Evaluation of High-density Lipoprotein Cholesterol Levels in Japanese Women

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(Received June 1, 2012; Accepted July 17, 2012)

Objective: The aim of the present study was to clarify the significance of high levels of high-density lipoprotein cholesterol (HDL-C) in Japanese women receiving an annual health check-up.
Methods: A total of 1879 women who were not taking medication for hypertension, diabetes or dyslipidemia, with no prior history of ischemic heart disease, cerebrovascular disease or chronic renal failure were analyzed. First, the association between HDL-C and homeostasis model assessment of insulin resistance (HOMA-IR) was studied. Next, the association between HDL-C and the number of metabolic syndrome (MetS) risk factors, including HOMA-IR, was determined. In addition, clinical parameters including HOMA-IR, number of MetS risk factors, smoking, exercise, and alcohol consumption habits were compared according to HDL-C level.
Results: HOMA-IR was lower in subjects with elevated HDL-C. Additionally, a lower body mass index (BMI), waist circumference (WC), fasting plasma glucose (FPG), and triglycerides (TG) were observed in subjects with higher HDL-C. Moreover, the proportion of subjects who were obese, or those who had high FPG, high TG, and a high number of MetS risk factors was lower in subjects with higher HDL-C. Both obesity and smoking were associated with reduced HDL-C levels. Increasing levels of alcohol consumption, from < 25 g/day, to 25 –< 50 g/day, to 50 –< 75 g/day, were associated with a progressive increase in HDL-C level, but a progressive reduction in HOMA-IR. However, this apparent benefit of alcohol intake on HDL-C and HOMA-IR disappeared in subjects who drank ≥ 75 g/day.
Conclusions: Female subjects who were not obese, did not smoke, and drank < 75 g alcohol/day had elevated HDL-C levels, which were associated with improved insulin sensitivity. Drinking alcohol in excess of 75 g/day appeared to provide no advantages in terms of HDL-C or HOMA-IR levels. Thus, it might be important for females to keep their alcohol intake below 75 g/day.

Key words: annual health check-ups, high-density lipoprotein cholesterol, insulin resistance, lifestyle habit

INTRODUCTION

Metabolic syndrome (MetS) is comprised of four major components, obesity, elevated blood pressure, elevated blood glucose, and dyslipidemia. The two lipid parameters of MetS are triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C). Although HDL-C reference values are not uniform across different populations, gender, race, among others, low HDL-C is generally considered a risk factor. For instance, a low level of HDL-C has been defined as < 40 mg/dl in both men and women according to the 2005 Japanese criteria [1], < 35 mg/dl in men and < 39 mg/dl in women according to the 1998 World Health Organization (WHO) criteria [2], and < 40 mg/dl in men and < 50 mg/dl in women by other criteria [3–6]. However, little information is available concerning the atherogenicity of high HDL-C in MetS.

The incidence of coronary artery disease including angina pectoris and myocardial infarction is lower in subjects with high levels of HDL-C [7–11], leading HDL-C to be termed "good cholesterol." The Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP ATPIII) [3] defines high HDL-C as ≥ 60 mg/dl, which is a negative risk factor for coronary artery disease.

In Japan, according to the primary hyperlipidemia research working group of the Ministry of Health, Labor and Welfare (MHLW) [12], an HDL-C ≥ 100 mg/dl was defined as high HDL-C or as familial hyper-HDL cholesterolemia when a clear family history was present. Causes of high HDL-C include cholesterol ester transfer protein (CETP) deficiency and excessive alcohol intake. Among cases with high HDL-C as a result of CETP deficiency, no clear consensus exists as to whether high HDL-C is protective against arteriosclerosis. In CETP-deficient patients, consideration regarding lifestyle habits is also important.

