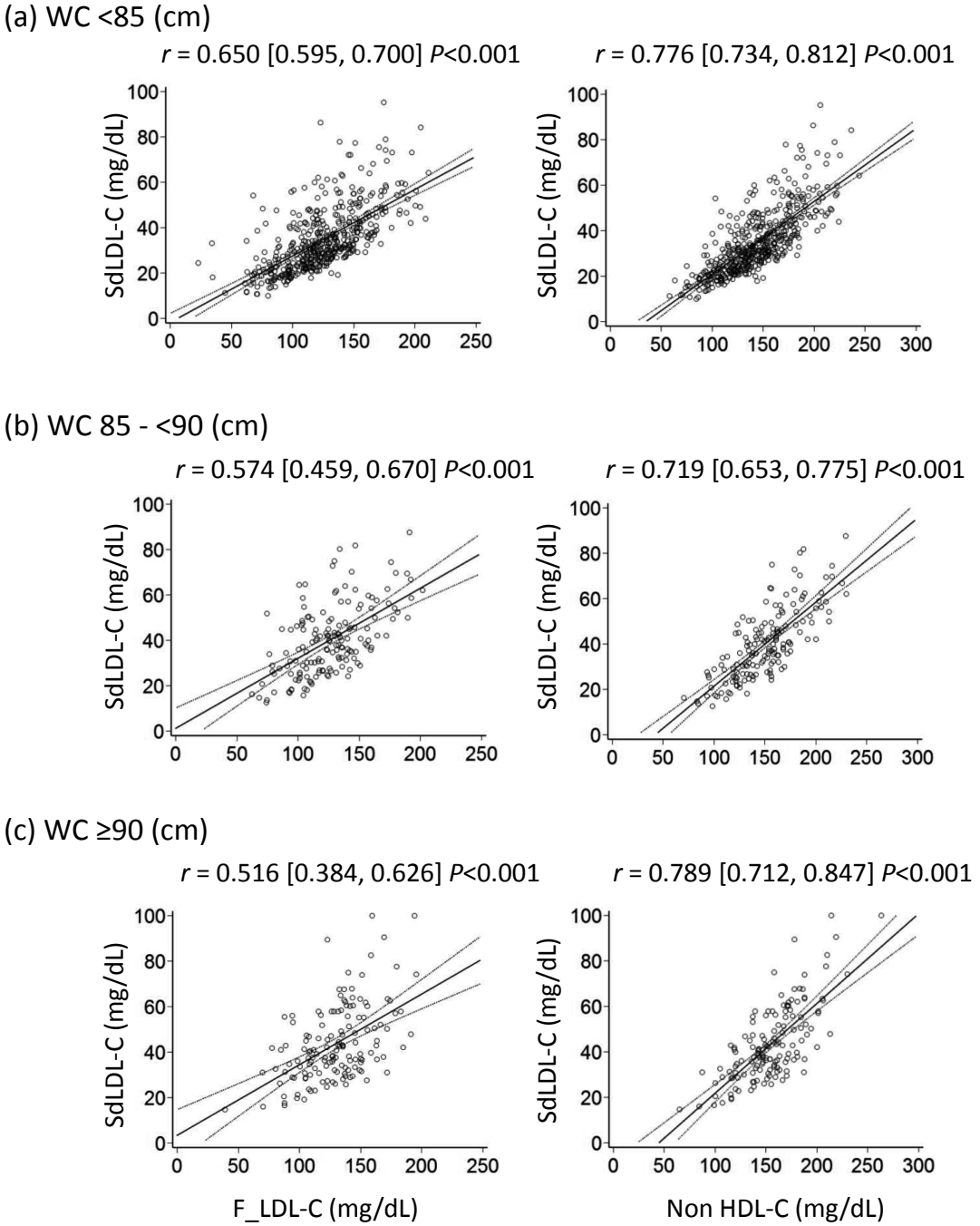

Fig. 3. Scatter plots and regression lines with 95% CIs for comparisons of sdLDL-C and lipid parameters when subjects were stratified by WC

Pearson's correlation coefficient with 95% CIs is indicated on the graph.
sdLDL-C, small-dense low-density lipoprotein cholesterol; WC, waist circumference; F_LDL-C, low-density lipoprotein cholesterol calculated using the Friedewald formula; non-HDL-C, non-high-density lipoprotein cholesterol; CIs, confidence intervals

LDL-C for sdLDL-C decreases as HOMA-IR increases. On the contrary, the correlation coefficients of non-HDL-C for sdLDL-C were higher than those of F_LDL-C in all classes and remain high even in subjects with HOMA-IR ≥ 2.5.

