Original Article

Relationship between Non-High-Density Lipoprotein Cholesterol and Low-Density Lipoprotein Cholesterol in the General Population: the KOBE Study and Tsuruoka Metabolomic Cohort Study

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Aim: The Japan Atherosclerosis Society (JAS) Guidelines for Diagnosis and Prevention of Atherosclerotic Cardiovascular Diseases for Japanese 2012 version have set a non-high-density lipoprotein cholesterol (non-HDL-C)-management target of low-density lipoprotein cholesterol (LDL-C) + 30 mg/dL. However, the actual difference between non-HDL-C and LDL-C is not clear. Therefore, we evaluated its joint distribution and assessed the validity of this criterion in the general Japanese population.

Methods: We used baseline cross-sectional data of 4,110 participants from two studies; the KOBE Study ($n=1,108$) and the Tsuruoka Metabolomic Cohort Study ($n=3,002$). To evaluate whether the difference between LDL-C and non-HDL-C in the general population match that of the current guidelines, we classified LDL-C levels into four groups according to the JAS Guideline and evaluated its agreement with the corresponding non-HDL-C group. Analysis was also done using six groups (the previous four groups plus the upper and lower cut-off values).

Results: The mean difference (mg/dL) between the non-HDL-C and LDL-C (for the KOBE Study and Tsuruoka Metabolomic Cohort Study, respectively) was 19.6 and 24.1 ($p<0.001$) for men and 15.9 and 18.3 ($p<0.001$) for women. In both the cohort studies, the difference was lower than 30 mg/dL. It was especially small among individuals with normal triglyceride levels.

Conclusions: In the general Japanese population, the difference between non-HDL-C and LDL-C was lower than the expected difference of 30 mg/dL. Changes to the criteria for non-HDL-C target levels may be considered in the future.

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Key words: Non-HDL-cholesterol, LDL-cholesterol, Community-based study

Introduction

The relationship between hypercholesterolemia

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and atherosclerosis has been established¹⁻³), and guidelines in multiple countries recommend atherosclerosis prevention in patients via hypercholesterolemia screening and treatment⁴⁻⁷). However, some guidelines recommend the use of non-high-density lipoprotein cholesterol (non-HDL-C) when triglyceride (TG) levels are high or as a secondary target after achieving the management target for low-density lipoprotein cholesterol (LDL-C)^{4, 6}). Non-HDL-C is a simple measure calculated by subtracting high-density lipoprotein

cholesterol (HDL-C) from the total cholesterol (TC) and has shown similar or stronger association with coronary artery disease (CAD) than LDL-C^{8,9)}.

According to the guidelines in the Western countries, TC is used for dyslipidemia screening^{4, 5, 7)}, although the Japan Atherosclerosis Society (JAS) Guidelines⁶⁾ recommend LDL-C as the screening parameter due to high HDL-C levels in the Japanese population¹⁰⁾. Therefore, LDL-C is measured during routine health checkup programs (specific health checkups) aimed at preventing cerebral/cardiovascular diseases among 40–74-year-old Japanese individuals¹¹⁾. For these specific health checkups, LDL-C is measured using the Friedewald formula¹²⁾ (the F formula) or the direct measuring method. However, the F formula cannot be used for non-fasting blood samples or when TG levels are ≥ 400 mg/dL and there is a doubt regarding whether the direct measuring method is accurate for LDL-C^{13, 14)}. Therefore, non-HDL-C needs to be evaluated for Japanese dyslipidemia screening. Numerous epidemiological and clinical studies have been conducted using TC or LDL-C for similar screening, although the currently recommended non-HDL-C target value is only defined as LDL-C + 30 mg/dL after the LDL-C target value has been achieved⁶⁾. Thus, the joint distribution of LDL-C and non-HDL-C must be verified in the general population for using non-HDL-C as a screening index.

Aim

The aim of this study was to investigate whether or not the difference between non-HDL-C and LDL-C levels is 30 mg/dL as indicated in the management targets of the current JAS guidelines in Japanese general populations.

Methods

Study Participants

This cross-sectional study assessed participants in the baseline surveys of two studies taking place in two geographically distinct regions: the Kobe Orthopedic and Biomedical Epidemiological study (the KOBE Study) and the Tsuruoka Metabolomic Cohort Study (the Tsuruoka Study).

The KOBE Study is a cohort study evaluating various health problems and their effects on the quality of life (QOL) in community-dwelling volunteers from Kobe city, Hyogo prefecture, located in the western part of mainland Japan. Volunteers were aged 40–74-year-old; did not have a history of malignant

neoplasm or cardiovascular disease; were not receiving treatment for hypertension, diabetes mellitus, or dyslipidemia; and were subjectively healthy based on self-reported result^{15–18)}. Between July 2010 and December 2011, 1,134 individuals were included in the baseline survey. Among these, 26 participants were excluded; three had fasted for <10 h; three had incomplete data; and three had high TG levels (≥ 400 mg/dL). Seventeen additional participants were excluded because they had reported the use of medication for hypertension, diabetes mellitus, or dyslipidemia after the recruiting process. Finally, we evaluated the data of 1,108 individuals (339 men, 769 women) in our analyses. The present study was approved by the Ethics Committee at the Institute of Biomedical Research and Innovation.