We previously studied the relationship between HDL-C and insulin resistance in 2129 men undergoing an annual health check-up, revealing an inverse association between HDL-C and HOMA-IR among non-MetS subjects. However, in MetS subjects, the HOMA-IR increased when HDL-C was ≥ 90 mg/dl. Since these results were mainly explained by heavy drinking, it is important to monitor the amount of alcohol consumption in persons with high HDL-C levels [13]. However,

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Table 1 Profile of subjects

Age (years)	47.9 ± 11.2
BMI (kg/m^2)	21.6 ± 3.1
WC (cm)	78.1 ± 8.9
SBP (mmHg)	112.8 ± 17.2
DBP (mmHg)	69.8 ± 11.5
FPG (mg/dl)	95.7 ± 15.8
F-IRI (μU/ml)	5.72 ± 3.78
HOMA-IR	1.39 ± 1.06
LDL-C (mg/dl)	118.3 ± 33.1
HDL-C (mg/dl)	72.4 ± 16.3
TG (mg/dl)	79.2 ± 42.6
AST (U/l)	19.7 ± 7.3
ALT (U/l)	17.2 ± 9.7
γ-GT (U/l)	23.3 ± 37.4

Mean ± SD

it is not clear whether the same relationships exist in women.

The aim of this study was to clarify the significance of high HDL-C levels in Japanese women receiving an annual health check-up. The evaluation focused on insulin resistance, a major component of MetS.

METHODS

Subjects

A total of 2201 women underwent annual health check-ups at the Health Evaluation and Promotion Center at Tokai University Hachioji Hospital between April 2007 and January 2010. After exclusion of women on medication for hypertension, diabetes or dyslipidemia, and those with a prior history of ischemic heart disease, cerebrovascular disease or chronic renal failure, 1879 women were included in this study.

Measurements and diagnosis of MetS

Blood pressure was measured with an automatic blood pressure monitor (TM-2655P; A&D, Tokyo, Japan) positioned on the upper right arm with the patient in a sitting position. Blood samples were collected in the early morning after overnight fasting. Waist circumference (WC) was measured at the level of the umbilicus while standing, and during slight expiration. Insulin was measured by fluorescence enzyme immunoassay (FEIA; ST AIA-PACK IRI; Toso, Tokyo, Japan). HOMA-IR was calculated using the following equation:

(fasting plasma glucose × fasting insulin) / 405 [14]. Low-density lipoprotein cholesterol (LDL-C), HDL-C, and TG levels were measured by visible spectrophotometry (Determiner L LDL-C, Determiner L HDL-C, Determiner L TG II, respectively; Kyowa Medex, Tokyo, Japan). Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transpeptidase (γ-GT) were measured following the standardized procedure outlined by the Japan Society of Clinical Chemistry (JSCC). All measurements were included in the routine health-check examinations. Verbal consent was obtained from subjects to use their anonymized health records for analysis. The study protocol was approved by the institutional ethics committee of the Tokai University School of Medicine.

MetS was diagnosed according to the criteria set forth by the International Diabetes Federation (IDF), American Heart Association (AHA), and National Heart, Lung, and Blood Institute (NHLBI) [6]. Specifically, MetS was diagnosed if subjects possessed at least three of the following five criteria: waist circumference ≥ 90 cm, elevated blood pressure (systolic ≥ 130 mmHg or diastolic ≥ 85 mmHg), fasting plasma glucose ≥ 100 mg/dl, triglycerides ≥ 150 mg/dl, and HDL-C < 50 mg/dl.

Statistical analysis

Initially, the association between HDL-C with HOMA-IR was analyzed by an analysis of variance (ANOVA) and Scheffe's multiple comparison test. Next, the association between HDL-C and the number of MetS risk factors was determined using two-way ANOVA and Scheffe's multiple comparison tests. In addition, clinical parameters including HOMA-IR, number of MetS risk factors, and smoking, exercise and alcohol consumption habits were compared according to HDL-C level. Subjects were classified as a smoker or non-smoker. Additionally, those who exercised for ≥ 30 min/day more than twice a week were classified as habitual exercisers. Alcohol consumption was surveyed by asking how many units of sake were consumed in a day, where 1 unit (180 ml) of sake was taken to be the equivalent to 25 g of alcohol. The comparison of mean values between two groups was performed by *t*-test, while comparison of mean values among more than two groups was performed by Scheffe's or Dunnett's multiple comparison tests. The Mantel-extension method [15] was used as a trend test. Ridit analysis [16] was used for comparing the distribution of alcohol consumption. Finally, multivariate analysis was used with HDL-C as a response variable and BMI, smoking, and habitual exercise as dependent variables. Variable selection was performed by stepwise procedure, and a dummy-variable model was designed after BMI and alcohol consumption were categorized. Statistical analysis was performed using SAS software version 9.2 (SAS Institute Inc., Cary, NC, USA). $p < 0.05$ was considered significant.