Fig. 5 shows scatter plots and regression lines with 95% CIs for comparisons of sdLDL-C with F_LDL-C and non-HDL-C when subjects were strati-

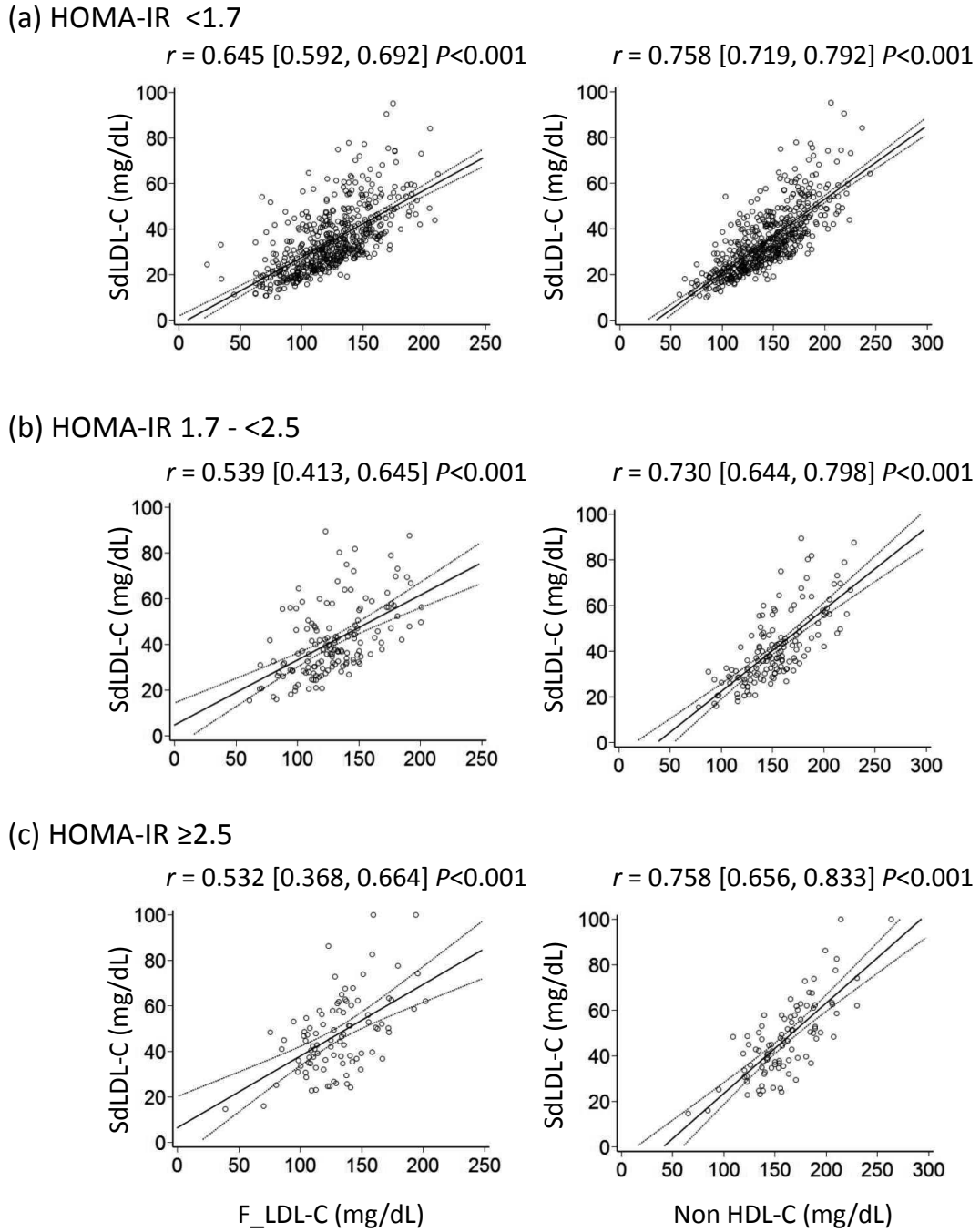

Fig. 4. Scatter plots and regression lines with 95% CIs for comparisons of sdLDL-C and lipid parameters when subjects were stratified by HOMA-IR

Pearson's correlation coefficient with 95% CIs is indicated on the graph.
sdLDL-C, small-dense low-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; F_LDL-C, low-density lipoprotein cholesterol calculated using the Friedewald formula; non-HDL-C, non-high-density lipoprotein cholesterol; CIs, confidence intervals

fied by TG levels. (a) The correlation coefficient of non-HDL-C for sdLDL-C was higher than that of F_LDL-C in normal TG levels (TG <150 mg/dL). (b) The correlation coefficient of non-HDL-C for sdLDL-C was higher than that of F_LDL-C in high TG levels (TG 150−<400 mg/dL).