The Tsuruoka Study evaluated the onset of malignant neoplasms and atherosclerosis in Tsuruoka city, Yamagata prefecture, located on the northeastern Japanese coast. Individuals aged 35–74-year-old (as of April 2012) and who were undergoing a routine health checkup in Tsuruoka city were recruited as participants for that study¹⁹⁾. We used a part of the baseline data of this cohort. A total of 4,277 individuals participated in the baseline survey between April 2012 and September 2013. Among these, 1,275 participants were excluded; 93 were out of the 40–75-year-old age range; 21 had no record of blood collection time; 81 had fasted for <10 h; 198 had incomplete data; 859 reported use of medication for dyslipidemia; 22 had high TG level (≥ 400 mg/dL); and one had a negative LDL-C value using the F formula. In the final analyses, 3,002 individuals (1,432 men, 1,570 women) were included. The study was approved by the Medical Ethics Committee of the School of Medicine, Keio University, Tokyo, Japan, and all the subjects gave written informed consent without any incentives.

Data Collection and Standardization

In both cohort studies, the participants completed a standardized self-administered questionnaire regarding lifestyle, which included questions on history of treatment and medication and smoking and drinking habits. The responses were confirmed by trained health professionals via interviews. Body mass index (BMI) was calculated as weight in kilograms divided by the subject's height in meters squared (kg/m^2). Serum lipid levels of the fasting blood samples were measured using an enzyme assay, which had been confirmed to be precise and valid for standardized testing by the Japan Medical Association. The following reagents were used for the KOBE Study: TC and

T-CHO Reagents, “Kokusai” (Sysmex corp., Hyogo, Japan); HDL-C Reagent, “Cholestest N HDL” (Sekisui Medical Co., Ltd., Tokyo, Japan); and TG Reagent, “Pureauto S TG-N” (Sekisui Medical Co., Ltd., Tokyo, Japan). The following reagents were used for the Tsuruoka Study: TC Reagent, “L-type wako CHO M” (Wako Pure Chemical Industries, Ltd., Osaka, Japan); HDL-C Reagent, “MetaboRead HDL-C2” (Kyowa Medex Co., Ltd., Tokyo, Japan); and TG Reagent, “Determinar LTG II” (Kyowa Medex Co., Ltd., Tokyo, Japan). The LDL-C levels were calculated using the F formula: $\text{LDL-C} = \text{TC} - \text{HDL-C} - (\text{TG}/5)^{11}$. This formula is known to be inaccurate for TG values ≥ 400 mg/dL. All calculated LDL-C values were rounded to the first decimal place before analysis.

Statistical Analysis

Laboratory findings were reported as mean $\pm$ standard deviation or median for continuous variables and as a proportion (%) for categorical variables. Continuous variables were compared using the *T*-test or Mann–Whitney *U*-test and categorical variables were compared using the chi-squared test. We used the standard cut-off values from the 2012 Guidelines for Prevention of Atherosclerotic Cardiovascular Disease^{6, 20} for the classification of LDL-C levels into four groups: <120 , 120–139, 140–159, and ≥ 160 mg/dL. Using cross tabulation, we evaluated its agreement with the corresponding non-HDL-C groups: <150 , 150–169, 170–189, and ≥ 190 mg/dL. Furthermore, we created two additional groups for both measures using the upper and lower cut-off values (LDL-C: <100 and ≥ 180 mg/dL, non-HDL-C: <130 and ≥ 210 mg/dL) as the LDL-C cut-off values are used as the secondary management target and diagnostic criterion for familial hyperlipidemia, respectively²¹. We also examined determinants of difference between the serum non-HDL-C level (TC – HDL-C) and LDL-C level (TC – HDL-C – TG/5), i.e., one fifth of serum TG levels.

For participants with high TG levels, the F formula is inaccurate, thus, there may be deviation of LDL-C from measurements derived using the betaquantification method (BQ method). Therefore, we added a stratified sensitivity analysis using TG levels of ≥ 150 and <150 mg/dL. Furthermore, because the lipid profiles were recognized differently in the KOBE Study and the Tsuruoka Study, we analyzed and presented our findings separately for each study population. Two-tailed *P* values of <0.05 were considered statistically significant in all analyses. Analyses were performed using STATA SE 13 data analysis and statistical software (Stata Corp Lp, College Station,

TX, USA).

Results

Baseline characteristics and serum lipid levels are shown in **Table 1**, stratified by the study population. The subjects of the Tsuruoka Study were older and had higher mean BMI than those of the KOBE Study. Both studies reported similar TC levels, although the LDL-C levels were significantly higher in the KOBE Study. The proportion of current smokers among men was higher in the Tsuruoka Study, although the ratio among women was similar in both studies. The ratio of current female drinkers was higher in the KOBE Study, although the ratio among men was similar in both studies. Among men, the mean difference $\pm$ standard deviation (range) between the non-HDL-C and LDL-C levels was 19.6 ± 9.5 (5–62) mg/dL (KOBE Study) and 24.1 ± 13.2 (5–79) mg/dL (Tsuruoka Study) ($p < 0.001$). The mean difference for women was 15.9 ± 7.7 (5–66) mg/dL (KOBE Study) and 18.3 ± 8.9 (5–77) mg/dL (Tsuruoka Study) ($p < 0.001$). In both studies, the difference was lower than the 30 mg/dL proposed in the current guidelines. When we performed the analyses stratified by sex and age (40–49, 50–59, 60–69, and 70–74 years) (data not shown), the greatest difference between the non-HDL-C and LDL-C levels was 59.8 ± 16.4 mg/dL (Tsuruoka Study: men, 40–49 years) and the smallest difference was 13.3 ± 7.0 mg/dL (KOBE Study: women, 40–49 years).