RESULTS

Subject characteristics are outlined in Table 1. The mean age of subjects was 47.9 years and the mean HDL-C level was 72.4 mg/dl.

Fig. 1 illustrates the comparison of HOMA-IR values between subjects stratified by HDL-C levels. One hundred twenty-nine (5.9%) study subjects had an HDL-C level < 50 mg/dl, whereas 126 subjects (5.7%) had an HDL-C level ≥ 100 mg/dl. Increasing HDL-C levels were correlated with lower HOMA-IR. Scheffe's multiple comparison test revealed that the HOMA-IR values in subjects with HDL-C < 50 mg/dl or between 50 and 59 mg/dl were significantly higher than those of subjects with any level higher than 59 mg/dl. The HOMA-IR levels among subjects with 60 to 69 mg/dl of HDL-C were significantly higher than those of subjects with an HDL-C level ≥ 100 mg/dl. The majority of subjects (58.4%) had no MetS risk factors, meanwhile 471 subjects (25.1%) had one risk factor, 204 subjects

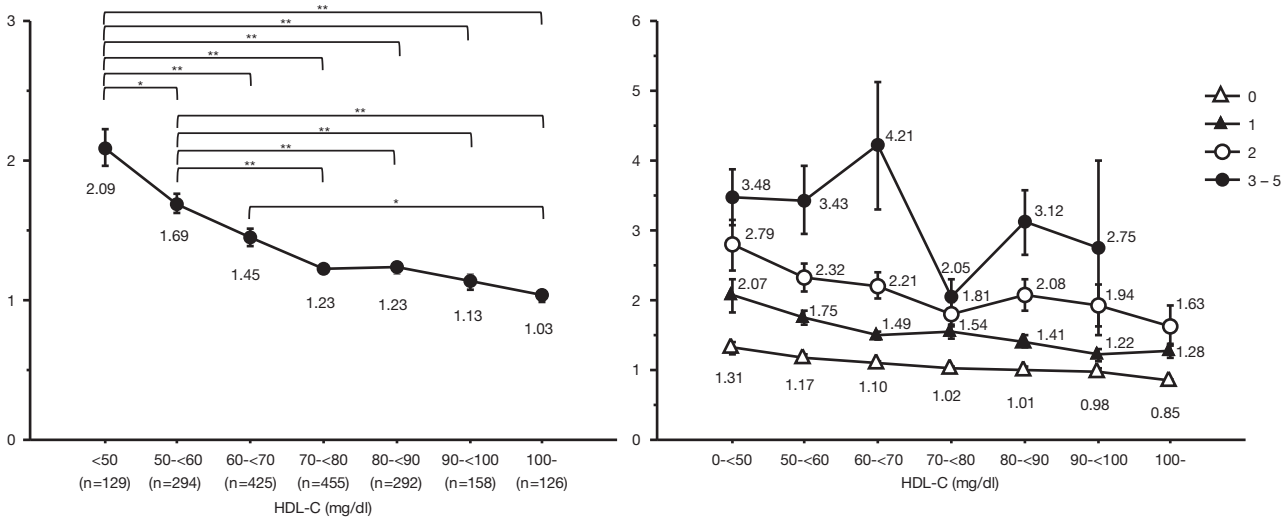

Fig. 1 HOMA-IR stratified by HDL-C levels and number of MetS risk factors.
Mean ± SE (left panel: all subjects; right panel: by number of MetS risk factors)
**: $p < 0.01$, *: $p < 0.05$ (Scheffe's multiple comparison test)
HOMA-IR, homeostasis model assessment of insulin resistance, HDL-C, high-density lipoprotein cholesterol

(10.9%) had two, 81 (4.3%) had three, 22 (1.2%) had four, and four (0.2%) had five. Increasing HDL-C levels were associated with lower HOMA-IR values regardless of the number of MetS risk factors.

Table 2 shows the clinical parameters of subjects stratified by HDL-C levels. Scheffe's multiple comparison tests revealed that BMI, WC, FPG, TG and HOMA-IR were significantly different between the groups. The general trend observed suggested that subjects with higher HDL-C had lower levels of clinical parameters.

