# INTERNAL MEDICINE

# Significance of High HDL Cholesterol Levels in Japanese Men with Metabolic Syndrome

Noboru Hiratsuka [1,2], Chizumi Yamada [1], Toshitake Mitsuhashi [1], Fumiyo Inabe [1],
Nami Araida [1] and Eiko Takahashi [1]

## Abstract

**Objective**  The objective was to clarify the significance of high high-density lipoprotein cholesterol (HDL-C) levels in the metabolic syndrome (MetS). The evaluation focused on insulin resistance as an indicator of early-stage MetS.

**Methods and Subjects**  Of 2705 men who first underwent an annual health check-up at Tokai University Hachioji Hospital, 2129 men were included in this study, after exclusion of those on medication for hypertension, diabetes or dyslipidemia, and those with a prior history of ischemic heart disease, cerebrovascular disease or chronic renal failure. MetS risk factors include the following five parameters: waist circumference, blood pressure, plasma glucose, triglycerides and HDL-C. The correlations between HDL-C and number of MetS risks with homeostasis model assessment of insulin resistance (HOMA-IR) were analyzed. HOMA-IR, number of risks, habits of smoking, exercise and drinking alcohol, stratified by HDL-C levels, were compared in MetS subjects.

**Results**  In cases with $\leq 2$ risk factors, the higher the HDL-C, the lower the HOMA-IR. However, with $\geq 3$ risk factors for MetS, the HOMA-IR increased when HDL-C was $\geq 90$ mg/dL. In MetS subjects, the rate of alcohol intake $\geq 75$ g/day was high when HDL-C was $\geq 90$ mg/dL.

**Conclusion**  In MetS subjects with high HDL-C levels, insulin resistance was increased. Therefore, in persons with high HDL-C levels, it is important to monitor the amount of alcohol consumption and reduce alcohol consumption to <75 g/day.

**Key words:** metabolic syndrome, high-density lipoprotein cholesterol, insulin resistance, heavy drinking

## Introduction

Four components included in the diagnostic criteria for the metabolic syndrome (MetS) are obesity, blood pressure, blood glucose and lipids. The two lipid parameters used are triglycerides and high-density lipoprotein cholesterol (HDL-C). Although HDL-C reference values are not uniform, low HDL-C is considered a risk, but the issue of high HDL-C has not been examined. Little information has been available concerning the atherogenicity of high HDL-C in MetS. In the 2005 Japanese criteria, <40 mg/dL in both men and women was defined as a risk factor (1); in the 1998 World Health Organization (WHO) criteria, <35 mg/dL in men and <39 mg/dL in women were defined as risk factors (2); and in other criteria, <40 mg/dL in men and <50 mg/dL in women were defined as risk factors (3-6).

In subjects with high levels of HDL-C, the incidence of coronary artery disease including angina pectoris and myocardial infarction is lower (7-11); thus, HDL-C has been called "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 an HDL-C $\geq 60$ mg/dL as a high HDL-C and a negative risk factor for coronary artery disease.

In Japan, in a Ministry of Health, Labor and Welfare (MHLW)-specified disease "primary hyperlipidemia research

working group" (leader: Tarui S) (12), an HDL-C ≥100 mg/dL was defined as high HDL-C and as familial hyper-HDL cholesterolemia in cases with a clear family history. Causes include cholesterol ester transfer protein (CETP) deficiency and excessive alcohol intake. Maruyama et al (13) reported that CETP activity was ≤75% of normal in 64% of 393 patients with an HDL-C ≥100 mg/dL and in 55% of 231 patients with an HDL-C of 75-99 mg/dL. In Japan, CETP deficiency is often reported as a cause of hyper-HDL cholesterolemia. In cases where high HDL-C is due to CETP deficiency, there is no clear consensus whether high HDL-C is protective against arteriosclerosis and caution about lifestyle habits is also important for CETP deficient patients. As the major HDL apolipoproteins are Apo AI and Apo AII, high HDL-C is often called hyperalphalipoproteinemia (HALP) in Western countries, but HDL-C reference values have not been established.

In addition, with high HDL-C levels, even more important is whether excessive cholesterol in the body can be cleared efficiently; measurement of cholesterol efflux capacity has even been recommended (14). However, this is not a parameter that can generally be measured and the reasons for decreased function are unclear.

In the present study, the objective was to clarify the significance of high HDL-C levels in MetS. The evaluation focused on insulin resistance, an indicator of early-stage MetS, in Japanese men who came for annual health check-ups.

## Materials and Methods

### Subjects

Among 2,705 men who first underwent annual health check-ups at the Health Evaluation and Promotion Center at Tokai University Hachioji Hospital between April 2007 and January 2010, 2,129 men were included in this study after exclusion of those on medication for hypertension, diabetes or dyslipidemia, and those with a prior history of ischemic heart disease, cerebrovascular disease or chronic renal failure. Verbal consent was obtained from the subjects to use the anonymized health records for analysis. This study was designed in compliance with the ethics regulations outlined in the Declaration of Helsinki, and was approved by the director of Tokai University Hachioji Hospital. The privacy of participants was completely protected by unlinkable anonymization.

### Measurements and diagnosis of MetS

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

assessment of insulin resistance (HOMA-IR) was calculated as (fasting plasma glucose × fasting insulin)/405 (15). Low-density lipoprotein cholesterol (LDL-C), HDL-C and triglyceride levels were measured by visible spectrophotometry (Determiner L LDL-C, Determiner L HDL-C, Determiner L TG II; Kyowa Medex, Tokyo, Japan). Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transpeptidase (γ-GT) were measured following the standardized procedure by Japan Society of Clinical Chemistry (JSCC).