We also evaluated the potential overlap between non-HDL-C and LDL-C levels based on the assumption of a 30 mg/dL difference as proposed in the current guidelines (KOBE Study: **Table 2-1**, Tsuruoka Study: **Table 2-2**). When we ignored the lowest of the four levels (LDL <120 mg/dL and non-HDL-C <150 mg/dL), we observed that the lowest LDL-C group exhibited the greatest overlap with the non-HDL-C group, corresponding to difference <30 mg/dL. For example, among men with LDL-C of 120–139 mg/dL, 63.6% of these men in the KOBE Study and 46.1% in the Tsuruoka Study were classified as having non-HDL-C of <150 mg/dL (rather than 150–169 mg/dL). Among the men in the LDL-C ≥ 140 categories, 41–49% in the KOBE Study and 18–37% in the Tsuruoka Study were classified as having a non-HDL-C level that differed from the LDL-C level by <30 mg/dL. Among women with a LDL-C level of 120–139 mg/dL, 70.6% of these women in the KOBE Study and 58.0% in the Tsuruoka Study were classified as having a non-HDL-C level of <150 mg/dL (rather than 150–169 mg/dL). Among women

Table 1. Characteristics and serum lipid levels in fasting participants by cohort study

	Kobe ^a	Tsuruoka ^b	<i>P</i> value ^c
MEN			
Number of fasting participants	339	1,432	
Age, years	60.9 (8.9)	61.9 (8.0)	0.054
Body mass index (kg/m ²)	22.8 (2.6)	23.5 (3.1)	<0.001
Use of antihypertensive agents (%)	0	28.4	NA
Use of oral hypoglycemic agents or insulin (%)	0	6.4	NA
Current smokers (%)	11.2	30.9	<0.001
Current drinkers (%)	77.0	77.7	0.73
Fasting blood glucose (mg/dL) ^d	93.7 (69–242)	104.9 (64–315)	<0.001
TC (mg/dL)	204.3 (28.5)	206.0 (34.0)	0.402
HDL-C (mg/dL)	60.7 (14.3)	64.4 (17.0)	<0.001
TG (mg/dL) ^e	87 (63, 120)	103 (74, 151)	<0.001
LDL-C (Friedewald, mg/dL)	124.0 (27.3)	117.5 (31.0)	<0.001
Non-HDL-C (mg/dL)	143.6 (29.5)	141.6 (35.1)	0.329
Non-HDL-C-LDL-C (mg/dL)	19.6 (9.5)	24.1 (13.2)	<0.001
WOMEN			
Number of fasting participants	769	1,570	
Age, years	58.0 (8.7)	61.3 (7.9)	<0.001
Body mass index (kg/m ²)	20.9 (2.7)	22.8 (3.4)	<0.001
Use of antihypertensive agents (%)	0	22.0	NA
Use of oral hypoglycemic agents or insulin (%)	0	3.6	NA
Current smokers (%)	2.1	3.0	0.375
Current drinkers (%)	36.7	27.8	<0.001
Fasting blood glucose (mg/dL) ^d	88.6 (71–333)	97.7 (57–195)	<0.001
TC (mg/dL)	221.3 (32.5)	219.9 (32.8)	0.331
HDL-C (mg/dL)	71.5 (15.7)	73.3 (17.3)	0.013
TG (mg/dL) ^e	70 (54, 96)	81 (61, 110)	<0.001
LDL-C (Friedewald, mg/dL)	133.9 (28.5)	128.3 (29.9)	<0.001
Non-HDL-C (mg/dL)	149.8 (31.6)	146.6 (32.6)	0.022
Non-HDL-C-LDL-C (mg/dL)	15.9 (7.7)	18.3 (8.9)	<0.001

TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; Non-HDL-C, non-high-density lipoprotein cholesterol; NA, not available. The LDL-C levels were calculated using the F formula: LDL-C = TC – HDL-C – (TG/5). Data are expressed as means (standard deviations) for continuous variables and percentages for categorical variables, specified if otherwise.

a) Kobe, Kobe Orthopedic and Biomedical Epidemiological study (the KOBE study).

b) Tsuruoka, Tsuruoka Metabolomic Cohort Study.

c) *P* values for comparison of variables between cohort groups by analysis of variance for categorical variables and *t*-test for continuous variables.

d) Mean (range).

e) Median (25th, 75th), Mann-Whitney's *U*-test.

in the LDL-C ≥ 140 categories, 38–60% in the KOBE study and 40–64% in the Tsuruoka Study were classified as having a non-HDL-C level that differed from the LDL-C level by <30 mg/dL.

When we included the lowest lipid levels (LDL-C <100 mg/dL and non-HDL-C <130 mg/dL), the lowest LDL-C level ignored a greatest overlap with the non-HDL-C group corresponding to a dif-

ference of <30 mg/dL (**Tables 3-1** and **3-2**). Among the men with LDL-C levels of 100–119 mg/dL, 60.6% in the KOBE Study and 54.6% in the Tsuruoka Study were classified as having non-HDL-C levels of <130 mg/dL (rather than 130–149 mg/dL). Among men with LDL-C ≥ 120 mg/dL, 48–64% in the KOBE Study and 26–46% in the Tsuruoka Study were classified as having a non-HDL-C value that dif-

Table 2-1. Cross-table between non-HDL-C and LDL-C categories according to the cut-off points of LDL-C based on the JAS guideline (Kobe)

	Non-HDL-C, mg/dL			
	< 150	150-169	170-189	190 ≤
MEN				
LDL-C, mg/dL				
< 120 (<i>n</i> = 150)	96.7	2.7	0.7	0
120-139 (<i>n</i> = 99)	63.6	32.3	4.0	0
140-159 (<i>n</i> = 56)	0	48.2	50.0	1.8
160 ≤ (<i>n</i> = 34)	0	0	41.2	58.8
WOMEN				
LDL-C, mg/dL				
< 120 (<i>n</i> = 244)	99.6	0	0.4	0
120-139 (<i>n</i> = 214)	70.6	28.0	1.4	0
140-159 (<i>n</i> = 167)	3.6	59.9	35.3	1.2
160 ≤ (<i>n</i> = 144)	0	0.7	38.2	61.1

LDL-C, low-density lipoprotein cholesterol; Non-HDL-C, non-high-density lipoprotein cholesterol. Data are expressed as the percentage of the number of participants being classified into each non-HDL-C group according to levels of LDL-C group. The shaded cells represent the % of non-HDL-C corresponding to the LDL-C management targets + 30 mg/dL, shown in JAS guidelines.