Table 3 lists the abnormality rates of clinical parameters and number of MetS risk factors of subjects stratified by HDL-C levels. The proportion of subjects with BMI ≥ 25 kg/m^2, WC ≥ 90 cm, FPG ≥ 100 mg/dl, TG ≥ 150 mg/dl, or HOMA-IR ≥ 1.7 decreased as HDL-C levels increased. In addition, the number of MetS risk factors was lower in subjects with higher HDL-C.

Table 4 lists the distribution of smoking, exercise habits, and daily alcohol consumption of subjects stratified by HDL-C levels. Although the proportion of subjects who smoked was inversely associated with HDL-C in < 100 mg/dl, the rate was slightly elevated in subjects with HDL-C ≥ 100 mg/dl. We found no apparent association between exercise habit and HDL-C level. The proportion of subjects who drank 25−75 g of alcohol per day was positively correlated with HDL-C level. Less than 2% of subjects in all groups drank ≥ 75 g/day.

Fig. 2 illustrates the HDL-C and HOMA-IR values in subjects according to BMI, smoking, exercise, and alcohol consumption. BMI was inversely correlated with HDL-C with increasing HOMA-IR. There was no significant difference between exercise habit and HDL-C or HOMA-IR. When HDL-C and HOMA-IR levels were compared to non-drinkers, the HDL-C level was significantly higher in subjects who drank 25−50 g/day and 50−75 g/day. Conversely, HOMA-IR was significantly lower in subjects who drank less than 25, 25 to 50, and 50−75 g/day. However, neither HDL-C nor HOMA-IR was significantly different in subjects who drank ≥ 75 g/day.

Table 5 outlines the results of the multivariate regression analysis. A dummy-variable logistic model was used for BMI and alcohol consumption (references: BMI < 22 kg/m^2, non-drinker for alcohol consumption). Exercise habit was not selected by a stepwise procedure. Among smokers, HDL-C level decreased as BMI increased. Although HDL-C positively correlated with an alcohol consumption of < 75 g/day, the correlation was not significant in subjects who drank ≥ 75 g/day.

DISCUSSION

In this study, we found that HOMA-IR was lower in subjects with elevated HDL-C levels. A lower BMI, WC, FPG and TG were also observed in subjects with higher HDL-C. Moreover, the proportion of patients who were obese, or those who had high FPG, high TG, and a high number of MetS risk factors decreased in subjects with higher HDL-C. In terms of lifestyle factors, HDL-C was decreased by the presence of obesity and smoking. Additionally, while HDL-C was increased in subjects who drank less than 75 g/day, it was not significantly different between subjects who drank ≥ 75 g/day and non-drinkers. Our previous study revealed that HOMA-IR increased in male subjects with MetS and those with HDL-C levels ≥ 90 mg/dl [14]. Since a large proportion of subjects in this category drank ≥ 75 g/day, an unhealthy lifestyle including drinking might have explained these findings. The different results reported in female subjects were likely due to the fact that few drank ≥ 75 g/day. Hence, HDL-C level was not significantly higher among this small group of females who drank ≥ 75 g/day compared to non-drinkers.

In the present study, 126 subjects (6.7%) had an HDL-C level of 100 mg/dl and 19 subjects (1.0%) had an HDL-C level < 40 mg/dl. According to the 5th Basic Survey of Cardiovascular Diseases conducted in 2000