All measurements were included in the routine health check examinations. For MetS diagnosis, diagnostic criteria (6) by the International Diabetes Federation (IDF), American Heart Association (AHA), and National Heart, Lung, and Blood Institute (NHLBI) were used. MetS was diagnosed if subjects possessed at least three of the following five criteria: waist circumference ≥85 cm, blood pressure (systolic ≥130 mmHg or diastolic ≥85 mmHg), fasting plasma glucose ≥100 mg/dL, triglycerides ≥150 mg/dL and HDL-C <40 mg/dL.

### Statistical analysis

Data are expressed as mean ± standard deviation or standard error values. The level of statistical significance was $p < 0.05$. Statistical analysis was performed using StatView 5.0J (Statistical Analysis System Inc., Cary, NC, U.S.A.). Initially, the correlation between HDL-C with HOMA-IR was analyzed by analysis of variance (ANOVA) and Scheffe's multiple comparison test. Next, the correlation between HDL-C and the number of MetS risks (0, 1, 2, and ≥3) with HOMA-IR was analyzed by two-way ANOVA and Scheffe's multiple comparison test. Increased waist circumference, elevated blood pressure, elevated fasting glucose, elevated triglycerides and low HDL-C defined by the previously-cited criteria (6) were regarded as MetS risks. In addition, in MetS subjects, clinical parameters including HOMA-IR, number of risks, habits of smoking, exercise and drinking alcohol were compared as stratified by HDL-C level. Smoking was classified as smoker or non-smoker; for exercise, ≥30 min/day more than twice per week was classified as habitual exercise, and for alcohol use, ≥75 g/day was classified as heavy drinking. Alcohol consumption was surveyed by asking how many units of sake were drunk in a day, and 1 unit (180 mL) of sake was calculated as 25 g of alcohol.

## Results

Table 1 shows the subjects' profiles. The mean age was 48.0 years and the mean HDL-C was 57.8 mg/dL. Figure 1 shows the HOMA-IR values by HDL-C levels. HDL-C was <50 mg/dL in 654 subjects (30.7%) and ≥90 mg/dL in 61 subjects (2.9%). For HDL-C <90 mg/dL, the higher the HDL-C, the lower the HOMA-IR, but for HDL-C ≥90 mg/dL, compared to 80-<90 mg/dL, HOMA-IR tended to be increased. Based on Scheffe's multiple comparison test, com-

**Table 1.  Profile of Subjects**

| | |
|---|---|
| Age (years) | 48.0 ± 11.5 |
| BMI (kg/m$^2$) | 23.7 ± 3.1 |
| WC (cm) | 84.7 ± 8.6 |
| SBP (mmHg) | 118.2 ± 16.3 |
| DBP (mmHg) | 76.0 ± 12.3 |
| FPG (mg/dL) | 101.2 ± 14.0 |
| F-IRI (μU/mL) | 6.54 ± 4.38 |
| HOMA-IR | 1.68 ± 1.29 |
| LDL-C (mg/dL) | 124.9 ± 31.1 |
| HDL-C (mg/dL) | 57.8 ± 14.2 |
| TG (mg/dL) | 123.2 ± 81.8 |
| AST (U/L) | 23.1 ± 10.6 |
| ALT (U/L) | 28.0 ± 20.1 |
| γ-GT (U/L) | 47.5 ± 52.6 |
| | Mean ± SD |

**BMI: body mass index, WC: waist circumference, SBP: systolic blood pressure, DBP:diastolic blood pressure, FPG: fasting plasma glucose, F-IRI: fasting immunoreactive insulin, HOMA-IR: homeostasis model assessment of insulin resistance, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, TG: triglyceride, AST: aspartate aminotransferase, ALT: alanine aminotransferase, γ-GT: gamma-glutamyl transpeptidase**



**Figure 1.  HOMA-IR stratified by HDL-C levels and number of risks. Mean±SE (Upper panel: All subjects; Lower panel: By number of risks). \*\*: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**

pared to HDL-C <50 mg/dL, there were significant differences in HOMA-IR at all other HDL-C levels. Compared to HDL-C 50-59 mg/dL, there were significant differences in HOMA-IR at the other HDL-C levels, except for HDL-C ≥90 mg/dL.

The number of risk factors was zero in 541 subjects (25.4%), one in 569 subjects (26.7%), two in 522 subjects (24.5%), three in 324 subjects (15.2%), four in 159 subjects (7.5%) and five in 14 subjects (0.7%). With HOMA-IR as the dependent variable and HDL-C level and number of risks as independent variables, the results of two-way ANOVA showed that HDL-C level (p<0.001) and number of risks (p<0.001) both strongly influenced HOMA-IR, and an interaction existed between them (p=0.0064). In MetS subjects with ≥3 risks, the higher the HDL-C, the lower was the HOMA-IR for HDL-C <90 mg/dL, but HOMA-IR tended to increase for HDL-C ≥90 mg/dL.