Table 2-2. Cross-table between non-HDL-C and LDL-C categories according to the cut-off points of LDL-C based on the JAS guideline (Tsuruoka)

	Non-HDL-C, mg/dL			
	< 150	150-169	170-189	190 ≤
MEN				
LDL-C, mg/dL				
< 120 (<i>n</i> = 766)	94.3	4.7	1.0	0
120-139 (<i>n</i> = 358)	46.1	41.1	10.1	2.8
140-159 (<i>n</i> = 173)	1.2	37.0	48.6	13.3
160 ≤ (<i>n</i> = 135)	0	0	18.5	81.5
WOMEN				
LDL-C, mg/dL				
< 120 (<i>n</i> = 631)	97.3	2.5	0.2	0
120-139 (<i>n</i> = 409)	58.0	38.4	3.2	0.5
140-159 (<i>n</i> = 307)	0.3	63.5	32.9	3.3
160 ≤ (<i>n</i> = 223)	0	0.5	40.4	59.2

LDL-C, low-density lipoprotein cholesterol; Non-HDL-C, non-high-density lipoprotein cholesterol. Data are expressed as the percentage of the number of participants being classified into each non-HDL-C group according to levels of LDL-C group. The shaded cells represent the % of non-HDL-C corresponding to the LDL-C management targets + 30 mg/dL, shown in JAS guidelines.

Table 3-1. Cross-table between non-HDL-C and LDL-C categories according to the cut-off points of LDL-C two additional groups based on the JAS guideline (Kobe)

	Non-HDL-C, mg/dL					
	< 130	130-149	150-169	170-189	190-209	210 ≤
MEN						
LDL-C, mg/dL						
< 100 (<i>n</i> = 56)	94.6	5.4	0	0	0	0
100-119 (<i>n</i> = 94)	60.6	34.0	4.3	1.1	0	0
120-139 (<i>n</i> = 99)	0	63.6	32.3	4.0	0	0
140-159 (<i>n</i> = 56)	0	0	48.2	50.0	1.8	0
160-179 (<i>n</i> = 26)	0	0	0	53.9	38.5	7.7
180 ≤ (<i>n</i> = 8)	0	0	0	0	50.0	50.0
WOMEN						
LDL-C, mg/dL						
< 100 (<i>n</i> = 89)	97.8	2.3	0	0	0	0
100-119 (<i>n</i> = 155)	79.4	20.0	0	0.7	0	0
120-139 (<i>n</i> = 214)	1.9	68.7	28.0	1.4	0	0
140-159 (<i>n</i> = 167)	0	3.6	59.9	35.3	1.2	0
160-179 (<i>n</i> = 101)	0	0	1.0	54.5	41.6	3.0
180 ≤ (<i>n</i> = 43)	0	0	0	0	44.2	55.8

LDL-C, low-density lipoprotein cholesterol; Non-HDL-C, non-high-density lipoprotein cholesterol. Data are expressed as the percentage of the number of participants being classified into each non-HDL-C group according to levels of LDL-C group. The shaded cells represent the % of non-HDL-C corresponding to the LDL-C management targets + 30 mg/dL, shown in JAS guidelines.

Table 3-2. Cross-table between non-HDL-C and LDL-C categories according to the cut-off points of LDL-C two additional groups based on the JAS guideline (Tsuruoka)

		Non-HDL-C, mg/dL					
		< 130	130-149	150-169	170-189	190-209	210 ≤
MEN							
LDL-C, mg/dL							
< 100 (<i>n</i> = 409)		91.4	6.1	2.4	0	0	0
100-119 (<i>n</i> = 357)		54.6	35.9	7.3	2.2	0	0
120-139 (<i>n</i> = 358)		0.3	45.8	41.1	10.1	2.2	0.6
140-159 (<i>n</i> = 173)		0	1.2	37.0	48.6	11.6	1.7
160-179 (<i>n</i> = 95)		0	0	0	26.3	52.6	21.1
180 ≤ (<i>n</i> = 40)		0	0	0	0	30.0	70.0
WOMEN							
LDL-C, mg/dL							
< 100 (<i>n</i> = 257)		96.9	3.1	0	0	0	0
100-119 (<i>n</i> = 374)		60.4	35.0	4.3	0.3	0	0
120-139 (<i>n</i> = 409)		0.7	57.2	38.4	3.2	0.2	0.2
140-159 (<i>n</i> = 307)		0	0.3	63.5	32.9	2.6	0.7
160-179 (<i>n</i> = 147)		0	0	0.7	60.5	36.1	2.7
180 ≤ (<i>n</i> = 76)		0	0	0	1.3	27.6	71.1

LDL-C, low-density lipoprotein cholesterol; Non-HDL-C, non-high-density lipoprotein cholesterol. Data are expressed as the percentage of the number of participants being classified into each non-HDL-C group according to levels of LDL-C group. The shaded cells represent the % of non-HDL-C corresponding to the LDL-C management targets + 30 mg/dL, shown in JAS guidelines.

ferred from the LDL-C level by <30 mg/dL. Among women with an LDL-C level of 100–119 mg/dL, 79.4% in the KOBE Study and 60.4% in the Tsuruoka Study were classified as having a non-HDL-C level of <130 mg/dL (rather than 130–149 mg/dL). Among the women with LDL-C ≥ 120 mg/dL, 44–69% in the KOBE Study and 27–64% of women in the Tsuruoka Study were classified as having a non-HDL-C that differed from the LDL-C level by <30 mg/dL.