Fig. 6 shows scatter plots and regression lines with 95% CIs for comparisons of sdLDL-C with F_

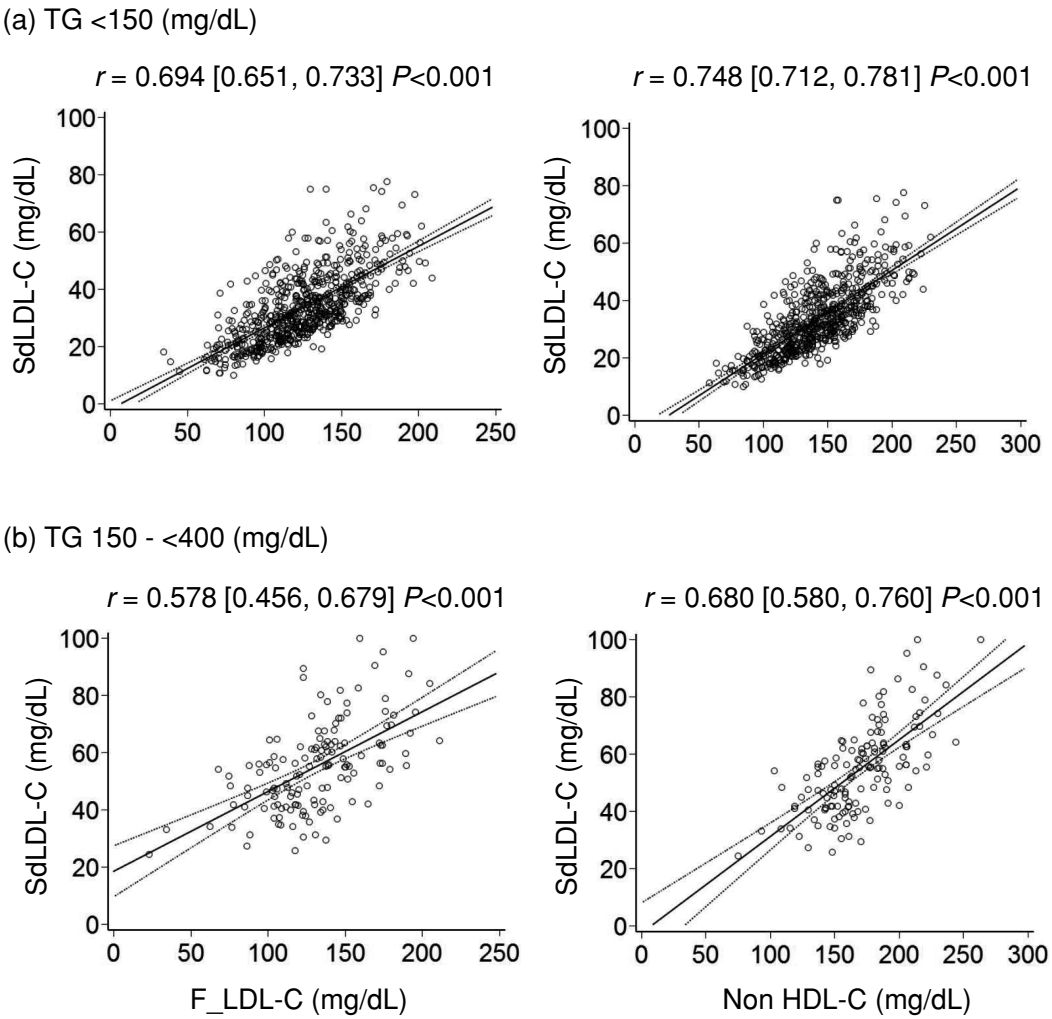

Fig. 5. Scatter plots and regression lines with 95% CIs for comparisons of sdLDL-C and lipid parameters when subjects were stratified by TG levels