Table 2 shows the clinical parameters and number of risks stratified by HDL-C levels in MetS subjects. A total of 497 subjects (23.3%) had MetS. The number of subjects according to HDL-C level was: <50, 254 subjects; 50-59, 132 subjects; 60-69, 67 subjects; 70-79, 25 subjects; 80-89, 8 subjects; and ≥90, 11 subjects. Based on Scheffe's multiple comparison test, there were significant differences for BMI, systolic blood pressure, diastolic blood pressure and age. For blood pressure, with HDL-C ≥90 mg/dL, the values
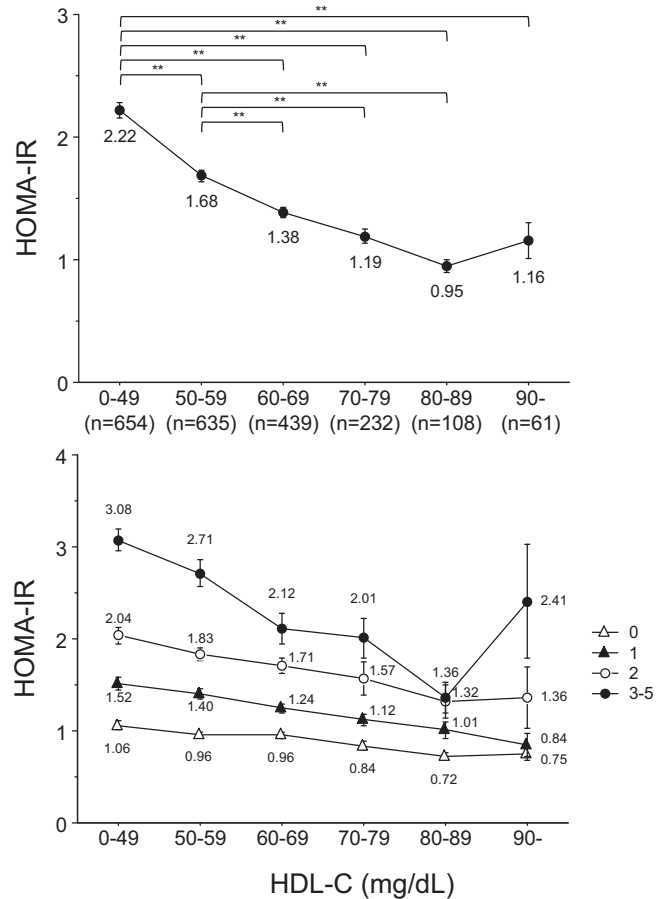
were higher (for systolic blood pressure, compared to HDL-C <50 mg/dL; for diastolic blood pressure, compared to HDL-C levels <70 mg/dL; there were significant differences). In addition, although the differences were not significant, fasting plasma glucose was the highest with an of HDL-C ≥90 mg/dL.

Figure 2 shows habits of smoking, exercise and drinking alcohol in subjects with MetS stratified by HDL-C levels. The proportions of subjects who smoked, habitually exercised (≥30 min/day more than twice per week) and drank alcohol heavily (≥75 g/day) were calculated. The proportion of smokers and the proportion of subjects who exercised ≥30 min/day at least twice a week showed no definite trends according to HDL-C levels. The proportion of subjects who drank ≥75 g/day of alcohol was <10% for HDL-C <80 mg/dL, 12.5% for HDL-C 80-89 mg/dL and increased to 45.5% for HDL-C ≥90 mg/dL. Moreover, the proportion of subjects who did not drink alcohol or drank <25 g/day of alcohol was ≥50% for HDL-C <80 mg/dL (<50, 50-59, 60-69, 70-79, and 80-89; 84.3%, 65.9%, 68.7%, 52.0%, and 62.5% respectively), in contrast to 27.3% for HDL-C ≥90 mg/dL.

**Table 2.   Clinical Parameters Stratified by HDL-C Levels in MetS Subjects**

| | HDL-C (mg/dL) | | | | | |
|---|---|---|---|---|---|---|
| | 0-49 | 50-59 | 60-69 | 70-79 | 80-89 | 90- |
| | (n=254) | (n=132) | (n=67) | (n=25) | (n=8) | (n=11) |
| Age (years) | 48.8 ± 10.7 | 50.8 ± 10.1 | 54.2 ± 9.4* | 54.5 ± 10.5 | 55.7 ± 8.7 | 56.3 ± 10.1 |
| BMI (kg/m$^2$) | 26.9 ± 3.3 | 26.6 ± 3.1 | 25.3 ± 2.7* | 25.1 ± 1.9 | 24.6 ± 2.9 | 25.2 ± 2.8 |
| WC (cm) | 93.3 ± 7.5 | 92.8 ± 6.6 | 90.6 ± 6.9 | 90.4 ± 4.8 | 91.4 ± 4.9 | 89.8 ± 6.6 |
| SBP (mmHg) | 128.1 ± 17.9 | 134.1 ± 14.8* | 134.0 ± 13.3 | 136.6 ± 16.4 | 129.9 ± 14.9 | 145.1 ± 19.3** |
| DBP (mmHg) | 82.6 ± 11.8 | 87.0 ± 11.0* | 86.8 ± 9.0 | 90.2 ± 12.6 | 85.4 ± 11.5 | 100.5 ± 9.8**,#,$ |
| FPG (mg/dL) | 110.6 ± 20.6 | 108.9 ± 14.8 | 111.9 ± 16.1 | 109.6 ± 6.7 | 111.1 ± 7.7 | 126.8 ± 31.2 |
| TG (mg/dL) | 203.9 ± 103.9 | 197.8 ± 103.0 | 171.7 ± 91.2 | 150.6 ± 64.6 | 113.9 ± 50.4 | 145.9 ± 74.3 |
| Metabolic risk | 3.5 ± 0.6 | 3.3 ± 0.5 | 3.2 ± 0.4 | 3.2 ± 0.4 | 3.0 ± 0.0 | 3.5 ± 0.5 |
| HOMA-IR | 3.1 ± 1.9 | 2.7 ± 1.7 | 2.1 ± 1.4 | 2.0 ± 1.1 | 1.4 ± 0.5 | 2.4 ± 2.0 |