We indicated the difference between non-HDL-C and LDL-C (one-fifth of serum TG levels) with or without contributing factors, which were considered to influence the difference between these two levels (Table 4). The difference between the non-HDL-C and LDL-C levels was significantly larger in men than women, in overweight (BMI ≥ 25 kg/m²) than normal weight participants, in participants with impaired fasting glucose (fasting blood glucose ≥ 110 mg/dL) than with normal fasting glucose, and in smokers than non-smokers. The difference between the non-HDL-C and LDL-C was also significantly larger in women using

antihypertensive agents than in those not using such agents; but in men, the difference was significantly larger in those who were not using antihypertensive agents than in those who were. We did not observe a significant difference between the participants with and without anti-diabetic medication or between drinkers and non-drinkers. Besides, any difference between the non-HDL-C and LDL-C levels did not exceed 30 mg/dL in this stratified analysis.

We also evaluated whether TG levels (normal: < 150 mg/dL, high: ≥ 150 mg/dL) affected this difference via subanalyses with stratification according to the TG levels (Supplementary Tables 1-2). Among participants with normal TG levels, the mean difference ± standard deviation (range) in men was 16.7 ± 5.8 (5–30) mg/dL (KOBE Study) and 17.8 ± 5.7 (5–30) mg/dL (Tsuruoka Study); the mean difference in women was 14.6 ± 5.4 (5–30) mg/dL (KOBE Study) and 16.2 ± 5.6 (5–30) mg/dL (Tsuruoka Study). All participants with normal TG levels had a difference of <20 mg/dL between the non-HDL-C and LDL-C levels. Among participants with high TG

Table 4. The mean difference between non-HDL-C and LDL-C according to contributed factors

	MEN			WOMEN		
	Presence	Absence	<i>P</i> value	Presence	Absence	<i>P</i> value
Sex	23.2 (12.7)	-	-	17.5 (8.6)	-	<0.001 ^a
Over-weight ^b	27.0 (13.6)	21.9 (12.1)	<0.001	21.5 (10.3)	16.6 (7.9)	<0.001
Use of antihypertensive agents	22.7 (11.2)	24.7 (13.9)	0.011	19.7 (9.5)	17.9 (8.7)	<0.001
Anti-diabetic medication ^c	24.4 (11.9)	24.1 (13.3)	0.816	18.9 (7.9)	18.3 (8.9)	0.612
Impaired fasting glucose ^d	26.0 (14.0)	22.5 (12.2)	<0.001	19.5 (8.8)	17.3 (8.5)	0.001
Smokers ^e	24.2 (13.1)	20.1 (10.5)	<0.001	18.8 (9.5)	17.4 (8.5)	0.014
Drinkers ^f	23.1 (12.8)	23.9 (12.4)	0.362	17.0 (8.9)	17.7 (8.4)	0.064

Data are expressed as means (standard deviations).

a) Men vs. women.

b) Body mass index ≥ 25 kg/m²

c) Use of antihypertensive agents.

d) Fasting blood glucose ≥ 110 mg/dL

e) Including past smokers.

f) Including past drinkers.

levels, the mean difference in men was 38.0 ± 7.7 (30–62) mg/dL (KOBE Study) and 42.6 ± 11.5 (30–79) mg/dL (Tsuruoka Study) and the mean differences in women were 37.8 ± 7.7 (31–66) mg/dL (KOBE Study) and 39.2 ± 9.2 (30–77) mg/dL (Tsuruoka Study). All participants with high TG levels had a difference of approximately 30 mg/dL between the non-HDL-C and LDL-C levels. However, in both populations, overlap between the non-HDL-C category and the category corresponding to LDL-C ± 30 mg/dL was highest.

Discussion

This study examined the distributions of non-HDL-C and LDL-C and their differences among two geographically distinct community-dwelling populations. The mean difference between the non-HDL-C and LDL-C levels was approximately 20 mg/dL in both regions for both sexes, which was lower than the 30 mg/dL difference indicated in the JAS Guideline for Diagnosis and Prevention of Atherosclerotic Cardiovascular Diseases for Japanese 2012 version. This discrepancy was especially remarkable for individuals with normal TG levels of <150 mg/dL.

Dyslipidemia is strongly associated with the onset of atherosclerosis and risk for CAD development and mortality is known to be associated with an increase in LDL-C¹⁾, TC^{3, 22, 23)}, TG^{24, 25)}, and non-HDL-C^{7, 26-28)} levels, as well as with decreases in HDL-C²³⁾. Japan has a lower mortality rate due to CAD than that of other countries²⁹⁻³²⁾, however, Westernization of the Japanese diet has led to increasing levels of TC and LDL-C and an increased onset of

CAD in some regions^{33, 34)}. Therefore, lipid management and prevention of these diseases are becoming important issues in Japan.