Table 2 Clinical parameters stratified by HDL-C levels

	HDL-C (mg/dl)					
	< 50 (n = 129)	50 – < 60 (n = 294)	60 – < 70 (n = 425)	70 – < 80 (n = 455)	80 - < 90 (n = 292)	90 – < 100 (n = 158)	100– (n = 126)
Age (years)	48.7 ± 11.5	47.6 ± 11.4	48.2 ± 11.4	46.6 ± 11.1	47.9 ± 10.7	48.7 ± 11.3	49.9 ± 10.7
BMI (kg/m^2)	23.6 ± 4.0	23.3 ± 3.6	21.8 ± 2.8$^{**, \#\#}$	21.0 ± 2.5$^{**, \#\#, \$}$	20.9 ± 2.4$^{**, \#\#, \$\$}$	20.7 ± 2.6$^{**, \#\#, \$}$	19.9 ± 2.1$^{**, \#\#, \$\$, +}$
WC (cm)	83.7 ± 9.3	81.9 ± 9.5	79.2 ± 8.6$^{**, \#\#}$	76.8 ± 8.2$^{**, \#\#, \$\$}$	75.8 ± 7.5$^{**, \#\#, \$\$}$	75.9 ± 8.5$^{**, \#\#, \$\$}$	73.3 ± 6.7$^{**, \#\#, \$\$, ++}$
SBP (mmHg)	116.7 ± 18.2	114.2 ± 18.2	111.7 ± 17.0	111.6 ± 16.6	113.3 ± 17.1	111.9 ± 16.5	113.3 ± 16.8
DBP (mmHg)	71.5 ± 11.2	70.2 ± 11.8	69.3 ± 11.4	69.1 ± 11.6	69.6 ± 11.3	70.2 ± 11.9	70.9 ± 11.3
FPG (mg/dl)	101.1 ± 24.1	99.7 ± 24.9	95.6 ± 13.5	94.3 ± 13.1$^{**, \#\#}$	94.1 ± 8.7$^{**, \#\#}$	92.6 ± 8.5$^{**, \#\#}$	93.8 ± 8.3**
TG (mg/dl)	121.2 ± 63.8	96.9 ± 52.5**	81.8 ± 37.0$^{**, \#\#}$	73.2 ± 36.6$^{**, \#\#}$	65.7 ± 28.8$^{**, \#\#, \$\$}$	64.0 ± 26.6$^{**, \#\#, \$\$}$	57.9 ± 20.7$^{**, \#\#, \$\$, +}$
HOMA-IR	2.09 ± 1.48	1.69 ± 1.27*	1.45 ± 1.27**	1.23 ± 0.77$^{**, \#\#}$	1.23 ± 0.78$^{**, \#\#}$	1.13 ± 0.67$^{**, \#\#}$	1.03 ± 0.53$^{**, \#\#, \$}$

Mean ± SD
$^{\#\#}p < 0.01$, $^{\#}p < 0.05$ (vs. HDL-C 50 – < 60 mg/dl), $^{\$\$}p < .01$, $^{\$}p < .05$ (vs. HDL-C 60 – < 70 mg/dl), $^{++}p < .01$, $^{+}p < .05$ (vs. HDL-C 70 – < 80 mg/dl) by Scheffe's multiple comparison test.

[16], an HDL-C level ≥ 100 mg/dl was observed among 1.2% of the sample (men 0.7%, women 1.6%) and an HDL-C level < 40 mg/dl was observed among 11.0% of the sample (men 17.3%, women 6.6%). By comparison, the prevalence of HDL-C ≥ 100 mg/dl in the present study was slightly higher and the prevalence of HDL-C < 40 mg/dl was lower. When selecting our population for analysis, those on medication for hypertension, diabetes or dyslipidemia, which are known risk factors for cardiovascular disease, and those who already had macrovascular disease were excluded. Therefore, the proportion of subjects with low HDL-C was relatively low. In addition, we recently reported that HDL-C levels differed significantly by sex. Indeed, HDL-C level was 10 mg/dl higher in female than in male subjects, even after adjustment for age, exercise habit, and BMI in healthy Japanese subjects [17].

Drinking moderate amounts of alcohol (30–40 g/day) can increase HDL-C levels and decrease CHD risk independent of other factors [18, 19]. In addition, drinking 30–40 g/day of alcohol for 3 weeks has been reported to increase HDL-C levels by a maximum of 12% regardless of the type of alcohol [20]. General recommendations suggest no more than 2 and 1 glasses/day of alcohol for men and women, respectively [21]. Additionally, regular alcohol consumption