Mean±SD

**:$p<0.01$, *:$p<0.05$ (vs. 0-49 mg/dL), ##:$p<0.01$, #:$p<0.05$ (vs. 50-59 mg/dL), $$:$p<0.01$, $:$p<0.05$ (vs. 60-69 mg/dL). BMI: body mass index, WC: waist circumference, SBP: systolic blood pressure, DBP: diastolic blood pressure, FPG: fasting plasma glucose, TG: triglyceride, HDL-C: high-density lipoprotein cholesterol
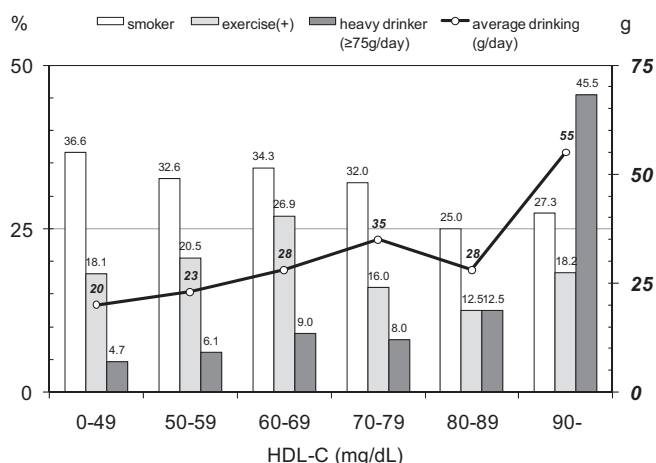


**Figure 2.   Lifestyle habits stratified by HDL-C levels in MetS subjects. HDL-C: high-density lipoprotein cholesterol, MetS: metabolic syndrome**

Figure 3 shows the HDL-C values in all subjects based on smoking, exercise, and alcohol consumption. For the non-smoker group and the habitual exercise group, HDL-C was significantly higher compared to the respective other groups. For alcohol consumption, between non-drinkers and other groups, and between the <25 g/day group and other groups, there were significant differences.

Table 3 shows the clinical parameters including HOMA-IR in all subjects stratified by alcohol consumption. Systolic and diastolic blood pressures were increased with alcohol consumption ≥50 g. The number of risks with alcohol consumption ≥75 g was increased. HOMA-IR showed a U-shaped pattern: it was highest in non-drinkers, lowest for alcohol consumption 50-74 g/day and increased for alcohol consumption ≥75 g. The proportion of MetS was 22.0% for non-drinkers, 22.9% for <25 g/day group, 22.9% for 25-49 g, 26.6% for 50-74 g, 31.5% for ≥75 g. We confirmed through questionnaire and interview by nurses that those with alcohol dependence, chronic liver dysfunction or chronic pancreatitis were not included in 108 subjects who drank ≥75 g/day of alcohol.

Figure 4 shows the HOMA-IR values based on presence or absence of MetS and stratified by HDL-C levels and alcohol consumption. In non-MetS subjects, the results of two-way ANOVA showed that HDL-C levels strongly influenced HOMA-IR ($p<0.001$) and the amount of alcohol was unrelated ($p=0.1405$). In MetS subjects, the results of two-way ANOVA showed no relation between HDL-C levels ($p=0.1961$) and the amount of alcohol ($p=0.5439$) with HOMA-IR. However, for HDL-C <90 mg/dL, irrespective of alcohol amount, HOMA-IR decreased as HDL-C increased, and for HDL-C ≥90 mg/dL, particularly with alcohol consumption ≥75 g, HOMA-IR was higher.

## Discussion

With an HDL-C of <90 mg/dL, the higher the HDL-C, the lower the HOMA-IR, but with an HDL-C ≥90 mg/dL, HOMA-IR tended to increase. Evaluation of the correlation between HDL-C and HOMA-IR based on the number of MetS risks showed that with ≤2 risks, the higher the HDL-C and the more HOMA-IR decreased. However, in MetS subjects with ≥3 risks, HOMA-IR was increased with HDL-C ≥90 mg/dL.