Currently, the JAS guidelines recommend the use of LDL-C as a screening index during specific health checkups for the identification and treatment of high-risk patients. However, there are several issues with the use of LDL-C in this screening process. For example, LDL-C is normally obtained using the F formula which requires a fasting blood sample. Unfortunately, it is difficult to enforce strict fasting conditions during routine health checkups among community-dwelling individuals. Thus, many Western countries use TC levels for screening tests or absolute risk estimations^{4, 5, 7)}. However, because Japanese HDL-C levels are higher than those of Western populations³⁵⁾, screening using TC may identify patients who do not actually have high LDL-C levels, thereby resulting in the possibility of incorrectly referring medical treatment. Furthermore, although the direct measurement method for LDL-C has been widely used in health checkups, its divergence from the betaquantification (BQ) method has raised questions regarding whether the direct method is appropriate for screening.

In contrast, non-HDL-C is not influenced by fasting conditions and includes LDL-C and all atherogenic lipoprotein (e.g., remnant lipoprotein). In addition, non-HDL-C levels are highly correlated with small dense LDL-C particles, and several cohort studies have reported that non-HDL-C and LDL-C equally predict the risk of atherosclerosis onset in the general population^{9, 36, 37)}. Other studies have also reported that non-HDL-C can predict atherosclerosis onset at a level that is equal to or higher than that of

LDL-C^{27, 38)}. Based on these reports, it appears that non-HDL-C may be more appropriate for population-based dyslipidemia screening. However, future prospective studies are needed to determine the appropriate cut-off value for non-HDL-C as the existing medical guidelines have focused on using LDL-C to identify patients who require therapeutic intervention.

The management standard for non-HDL-C is set at 30 mg/dL above the corresponding LDL-C level in the National Cholesterol Education Program Adult Treatment Panel III guidelines and the European Society of Cardiology/European Atherosclerosis Society guidelines^{4, 7, 39)}. The JAS guidelines also use a similar cut-off value based on previous studies^{40, 41)}. However, these guidelines were tested in dyslipidemia patients, and non-HDL-C was a secondary target after achieving the LDL-C target. Thus, non-HDL-C has not been validated for screening in the general population. Based on our findings, the difference between non-HDL-C and LDL-C levels was < 30 mg/dL for various subgroups, and this difference was especially small among patients with normal TG levels of < 150 mg/dL. Therefore, the difference of 30 mg/dL may not be suitable as an appropriate non-HDL-C cut-off value when screening a relatively healthy population. In a previous study in Japan, the contributing factors that greatly influenced the difference between the LDL-C and non-HDL-C levels, such as the prevalence of men and mean fasting blood glucose levels, were higher than those in the present study⁴¹⁾. Furthermore, in these previous studies, their high prevalence of diabetes, i.e., 70% and 28%, might contribute to high serum levels of TG^{40, 41)}. On the contrary, in the present study, proportion of those who were taking oral hypoglycemic agents or being under insulin injection was none in the KOBE Study and low in the Tsuruoka Study (6.4%). Accordingly, above-mentioned difference in participant's backgrounds may be major reasons for difference in TG levels between previous studies and ours. For setting clinical criteria for non-HDL-C in general population, it is necessary to consider distribution of diabetes and other medical histories.

The present study has several limitations. First, we used a cross-sectional design using a healthy population that allows us to evaluate only the joint distribution of non-HDL-C and LDL-C at one point. A large-scale prospective study with atherosclerosis as an endpoint is needed to determine the validity of the cut-off value for non-HDL-C screening. Second, although our findings were similar in the two geographically distinct regions, it is possible that they may not extrapolate to the general Japanese popula-

tion. However, because the lipid profiles in both regions were similar to that of the 2012 Japanese National Health and Nutrition Survey⁴²⁾, it appears that these profiles are representative of the general Japanese population. Third, it is possible that the measurements of LDL-C levels deviated from the true values even when the F formula was used, given its deviation from the BQ method. However, we could not use the BQ method because of the large number of studied subjects. Measurements of the TC, HDL-C, and TG levels were all derived using standardized reagents that were approved by the Japan Medical Association.

Conclusions

We examined the association between non-HDL-C and LDL-C according to lipid profiles and cut-off values among baseline cross-sectional data from two studies. The observed difference between the non-HDL-C and LDL-C levels was approximately 20 mg/dL, which is smaller than 30 mg/dL that is indicated in the JAS Guideline for Diagnosis and Prevention of Atherosclerotic cardiovascular Diseases for Japanese 2012 version. Furthermore, the difference was even smaller among participants with normal TG levels. Changes to the criteria for non-HDL-C target levels should be considered in the future. In this study, with a perspective of variance with LDL-C that is examined most with association of atherosclerosis in the previous study, the serum level of non-HDL-C was examined in two areas. Future prospective studies are needed to evaluate the association of both serum LDL-C and non-HDL-C with atherosclerosis.

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Conflicts of Interest

There are no conflicts of interest related to the present study.

Declaration

Kazuyo Kuwabara had full access to all study data, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Supplementary Table 1-1. Cross-table between non-HDL-C and LDL-C categories according to the cut-off points of LDL-C based on the JAS guideline for participants with triglyceride < 150 mg/dL (Kobe)

	Non-HDL-C, mg/dL			
	< 150	150-169	170-189	190 ≤
MEN				
LDL-C, mg/dL				
< 120 (<i>n</i> = 126)	100.0	0	0	0
120-139 (<i>n</i> = 91)	69.2	30.8	0	0
140-159 (<i>n</i> = 47)	0	57.5	42.6	0
160 ≤ (<i>n</i> = 29)	0	0	48.3	51.7
WOMEN				
LDL-C, mg/dL				
< 120 (<i>n</i> = 237)	100.0	0	0	0
120-139 (<i>n</i> = 206)	73.3	26.7	0	0
140-159 (<i>n</i> = 159)	3.8	62.9	33.3	0
160 ≤ (<i>n</i> = 123)	0	0.8	44.7	54.5

LDL-C, low-density lipoprotein cholesterol; Non-HDL-C, non-high-density lipoprotein cholesterol. Data are expressed as the percentage of the number of participants being classified into each non-HDL-C group according to levels of LDL-C group. The shaded cells represent the % of non-HDL-C corresponding to the LDL-C management targets + 30 mg/dL, shown in JAS guidelines.