Pearson's correlation coefficient with 95% CIs is indicated on the graph.
sdLDL-C, small-dense low-density lipoprotein cholesterol; TG, triglyceride; F_LDL-C, low-density lipoprotein cholesterol calculated using the Friedewald formula; non-HDL-C, non-high-density lipoprotein cholesterol; CIs, confidence intervals

LDL-C and non-HDL-C when subjects were stratified by F_LDL-C levels. (a) The correlation coefficient of non-HDL-C for sdLDL-C was higher than that of F_LDL-C in normal F_LDL-C levels (F_LDL-C < 140 mg/dL). (ab) The correlation coefficient of non-HDL-C for sdLDL-C was higher than that of F_LDL-C in high F_LDL-C levels (F_LDL-C ≥140 mg/dL).

Fig. 7 shows scatter plots and regression lines with 95% CIs for comparisons of sdLDL-C with TC, TC/HDL-C, and non-HDL-C/HDL-C in subjects with TG levels < 400 mg/dL. The ratios of TC, TC/HDL-C, and non-HDL-C/HDL-C were previously proposed lipid markers and were designed to associate higher values with an increased risk of acute myocardial infarction and lower values with a reduced risk[24] of myocardial infarction. The TC/HDL-C ratio is identical to the non-HDL-C/HDL-C ratio because they are linier transformations of each other[25]. The correlation coefficients of TC/HDL-C and non-HDL-C/HDL-C were significantly higher than those of TC. However, they were lower than that of non-HDL-C (**Fig. 1**). In addition, ROC curves to evaluate the discriminatory ability for more than fourth quartile value of sdLDL-C (46 mg/dL) were created (data not shown) and AUCs were calculated. The AUC (95% CI) was 0.868 (0.839, 0.897) for TC/HDL-C and non-HDL-C/HDL-C, which showed a significantly higher predictive value for fourth quartile value of