In MetS subjects with HDL-C ≥90 mg/dL, blood pressure was significantly higher, and fasting plasma glucose was also the highest although not significantly different. Regarding lifestyle habits, a high proportion of these subjects drank ≥75 g/day of alcohol. Unhealthy lifestyle habits in-
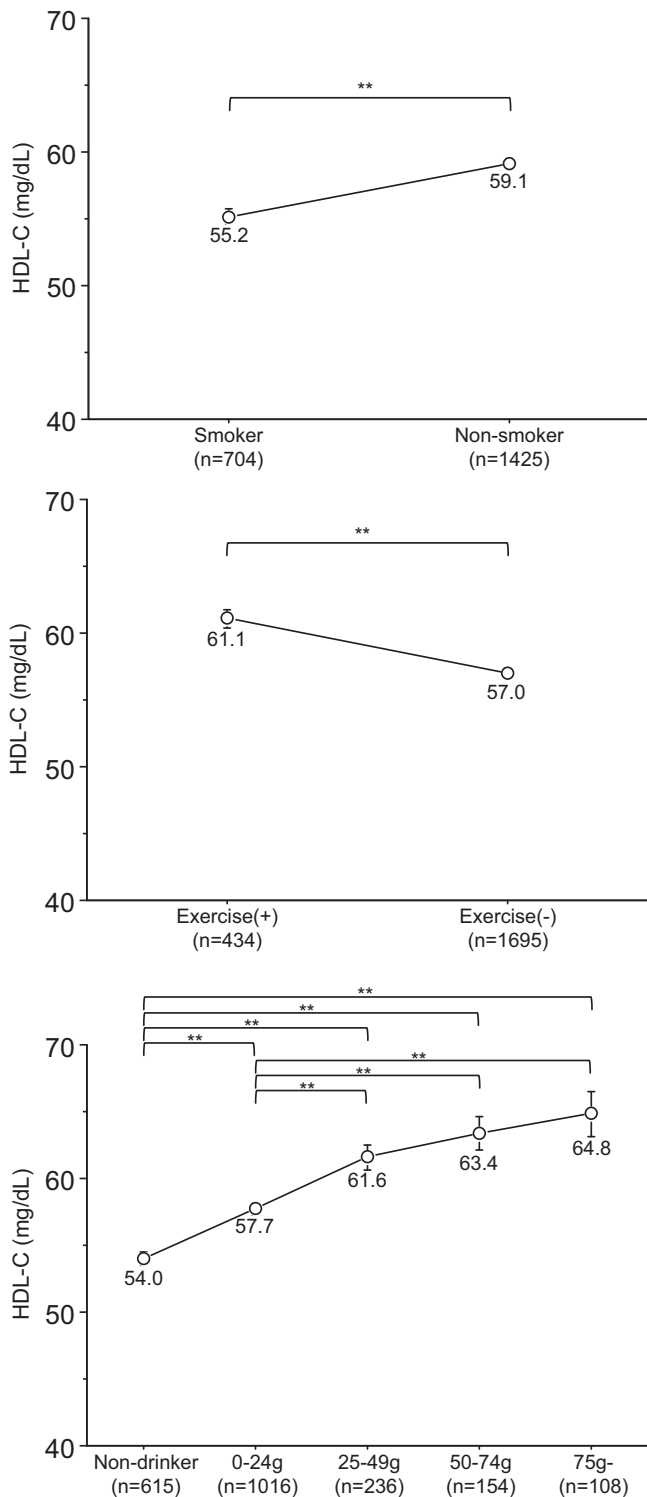
**Figure 3.** Lifestyle habits and HDL-C. Mean±SE, **:p<0.01, *:p<0.05 (unpaired *t*-test, Scheffe's multiple comparison test). HDL-C: high-density lipoprotein cholesterol

cluding excessive drinking might lead to the clustering of metabolic risk factors and the progression of MetS in association with insulin resistance.

In the present study, 19 subjects (0.9%) had an HDL-C of ≥100 mg/dL and 151 subjects (7.1%) had an HDL-C of < 40 mg/dL. In 2000, in the "5th Basic Survey of Cardiovascular Diseases" (16), HDL was ≥100 mg/dL in 1.2%

(men 0.7%, women 1.6%) and <40 mg/dL in 11.0% (men 17.3%, women 6.6%). In the present study results, the prevalence of HDL-C ≥100 mg/dL was nearly the same but 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 this study, we focused on HDL-C and evaluated HDL-C and triglycerides as different risks. Therefore, we used the diagnostic criteria (6) proposed by the IDF, AHA, NHLBI and others in which HDL-C and triglycerides are evaluated as independent parameters, rather than the Japanese criteria in which dyslipidemia is defined by either an HDL-C of <40 mg/dL or triglycerides of ≥150 mg/dL.

It is known that drinking moderate amounts of alcohol (30-40 g/day) can increase HDL-C levels and decrease CHD risk independent of other factors (17, 18). 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 (19). Of the HDL-C subfractions, HDL3-C shows a strong positive correlation with the amount of alcohol consumption, and even after adjustment for smoking, BMI, and triglycerides, statistical significance has been reported (20). Moderate or heavy alcohol intake increases HDL3 but not HDL2 (21). HDL3, increased by alcohol consumption, may have less of a protective effect than HDL2 against ischemic heart disease, but some cardioprotective effects cannot be excluded (22). Regarding alcohol consumption, no more than 2 glasses/day for men and 1 glass/day for women is recommended, but regular alcohol consumption should not be advised in persons who do not drink (23). In the present study, HDL-C was 20% higher (54.0 mg/dL vs. 64.8 mg/dL) in subjects who drank ≥75 g/day of alcohol compared to non-drinkers.

Smoking decreases HDL-C (24), and tobacco smoke is a cause of oxidative stress which leads to HDL dysfunction (25). Maeda et al reported that smoking cessation increases HDL-C by about 4 mg/dL without any changes in LDL-C or triglycerides (26). In the present study, non-smokers had a 7% increase in HDL-C compared to smokers (57.0 mg/dL vs. 61.1 mg/dL), but in MetS subjects, there was no correlation between HDL-C levels and smoking rates, and thus this was probably not a factor in the increased HDL-C.