Supplementary Table 1-3. Cross-table between non-HDL-C and LDL-C categories according to the cut-off points of LDL-C based on the JAS guideline for participants with triglyceride < 150 mg/dL (Tsuruoka)

	Non-HDL-C, mg/dL			
	< 150	150-169	170-189	190 ≤
MEN				
LDL-C, mg/dL				
< 120 (<i>n</i> = 608)	100.0	0	0	0
120-139 (<i>n</i> = 262)	63.0	37.0	0	0
140-159 (<i>n</i> = 123)	1.6	52.0	46.3	0
160 ≤ (<i>n</i> = 75)	0	0	33.3	66.7
WOMEN				
LDL-C, mg/dL				
< 120 (<i>n</i> = 578)	100.0	0	0	0
120-139 (<i>n</i> = 369)	64.2	35.8	0	0
140-159 (<i>n</i> = 284)	0.4	68.7	31.0	0
160 ≤ (<i>n</i> = 199)	0	0.5	45.2	54.3

LDL-C, low-density lipoprotein cholesterol; Non-HDL-C, non-high-density lipoprotein cholesterol. Data are expressed as the percentage of the number of participants being classified into each non-HDL-C group according to levels of LDL-C group. The shaded cells represent the % of non-HDL-C corresponding to the LDL-C management targets + 30 mg/dL, shown in JAS guidelines.

Supplementary Table 1-2. Cross-table between non-HDL-C and LDL-C categories according to the cut-off points of LDL-C based on the JAS guideline for participants with triglyceride ≥ 150 mg/dL (Kobe)

	Non-HDL-C, mg/dL			
	150	150-169	170-189	190 ≤
MEN				
LDL-C, mg/dL				
< 120 (<i>n</i> = 24)	79.2	16.7	4.2	0
120-139 (<i>n</i> = 8)	0	50.0	50.0	0
140-159 (<i>n</i> = 9)	0	0	88.9	11.1
160 ≤ (<i>n</i> = 5)	0	0	0	100.0
WOMEN				
LDL-C, mg/dL				
< 120 (<i>n</i> = 7)	85.7	0	14.3	0
120-139 (<i>n</i> = 8)	0	62.5	37.5	0
140-159 (<i>n</i> = 8)	0	0	75.0	25.0
160 ≤ (<i>n</i> = 21)	0	0	0	100.0

LDL-C, low-density lipoprotein cholesterol; Non-HDL-C, non-high-density lipoprotein cholesterol. Data are expressed as the percentage of the number of participants being classified into each non-HDL-C group according to levels of LDL-C group. The shaded cells represent the % of non-HDL-C corresponding to the LDL-C management targets + 30 mg/dL, shown in JAS guidelines.

Supplementary Table 1-4. Cross-table between non-HDL-C and LDL-C categories according to the cut-off points of LDL-C based on the JAS guideline for participants with triglyceride ≥ 150 mg/dL (Tsuruoka)

	Non-HDL-C, mg/dL			
	< 150	150-169	170-189	190 ≤
MEN				
LDL-C, mg/dL				
< 120 (<i>n</i> = 158)	72.2	22.8	5.1	0
120-139 (<i>n</i> = 96)	0	52.1	37.5	10.4
140-159 (<i>n</i> = 50)	0	0	54.0	46.0
160 ≤ (<i>n</i> = 60)	0	0	0	100.0
WOMEN				
LDL-C, mg/dL				
< 120 (<i>n</i> = 53)	67.9	30.2	1.9	0
120-139 (<i>n</i> = 40)	0	62.5	32.5	5.0
140-159 (<i>n</i> = 23)	0	0	56.5	43.5
160 ≤ (<i>n</i> = 24)	0	0	0	100.0

LDL-C, low-density lipoprotein cholesterol; Non-HDL-C, non-high-density lipoprotein cholesterol. Data are expressed as the percentage of the number of participants being classified into each non-HDL-C group according to levels of LDL-C group. The shaded cells represent the % of non-HDL-C corresponding to the LDL-C management targets + 30 mg/dL, shown in JAS guidelines.

Supplementary Table 2-1. Cross-table between non-HDL-C and LDL-C categories according to the cut-off points of LDL-C two additional groups based on the JAS guideline for participants with triglyceride < 150 mg/dL (Kobe)

	Non-HDL-C, mg/dL					
	< 130	130-149	150-169	170-189	190-209	210 ≤
MEN						
LDL-C, mg/dL						
< 100 (n = 46)	100.0	0	0	0	0	0
100-119 (n = 80)	71.3	28.8	0	0	0	0
120-139 (n = 91)	0	69.2	30.8	0	0	0
140-159 (n = 47)	0	0	57.5	42.6	0	0
160-179 (n = 23)	0	0	0	60.9	39.1	0
180 ≤ (n = 6)	0	0	0	0	66.7	33.3
WOMEN						
LDL-C, mg/dL						
< 100 (n = 86)	100.0	0	0	0	0	0
100-119 (n = 151)	81.5	18.5	0	0	0	0
120-139 (n = 206)	1.9	71.4	26.7	0	0	0
140-159 (n = 159)	0	3.8	62.9	33.3	0	0
160-179 (n = 88)	0	0	1.1	62.5	36.4	0
180 ≤ (n = 35)	0	0	0	0	54.3	45.7

LDL-C, low-density lipoprotein cholesterol; Non-HDL-C, non-high-density lipoprotein cholesterol. Data are expressed as the percentage of the number of participants being classified into each non-HDL-C group according to levels of LDL-C group. The shaded cells represent the % of non-HDL-C corresponding to the LDL-C management targets + 30 mg/dL, shown in JAS guidelines.