Table 3 Abnormality rates and number of MetS risks stratified by HDL-C levels

	HDL-C (mg/dl)							Trend[$]
	< 50 (n = 129)	50 − < 60 (n = 294)	60 − < 70 (n = 425)	70 − < 80 (n = 455)	80 − < 90 (n = 292)	90 − < 100 (n = 158)	100− (n = 126)	*p*
BMI ≧ 25 kg/m^2	37 (28.7%)	79 (26.9%)	54 (12.7%)	34 (7.5%)	16 (5.5%)	8 (5.1%)	1 (0.8%)	< 0.01
WC ≧ 90 cm	29 (22.5%)	53 (18.0%)	47 (11.1%)	29 (6.4%)	16 (5.5%)	10 (6.3%)	2 (1.6%)	< 0.01
SBP ≧ 130 mmHg	30 (23.3%)	57 (19.4%)	60 (14.1%)	65 (14.3%)	47 (16.1%)	23 (14.6%)	24 (19.0%)	NS
DBP ≧ 85 mmHg	14 (10.9%)	37 (12.6%)	44 (10.4%)	43 (9.5%)	21 (7.2%)	22 (13.9%)	16 (12.7%)	NS
FPG ≧ 100 mg/dl	47 (36.4%)	92 (31.3%)	101 (23.8%)	87 (19.1%)	58 (19.9%)	23 (14.6%)	27 (21.4%)	< 0.01
TG ≧ 150 mg/dl	30 (23.3%)	39 (13.3%)	26 (6.1%)	18 (4.0%)	7 (2.4%)	3 (1.9%)	0 (0.0%)	< 0.01
HOMA-IR ≧ 1.7	67 (51.9%)	112 (38.1%)	113 (26.6%)	76 (16.7%)	56 (19.2%)	26 (16.5%)	12 (9.5%)	< 0.01
MetS risk (WC, BP, FPG, TG, HDL-C)								
0	0 (0.0%)	147 (50.0%)	260 (61.2%)	305 (67.0%)	196 (67.1%)	110 (69.6%)	79 (62.7%)	
1	51 (39.5%)	78 (26.5%)	105 (24.7%)	102 (22.4%)	65 (22.3%)	32 (20.3%)	38 (30.2%)	
2	36 (27.9%)	43 (14.6%)	40 (9.4%)	37 (8.1%)	25 (8.6%)	14 (8.9%)	9 (7.1%)	
3	26 (20.2%)	19 (6.5%)	19 (4.5%)	11 (2.4%)	5 (1.7%)	1 (0.6%)	0 (0.0%)	
4	12 (9.3%)	7 (2.4%)	1 (0.2%)	0 (0.0%)	1 (0.3%)	1 (0.6%)	0 (0.0%)	
5	4 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
mean ± SD	2.1 ± 1.1	0.8 ± 1.0**	0.6 ± 0.9$^{**,\#\#}$	0.5 ± 0.7$^{**,\#\#}$	0.5 ± 0.8$^{**,\#\#}$	0.4 ± 0.7$^{**,\#\#}$	0.4 ± 0.6$^{**,\#\#}$	

[$] Trend test by Mantel-extension method (NS: $p > 0.05$)
$^{**}p < 0.01$, $^{*}p < 0.05$ (vs. HDL-C < 50 mg/dl), $^{\#\#}p < .01$, $^{\#}p < .05$ (vs. HDL-C 50 - < 60 mg/dl) by Scheffe's multiple comparison test

Table 4 Lifestyle habits stratified by HDL-C levels

	HDL-C (mg/dl)						
	< 50 (n = 129)	50 − < 60 (n = 294)	60 − < 70 (n = 425)	70 − <80 (n = 455)	80 − < 90 (n = 292)	90 − < 100 (n = 158)	100− (n = 126)
Smoking	24 (18.6%)	47 (16.0%)	48 (11.3%)	55 (12.1%)	23 (7.9%)	8 (5.1%)	14 (11.1%)
Exercise (+)	21 (16.3%)	43 (14.6%)	70 (16.5%)	94 (20.7%)	60 (20.5%)	34 (21.5%)	21 (16.7%)
Alcohol consumption							
Non-drinker	89 (69.0%)	183 (62.2%)	268 (63.1%)	255 (56.0%)	175 (59.9%)	87 (55.1%)	61 (48.4%)
< 25g	37 (28.7%)	100 (34.0%)	141 (33.2%)	175 (38.5%)	100 (34.2%)	58 (36.7%)	43 (34.1%)
25 − < 50g	2 (1.6%)	6 (2.0%)	14 (3.3%)	15 (3.3%)	11 (3.8%)	9 (5.7%)	12 (9.5%)
50 − < 75g	0 (0.0%)	2 (0.7%)	2 (0.5%)	7 (1.5%)	4 (1.4%)	3 (1.9%)	8 (6.3%)
75g−	1 (0.8%)	3 (1.0%)	0 (0.0%)	3 (0.7%)	2 (0.7%)	1 (0.6%)	2 (1.6%)
mean ridit	0.500	0.535*	0.531*	0.568**	0.550**	0.577**	0.624*