Regular aerobic exercise increases HDL-C via various mechanisms by about 5% within 2 months after initiation (27, 28). To increase HDL-C, active aerobic exercise more than 30 min each time, at least a total of 120 min per week is preferable (23, 29). In the present study, subjects who exercised ≥30 min/day more than 2 days per week had a 7% increase in HDL-C compared to non-exercisers (55.2 mg/dL vs. 59.1 mg/dL). However, in MetS subjects, the proportion who exercised did not differ by HDL-C lev-

**Table 3.   Clinical Parameters Stratified by Alcohol Consumption**

| | alcohol consumption (g/day) | | | | |
|---|---|---|---|---|---|
| | Non-drinker | 0-24 | 25-49 | 50-74 | 75- |
| | (n=615) | (n=1016) | (n=236) | (n=154) | (n=108) |
| Age (years) | 47.9 ± 12.3 | 47.0 ± 11.5 | 50.7 ± 10.7 | 51.6 ± 10.1 | 48.1 ± 9.3 |
| BMI (kg/m$^2$) | 23.7 ± 3.3 | 23.8 ± 3.2 | 23.2 ± 2.9 | 23.4 ± 2.6 | 24.0 ± 3.0 |
| WC (cm) | 84.3 ± 9.0 | 84.8 ± 8.6 | 84.2 ± 8.2 | 84.7 ± 7.3 | 86.4 ± 7.9 |
| SBP (mmHg) | 116.7 ± 16.1 | 117.1 ± 15.9 | 120.4 ± 17.4 | 124.9 ± 16.6**,## | 122.5 ± 15.3*,# |
| DBP (mmHg) | 74.1 ± 12.3 | 75.5 ± 11.7 | 77.2 ± 13.0* | 80.9 ± 11.7**,# | 80.7 ± 12.8**,## |
| FPG (mg/dL) | 101.1 ± 15.7 | 100.7 ± 13.6 | 102.2 ± 12.7 | 101.3 ± 9.2 | 104.3 ± 16.5 |
| TG (mg/dL) | 119.2 ± 71.1 | 123.1 ± 80.4 | 118.5 ± 98.6 | 132.2 ± 93.4 | 144.3 ± 90.9 |
| Metabolic risk | 1.5 ± 1.2 | 1.5 ± 1.3 | 1.6 ± 1.3 | 1.8 ± 1.3 | 1.9 ± 1.3*,# |
| HOMA-IR | 1.8 ± 1.4 | 1.7 ± 1.3 | 1.5 ± 1.2* | 1.4 ± 0.8** | 1.6 ± 1.2 |

Mean±SD

\*\*:$p<0.01$, \*:$p<0.05$ (vs. Non-drinker), ##:$p<0.01$, #:$p<0.05$ (vs. 0-24 g/day). BMI: body mass index, WC: waist circumference, SBP: systolic blood pressure, DBP: diastolic blood pressure, FPG: fasting plasma glucose, TG: triglyceride, HDL-C: high-density lipoprotein cholesterol, HOMA-IR: homeostasis model assessment of insulin resistance
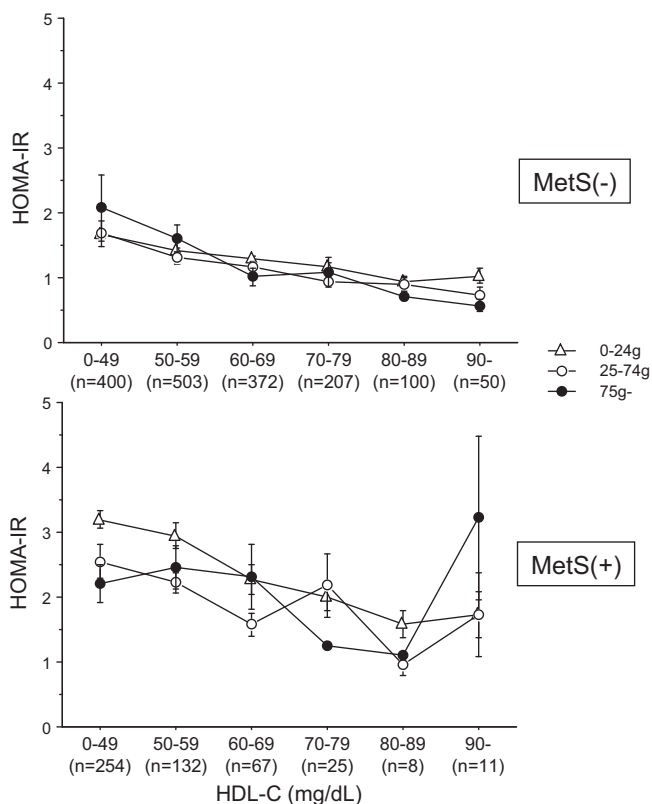


**Figure 4.   HOMA-IR based on the presence or absence of MetS and stratified by HDL-C levels and alcohol consumption. Mean±SE. HOMA-IR: homeostasis model assessment of insulin resistance, HDL-C: high-density lipoprotein cholesterol, MetS: metabolic syndrome**

els, so it is unlikely that HDL-C increased because of exercise.