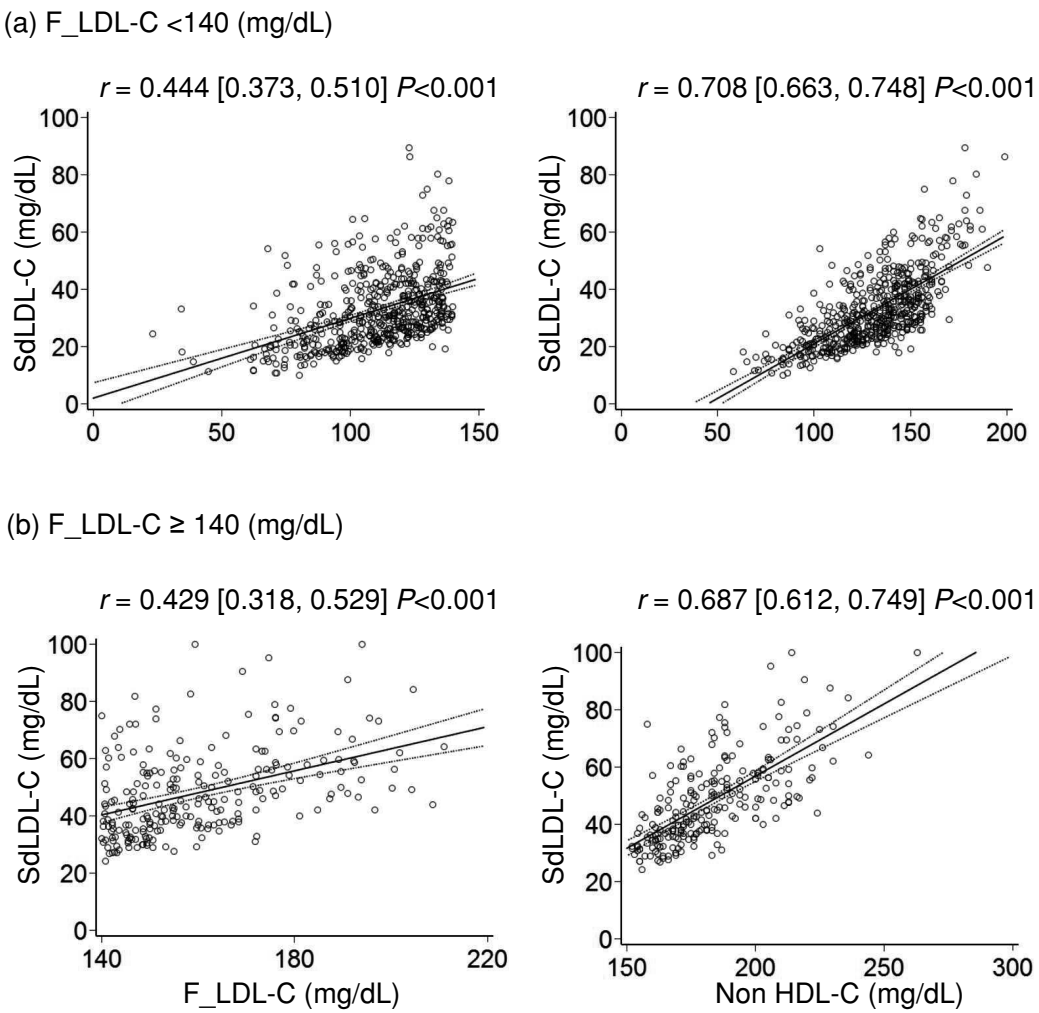

Fig. 6. Scatter plots and regression lines with 95% CIs for comparisons of sdLDL-C and lipid parameters when subjects were stratified by F_LDL-C levels

Pearson's correlation coefficient with 95% CIs is indicated on the graph.
sdLDL-C, small-dense low-density lipoprotein cholesterol; F_LDL-C, low-density lipoprotein cholesterol calculated using the Friedewald formula; non-HDL-C, non-high-density lipoprotein cholesterol; CIs, confidence intervals

sdLDL-C than that of TC [0.761 (0.721,0.822)], but they were not better than that of non-HDL-C (**Fig. 2**). Together, although these markers were useful surrogate lipid markers of sdLDL-C in subjects with TG <400 mg/dL, they did not surpass non-HDL-C.

Discussion

In this study, we demonstrated that the correlation between sdLDL-C and non-HDL-C was stronger than not only F_LDL-C but also TC, TC/HDL-C, and non-HDL-C/HDL-C. Therefore, we concluded that non-HDL-C was a better surrogate lipid marker of sdLDL-C level than other markers, including F_LDL-C, in Japanese subjects with TG levels <400 mg/dL. Accordingly, we should take advantage of non-HDL-C measurements in subjects with TG levels <400 mg/dL for CHD risk stratification.

Recently, non-HDL-C has emerged as a superior lipid surrogate maker for CHD risk and treatment assessments. More recent study suggested even obese boys with MetS may have a higher risk of development of CHD, since they exhibited elevated non-HDL-C levels[26]. Non-HDL-C can be directly calculated from values determined through routine lipid panels, and requires no additional measurements or expenses. Therefore, non-HDL-C is readily available for routine clinical use. In addition, non-HDL-C offers

the advantage of cluster measurement of all lipoproteins currently believed to contribute to atherosclerosis, such as very low-density lipoprotein, intermediate-density lipoprotein, chylomicron remnants, lipoprotein (a), and LDL, all of which are apolipoprotein B-containing lipoproteins. We are particularly interested in sdLDL-C because it is considered to be more atherogenic than LDL. Several metabolic features, such as small sizes of particles, lower affinity than larger LDL particles for LDL receptors[3, 10, 27, 28], and high susceptibility to oxidization[24, 29], explain the atherogenic properties of sdLDL particles.

In an 11.7 year prospective study using 2034 Japanese participants (968 men and 1066 women) aged 30-79 without a history of cardiovascular disease (CVD), it was revealed that increasing quartiles of sdLDL-C were associated with increased risk of CVD[30]. The hazard ratio of fourth quartile in men was 3.53 (95% CI: 1.31-9.86) in a multivariable-adjusted model. The range (mean) sdLDL-C of fourth quartile was 53.5-119.6 (67.3) mg/dL, indicating that subjects with more than 53.5 mg/dL of sdLDL-C were 3.53 times susceptible to CVD. In 481 Japanese-American studies, average sdLDL-C in subjects with impaired glucose tolerance and diabetes mellitus was 43.7 and 47.5 mg/dL, respectively, both of which were significantly higher than that of normal glucose tolerance (33.7 mg/dL)[31]. Moreover, according to JAS recommendation, the serum lipid management goal of non-HDL-C for subjects in Category III was <150 mg/dL[16]. In agreement with this recommendation, we showed the optimal cut-off point of non-HDL-C was 158 mg/dL for the fourth quartile of sdLDL-C. Together, the fourth quartile of sdLDL-C (46 mg/dL) in this study was slightly lower than that of the result by Arai *et al.*[30], however, it might be sufficient to include the subjects with high insulin resistance[31].