Supplementary Table 2-2. Cross-table between non-HDL-C and LDL-C categories according to the cut-off points of LDL-C two additional groups based on the JAS guideline for participants with triglyceride ≥ 150 mg/dL (Kobe)

	Non-HDL-C, mg/dL					
	< 130	130-149	150-169	170-189	190-209	210 ≤
MEN						
LDL-C, mg/dL						
< 100 (n = 10)	70.0	30.0	0	0	0	0
100-119 (n = 14)	0	64.3	28.6	7.1	0	0
120-139 (n = 8)	0	0	50.0	50.0	0	0
140-159 (n = 9)	0	0	0	88.9	11.1	0
160-179 (n = 3)	0	0	0	0	33.3	66.7
180 ≤ (n = 2)	0	0	0	0	0	100.0
WOMEN						
LDL-C, mg/dL						
< 100 (n = 3)	33.3	66.7	0	0	0	0
100-119 (n = 4)	0	75.0	0	25.0	0	0
120-139 (n = 8)	0	0	62.5	37.5	0	0
140-159 (n = 8)	0	0	0	75.0	25.0	0
160-179 (n = 13)	0	0	0	0	76.9	23.1
180 ≤ (n = 8)	0	0	0	0	0	100.0

LDL-C, low-density lipoprotein cholesterol; Non-HDL-C, non-high-density lipoprotein cholesterol. Data are expressed as the percentage of the number of participants being classified into each non-HDL-C group according to levels of LDL-C group. The shaded cells represent the % of non-HDL-C corresponding to the LDL-C management targets + 30 mg/dL, shown in JAS guidelines.

Supplementary Table 2-3. Cross-table between non-HDL-C and LDL-C categories according to the cut-off points of LDL-C two additional groups based on the JAS guideline for participants with triglyceride < 150 mg/dL (Tsuruoka)

	Non-HDL-C, mg/dL					
	< 130	130-149	150-169	170-189	190-209	210 ≤
MEN						
LDL-C, mg/dL						
< 100 (<i>n</i> = 317)	100.0	0	0	0	0	0
100-119 (<i>n</i> = 291)	67.0	33.0	0	0	0	0
120-139 (<i>n</i> = 262)	0.4	62.6	37.0	0	0	0
140-159 (<i>n</i> = 123)	0	1.6	52.0	46.3	0	0
160-179 (<i>n</i> = 52)	0	0	0	48.1	51.9	0
180 ≤ (<i>n</i> = 23)	0	0	0	0	52.2	47.8
WOMEN						
LDL-C, mg/dL						
< 100 (<i>n</i> = 239)	100.0	0	0	0	0	0
100-119 (<i>n</i> = 339)	66.7	33.3	0	0	0	0
120-139 (<i>n</i> = 369)	0.8	63.4	35.8	0	0	0
140-159 (<i>n</i> = 284)	0	0.4	68.7	31.0	0	0
160-179 (<i>n</i> = 130)	0	0	0.8	68.5	30.8	0
180 ≤ (<i>n</i> = 69)	0	0	0	1.5	30.4	68.1

LDL-C, low-density lipoprotein cholesterol; Non-HDL-C, non-high-density lipoprotein cholesterol. Data are expressed as the percentage of the number of participants being classified into each non-HDL-C group according to levels of LDL-C group. The shaded cells represent the % of non-HDL-C corresponding to the LDL-C management targets + 30 mg/dL, shown in JAS guidelines.

Supplementary Table 2-4. Cross-table between non-HDL-C and LDL-C categories according to the cut-off points of LDL-C two additional groups based on the JAS guideline for participants with triglyceride ≥ 150 mg/dL (Tsuruoka)

	Non-HDL-C, mg/dL					
	< 130	130-149	150-169	170-189	190-209	210 ≤
MEN						
LDL-C, mg/dL						
< 100 (<i>n</i> = 92)	62.0	27.2	10.9	0	0	0
100-119 (<i>n</i> = 66)	0	48.5	39.4	12.1	0	0
120-139 (<i>n</i> = 96)	0	0	52.1	37.5	8.3	2.1
140-159 (<i>n</i> = 50)	0	0	0	54.0	40.0	6.0
160-179 (<i>n</i> = 43)	0	0	0	0	53.5	46.5
180 ≤ (<i>n</i> = 17)	0	0	0	0	0	100.0
WOMEN						
LDL-C, mg/dL						
< 100 (<i>n</i> = 18)	55.6	44.4	0	0	0	0
100-119 (<i>n</i> = 35)	0	51.4	45.7	2.9	0	0
120-139 (<i>n</i> = 40)	0	0	62.5	32.5	2.5	2.5
140-159 (<i>n</i> = 23)	0	0	0	56.5	34.8	8.7
160-179 (<i>n</i> = 17)	0	0	0	0	76.5	23.5
180 ≤ (<i>n</i> = 7)	0	0	0	0	0	100.0

LDL-C, low-density lipoprotein cholesterol; Non-HDL-C, non-high-density lipoprotein cholesterol. Data are expressed as the percentage of the number of participants being classified into each non-HDL-C group according to levels of LDL-C group. The shaded cells represent the % of non-HDL-C corresponding to the LDL-C management targets + 30 mg/dL, shown in JAS guidelines.