In general, weight loss increases HDL-C in overweight or obese subjects (30). HDL-C decreases slightly while losing weight, but HDL-C levels increase by 0.35 mg/dL for every kilogram of weight loss when a stabilized diet is achieved (31). In addition, risk factors for cardiovascular disease are improved by weight reduction regardless of whether drugs are used (32-34). In overweight and obese persons, weight loss of 2 kg per month to achieve a BMI of <25 kg/m$^2$ (<24 kg/m$^2$ in Asians) is recommended (23). In the present study, BMI and waist circumference were similar in MetS subjects among HDL-C levels of ≥60 mg/dL.

The results of our study on the relationship between high HDL-C and lifestyle habits in MetS subjects are summarized as follows; heavy drinking had the strongest influence, whereas exercise, smoking and obesity seemed not to have much influence.

In a meta-analysis of the association between alcohol consumption and MetS, the amount of alcohol consumption with the lowest odds ratios was <40 g/day in men and <20 g/day in women for MetS prevalence (35). With even mild alcohol consumption, there are increases in hypertension, impaired glucose tolerance and hypertriglyceridemia (36-38). In the present study, compared to the group with alcohol consumption <25 g/day, systolic and diastolic blood pressure were higher in the group with ≥50 g/day, and the number of MetS risks was greater in the group with ≥75 g/day. In a study comparing HOMA-IR, in which subjects were divided into non-drinkers, low (<25 g), moderate-to-high (25-<62.5 g) and very high (≥62.5 g) daily alcohol consumption groups, HOMA-IR showed a U-shaped relationship with alcohol after adjustment for age, sex, smoking, exercise and educational level (39). In the present study as well, there was a U-shaped relationship with alcohol consumption. Alcohol consumption reduced plasma cholesteryl ester trans-

fer protein (CETP) and is associated with increased HDL-C (40). Heavy drinker also showed high blood pressure, FPG, TG, BMI and WC, which might result in insulin resistance. Their lifestyle habits may affect their insulin resistance.

There is a U-shaped relationship between alcohol consumption with MetS and arteriosclerosis, with ≥75-100 g/day having an adverse impact. However, in subjects with high HDL-C levels, the opportunities for receiving guidance on exercise and smoking cessation, which increase HDL-C, may not only be decreasing, but perhaps excessive drinking is also overlooked and guidance on diet is not being provided, because the incidence of coronary artery disease including angina pectoris and myocardial infarction is considered lower.

We were not able to fully explain the causes of insulin resistance in MetS subjects with HDL-C ≥90 mg/dL by alcohol intake, because the proportion of the subjects who drank ≥75 g/day was only about a half even in this group. As Hirano et al reported that CETP deficiency was associated with increased atherogenicity (41), it is necessary to elucidate the genetic factors including CETP gene mutation.

Because the present study was a cross-sectional study, a cause-and-effect relationship could not be ascertained. With regard to the correlation between high HDL-C and insulin resistance and the influence of heavy drinking in MetS subjects, it will be necessary to wait for the results of a longitudinal study that is currently underway.

## Conclusion

In general, high HDL-C is associated with low insulin resistance. However, in MetS subjects, high HDL-C is associated with high insulin resistance and the influence of heavy alcohol consumption seems to be strong. In subjects with high HDL-C levels, detailed information about lifestyle-related behaviors with a focus on alcohol consumption should be obtained. In persons with high HDL-C levels, it is important to check the amount of alcohol consumption and reduce alcohol consumption to <75 g/day.

**The authors state that they have no Conflict of Interest (COI).**

### References

1. Teramoto T, Sasaki J, Ueshima H, et al. Metabolic syndrome. J Atheroscler Thromb **15**: 1-15, 2008.
2. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications, part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med **15**: 539-553, 1998.
3. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III): Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation **106**: 3143-3421, 2002.
4. Alberti KG, Zimmet P, Shaw J; IDF Epidemiology Task Force Consensus Group. The metabolic syndrome: a new worldwide definition. Lancet **366**: 1059-1062, 2005.
5. Grundy SM, Cleeman JI, Daniels SR, et al; American Heart Association; National Heart, Lung, and Blood Institute. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation **112**: 2735-2752, 2005.
6. Alberti KG, Eckel RH, Grundy SM, et al; International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation **120**: 1640-1645, 2009.
7. Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR. High density lipoprotein as a protective factor against coronary heart disease. The Framingham Study. Am J Med **62**: 707-714, 1977.
8. Wilson PW, Garrison RJ, Castelli WP, Feinleib M, McNamara PM, Kannel WB. Prevalence of coronary heart disease in the Framingham Offspring Study: role of lipoprotein cholesterols. Am J Cardiol **46**: 649-654, 1980.
9. Castelli WP, Garrison RJ, Wilson PW, et al. Incidence of coronary heart disease and lipoprotein cholesterol levels. The Framingham Study. JAMA **256**: 2835-2838, 1986.
10. Gordon DJ, Probstfield JL, Garrison RJ, et al. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. Circulation **79**: 8-15, 1989.
11. Barter P, Gotto AM, LaRosa JC, et al. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. N Engl J Med **357**: 1301-1310, 2007.
12. Tarui S. The report of Ministry of Health, Labor and Welfare research working group on primary hyperlipidemia. 1987 (in Japanese).
13. Maruyama T, Sakai N, Ishigami M, et al. Prevalence and phenotypic spectrum of cholesteryl ester transfer protein gene mutations in Japanese hyperalphalipoproteinemia. Atherosclerosis **166**: 177-185, 2003.
14. Khera AV, Cuchel M, de la Llera-Moya M, et al. Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. NEJM **364**: 127-135, 2011.
15. Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia **28**: 412-419, 1985.
16. Ministry of Health, Labour and Welfare. The 5th Basic Survey of Cardiovascular Diseases, 2001 (in Japanese, http://www.mhlw.go.jp/toukei/saikin/hw/kenkou/jyunkan/jyunkan00/gaiyo.html).
17. Valmadrid CT, Klein R, Moss SE, et al. Alcohol intake and the risk of coronary heart disease mortality in persons with older-onset diabetes mellitus. JAMA **282**: 239-246, 1999.
18. Gaziano JM, Buring JE, Breslow JL, et al. Moderate alcohol intake, increased levels of high-density lipoprotein and its subfractions, and decreased risk of myocardial infarction. N Engl J Med **329**: 1829-1834, 1993.
19. Rimm EB, Moats C. Alcohol and coronary heart disease: drinking patterns and mediators of effect. Ann Epidemiol **17**(suppl): S3-S7, 2007.
20. Diehl AK, Fuller JM, Mattock MB, et al. The relationship of high density lipoproteins to alcohol consumption, and other lifestyle