Another advantage of non-HDL-C measurements is they do not require fasting. In practical clinical situations, blood samples are not always collected under fasting conditions. Non-HDL-C can be accurately evaluated from specimens, regardless of collection time, and no special patient preparation is required.

Recent studies on the relationship between non-HDL-C levels and MetS suggested that measurement of non-HDL-C serves as a useful way to identify subjects at high risk of MetS[32, 33]. Insulin resistance may be a linking factor for the cluster of abnormalities that comprise MetS[34]. However, the relationship between non-HDL-C versus MetS and insulin resistance is still in debate[33, 34]. The ability of non-HDL-C thresholds to identify adolescents at increased risk for MetS has been reported[37]. On the contrary, more recent study did not support the measurement of non-HDL-C

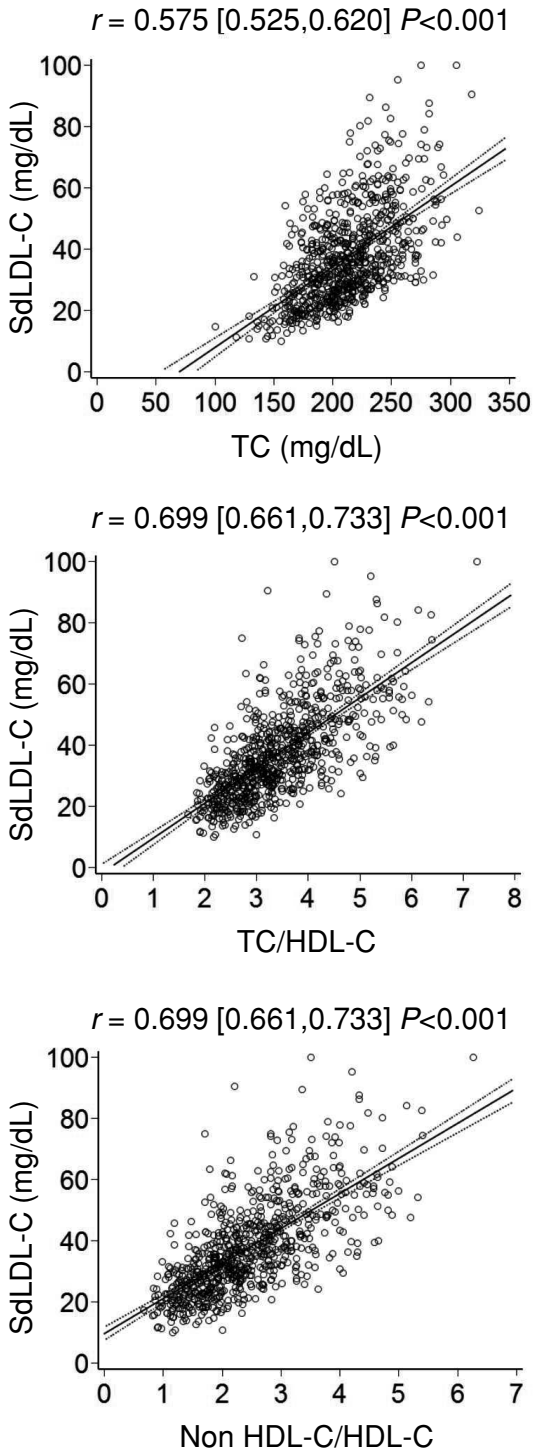

Fig. 7. Scatter plots and regression lines with 95% CIs for comparisons of sdLDL-C and lipid parameters in subjects with TG levels <400 mg/dL