$^{**}p < 0.01$, $^{*}p < 0.05$ (vs. HDL-C < 50 mg/dl) by ridit analysis

should not be advised in persons who do not drink. In the present study, HDL-C was 21% higher (71.2 mg/dl vs. 86.1 mg/dl) in subjects who drank 50−75 g/day of alcohol compared to non-drinkers. However, HDL-C was not significantly different among those who drank ≥ 75 g/day of alcohol.

In a meta-analysis of the association between alcohol consumption and MetS, the lowest odds ratios of MetS was observed with an alcohol consumption of < 40 g/day among men and < 20 g/day among women [22]. In a study of 6172 subjects aged 35−75 years who were divided into non-drinkers, and low (< 25 g), moderate-to-high (25 to < 62.5 g) and very high (≥ 62.5 g) daily alcohol consumption groups, the HOMA-IR levels were 2.47, 2.14, 2.27, 2.53, respectively, indicating a U-shaped relationship with alcohol after adjustment for age, sex, smoking, exercise and educational level [23]. We also observed a U-shaped relationship with alcohol consumption in the present study. Indeed, our findings suggest that alcohol consumption ≥ 75 g/day has a negative influence on MetS and HOMA-IR.

In general, weight loss increases HDL-C in overweight or obese subjects [24]. While HDL-C levels decrease slightly during weight loss, they increase by 0.35 mg/dL for every kilogram of weight loss once a stabilized diet is achieved [25]. In overweight and obese persons, a weight loss of 2 kg per month is recommended to achieve a BMI of < 25 kg/m^2 (< 24 kg/m^2 in Asians) [21]. In the present study, HDL-C level was approximately 15 mg/dL lower when subjects with a BMI ≥ 26 kg/m^2 were compared to subjects with a BMI < 22 kg/m^2.

Smoking decreases HDL-C level [26] as a likely consequence of the fact that tobacco smoke causes oxidative stress which leads to HDL dysfunction [27]. Maeda *et al.* reported that smoking cessation increases HDL-C by about 4 mg/dL without any changes in LDL-C or triglycerides [28]. In the present study, nonsmokers