factors, and coronary heart disease. Atherosclerosis **69**: 145-153, 1988.

21. Sillanaukee P, Koivula T, Jokeia H, et al. Relationship of alcohol consumption to changes in HDL-subfractions. Eur J Clin Invest **23**: 486-491, 1993.

22. Lamarche B, Moorjani S, Cantin B, et al. Associations of HDL$_2$ and HDL$_3$ subfractions with ischemic heart disease in men. Prospective results from the Quebec Cardiovascular Study. Arterioscler Thromb Vasc Biol **17**: 1098-1105, 1997.

23. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Executive Summary of The Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA **285**: 2486-2497, 2001.

24. Khurana M, Sharma D, Khandelwal PD. Lipid profile in smokers and tobacco chewers. a comparative study. J Assoc Physicians India **48**: 895-897, 2000.

25. Ansell BJ, Fonarow GC, Fogelman AM. High-density lipoprotein: is it always atheroprotective? Curr Atheroscler Rep **8**: 405-411, 2006.

26. Maeda K, Noguchi Y, Fukui T. The effects of cessation from cigarette smoking on the lipid and lipoprotein profiles: a meta-analysis. Prev Med **37**: 283-290, 2003.

27. Kraus WE, Houmard JA, Duscha BD, et al. Effects of the amount and intensity of exercise on plasma lipoproteins. N Engl J Med **347**: 1483-1492, 2002.

28. Roberts CK, Ng C, Hama S, et al. Effect of a short-term diet and exercise intervention on inflammatory/anti-inflammatory properties of HDL in overweight/obese men with cardiovascular risk factors. J Appl Physiol **101**: 1727-1732, 2006.

29. Kodama S, Tanaka S, Saito K, et al. Effect of aerobic exercise training on serum levels of high-density lipoprotein cholesterol: a meta-analysis. Arch Intern Med **167**: 999-1008, 2007.

30. Weisweiler P. Plasma lipoproteins and lipase and lecithin: cholesterol acyltransferase activities in obese subjects before and after weight reduction. J Clin Endocrinol Metab **65**: 969-973, 1987.

31. Dattilo AM, Kris-Etherton PM. Effects of weight reduction on blood lipids and lipoproteins: a meta-analysis. Am J Clin Nutr **56**: 320-328, 1992.

32. Burke V, Beilin LJ, Cutt HE, et al. A lifestyle program for treated hypertensives improved health-related behaviors and cardiovascular risk factors, a randomized controlled trial. J Clin Epidemiol **60**: 133-141, 2007.

33. Després JP, Golay A, Sjostrom L. Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. N Engl J Med **353**: 2121-2134, 2005.

34. Pi-Sunyer FX, Aronne LJ, Heshmati HM, et al. Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. JAMA **295**: 761-775, 2006.

35. Alkerwi A, Boutsen M, Vaillant M, et al. Alcohol consumption and the prevalence of metabolic syndrome: a meta-analysis of observational studies. Atherosclerosis **204**: 624-635, 2009.

36. Kiyohara Y, Kato I, Iwamoto H, et al. The impact of alcohol and hypertension on stroke incidence in a general Japanese population. The Hisayama Study. Stroke **26**: 368-372, 1995.

37. Xin X, He J, Frontini MG, et al. Effects of alcohol reduction on blood pressure: a meta-analysis of randomized controlled trials. Hypertension **38**: 1112-1117, 2001.

38. Kato I, Kiyohara Y, Kubo M, et al. Insulin-mediated effects of alcohol intake on serum lipid levels in a general population: the Hisayama Study. J Clin Epidemiol **56**: 196-204, 2003.

39. Clerc O, Nanchen D, Cornuz J, et al. Alcohol drinking, the metabolic syndrome and diabetes in a population with high mean alcohol consumption. Diabet Med **27**: 1241-1249, 2010.

40. Hannuksela M, Marcel YL, Kesäniemi YA, Savolainen MJ. Reduction in the concentration and activity of plasma cholesteryl ester transfer protein by alcohol. J Lipid Res **33**: 737-744, 1992.

41. Hirano K, Yamashita S, Nakajima N, et al. Genetic cholesteryl ester transfer protein deficiency is extremely frequent in the Omagari area of Japan. Marked hyperalphalipoproteinemia caused by CETP gene mutation is not associated with longevity. Arterioscler Thromb Vasc Biol **17**: 1053-1059, 1997.