Pearson's correlation coefficient with 95% CIs is indicated on the graph.
sdLDL-C, small-dense low-density lipoprotein cholesterol; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; CIs, confidence intervals

concentration as an effective means to predict MetS or the presence of insulin resistance[35]. It is difficult to compare these results due to the absence of a standardized pediatric MetS diagnostic criterion and disparities in lipid measurements between children and adults. The subjects with high LDL-C levels may have high non-HDL-C levels. Because diagnostic criteria for MetS do not include LDL-C levels, the existence of subjects with high non-HDL-C levels because of high LDL-C levels may explain why non-HDL-C is an effective predictor of CHD but it is less effective in identifying subjects with the MetS or insulin resistance[36]. Although we did not conduct detailed study on this issue, the relationships between sdLDL-C and non-HDL-C levels remained strong regardless of HOMA-IR levels. We were not able to conclude the relationships between non-HDL-C versus MetS and insulin resistance, but the following differences might be considered. Comparing the study subjects[35] with our subjects, they are mixed ethnic groups and approximately 40% were diagnosed as MetS (less than 7% of our subjects who met MetS criteria), and included more obese subjects. Differences for the evaluation of insulin resistance (measurements of insulin-mediated glucose uptake using the insulin suppression test[35] versus HOMA-IR in this study) might also be considered. However, given the importance of the MetS as a risk factor for type 2 diabetes mellitus and CHD[34], the ability of a non-fasting measurement to identify individuals at increased risk would be of considerable clinical benefit. Another study reported a close association between non-HDL-C levels and MetS in adults with and without diabetes mellitus, but information about use of lipid-lowering therapy was missing[32]. Therefore, more detailed study on the relationship between non-HDL-C, MetS and insulin resistance may be necessary in various groups of ethnic, age, and metabolic abnormalities.

WC is a simple marker of abdominal obesity and a strong predictor of morbidity and mortality that is independent of BMI. Studies have shown that fat accumulation leads to the dysregulation of adipocytokines, which participate in the pathogenesis of obesity and insulin resistance[37-40]. Additionally, visceral adiposity appears to confer increased insulin resistance risk, compared to that conferred by subcutaneous fat[41]. Therefore, we chose WC in addition to HOMA-IR for stratification of our subjects.

Non-HDL-C will likely increase in the subjects with obesity, insulin resistance, and hyperglycemia, with their accompanying increases in TG-rich lipoproteins[42]. To exclude the possibility that TG-rich lipoproteins affect the relationship between non-HDL-C and sdLDL-C, we compared their relationship with that of F_LDL-C and sdLDL-C in the subjects stratified by TG levels. Because it is also known that non-HDL-C serves as an indirect marker for increased LDL[42], LDL-C levels might affect the relationship between non-HDL-C and sdLDL-C. Thus, we compared their relationship with that of F_LDL-C and sdLDL-C in the subjects stratified by F_LDL-C levels. Non-HDL-C always showed better relationships with sdLDL-C than F_LDL-C in the subjects stratified by WC, HOMA-IR, TG, and F_LDL-C levels, as judged by correlation coefficients.

We could compare the correlation of sdLDL-C and non-HDL-C or LDL-C in various types of glucose metabolism and evaluate the accumulation of sdLDL in not only the status of lipoprotein disorders but also in glucose or metabolic disorders. However, the numbers of subjects with FPG ≥126 mg/dL or HbA1c ≥6.5% were only 36 and 21, respectively, in our study subjects. Thus, our study subjects may not be suitable for the analysis on the relationship between sdLDL-C and F_LDL-C or non-HDL-C in various glycemic conditions. The relationship between sdLDL-C and F_LDL-C or non-HDL-C with or without existence of MetS may be important. However, only 54 subjects who met Japanese criteria for MetS were found in our study subjects. Again, our study subjects may not be suitable for this analysis. It will be interesting to analyze these important issues in a different population.

Limitation of our study was its cross-sectional nature, which prevented the establishment of a causal relationship. Association between the F_LDL-C or non-HDL-C and sdLDL-C may possibly have been confounded by factors such as diet, alcohol consumption, and exercise. In addition, information regarding mutations in lipid-related genes that may have confounded these relationships was not available. The subjects of this study were middle-aged Japanese individuals, and it is possible that the relationships between F_LDL-C or non-HDL-C and sdLDL-C are affected by age and ethnicity. Moreover, detailed information regarding hypertension was omitted from this study. Finally, our results were calculated from data of only a fraction of the subjects who underwent annual health examinations, and therefore they may not be generalized to all Japanese subjects.

Conclusion

Non-HDL-C is one of the useful surrogate lipid markers for atherogenic sdLDL, at least in Japanese subjects with TG levels <400 mg/dL. Our data suggest that non-HDL-C levels should be reported in all routine lipid profiles and used regularly in dyslipid-

emia management for the optimal prevention of atherosclerosis and cardiovascular disease.

COI Statement

There are no conflicts of interest to declare.

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