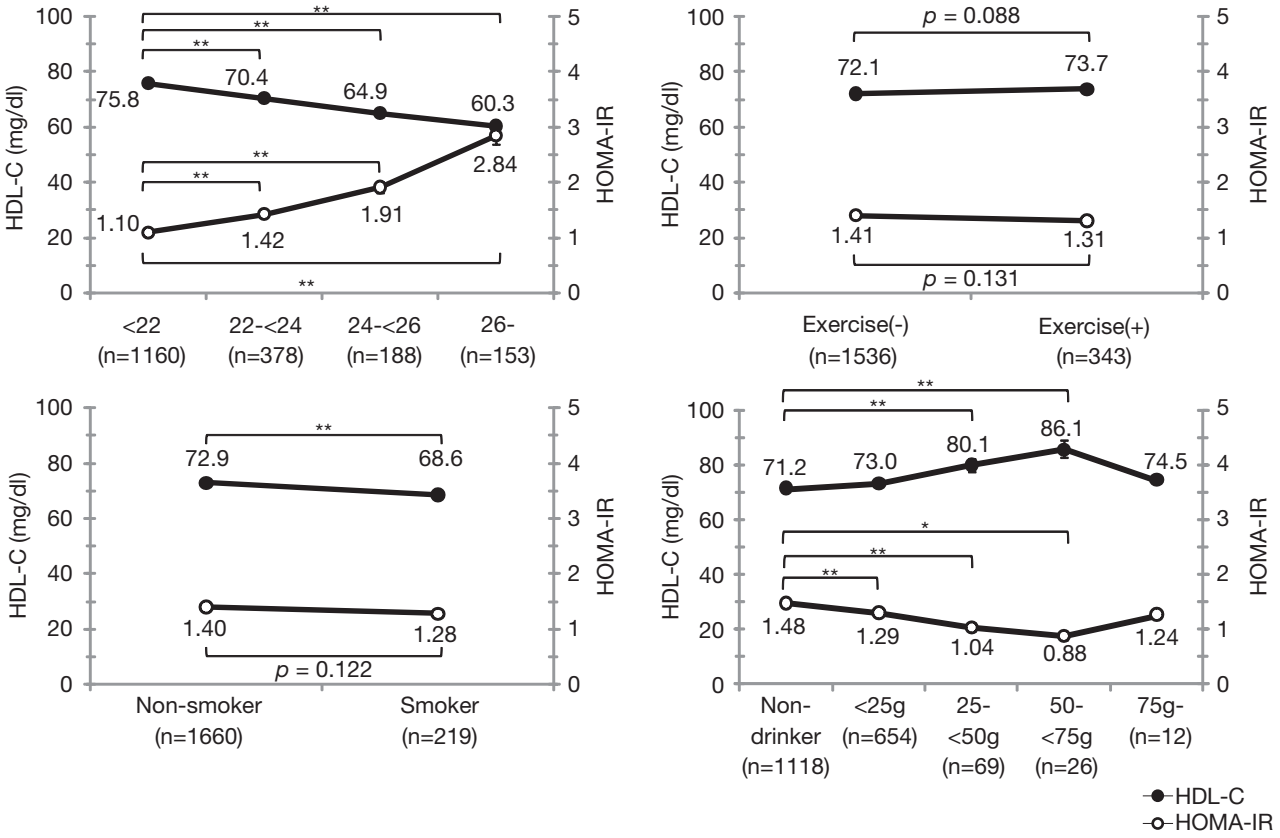

Fig. 2 HDL-C and HOMA-IR stratified by BMI or lifestyle habits.
Mean ± SE, **: $p < 0.01$, *: $p < 0.05$ (unpaired *t*-test, or Dunnett's multiple comparison test)
BMI: body mass index, HDL-C: high-density lipoprotein cholesterol, HOMA-IR: homeostasis model assessment of insulin resistance

Table 5 Results of multivariate regression analyses for HDL-C

Variable		Coefficient	*p*
BMI (kg/m²)	22 – < 24	- 5.253	< 0.001
	24 – < 26	- 10.691	< 0.001
	26 –	- 15.003	< 0.001
Smoking		- 5.327	< 0.001
Alcohol consumption (g/day)	< 25	1.876	0.013
	25 – < 50	8.454	< 0.001
	50 – < 75	15.005	< 0.001
	75 –	5.426	0.227
Constant		75.126	

had a 6% higher HDL-C level by comparison to smokers (72.9 mg/dl vs. 68.6 mg/dl).

Via a variety of mechanisms, regular aerobic exercise increases HDL-C levels by about 5% within 2 months of initiation [29, 30]. More than 30 min of aerobic exercise per session and a total of at least 120 min per week are recommended to increase HDL-C levels [21, 31]. In the present study, subjects who exercised ≥ 30 min/day more than twice a week did not have a significantly higher HDL-C level compared to non-exercisers. A possible explanation for this finding may be a lack of intense exercise among female subjects, which may be necessary to alter lipoprotein levels.

Overall, obesity, smoking and heavy drinking (< 75 g/day of alcohol) had the strongest influence on HDL-C levels in women, whereas exercise seemed not to have much influence, which contrasts with our findings in men. Since the present study was a cross-sectional, a cause-and-effect relationship could not be ascertained.

CONCLUSIONS

Female subjects who were not obese, did not smoke, and drank < 75 g of alcohol per day had elevated HDL-C levels, which were associated with improved insulin sensitivity. However, drinking alcohol in excess of 75 g/day appeared to provide no advantages in terms of HDL-C and HOMA-IR levels. Thus, it might be important for females to keep their alcohol intake below 75 g/day.

ACKNOWLEDGEMENTS

The authors declare no conflicts of interest.

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