

Protective effect of alcohol consumption for fatty liver but not metabolic syndrome

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Abstract

AIM: To investigate the effect of alcohol on the metabolic syndrome (MS) and fatty liver in Japanese men and women.

METHODS: A cross-sectional study was conducted in a medical health checkup program at a general hospital. This study involved 18 571 Japanese men and women, 18-88 years of age, with a mean body mass index of 22.6 kg/m². A standardized questionnaire was administered. The total amount of alcohol consumed per week was calculated, and categorized into four grades. Fatty liver was examined by ultrasound modified criteria of the revised National Cholesterol Educa-

tion Program Adult Treatment Panel III and the new International Diabetes Federation.

RESULTS: The prevalence of fatty liver decreased in men and women with light to moderate alcohol consumption, whereas the prevalence of MS was not so changed. The prevalence of fatty liver of any grade in men was lower than that in those with no or minimal alcohol consumption. In women with light to moderate alcohol consumption, prevalence of fatty liver was lower than that in women with no or minimal alcohol consumption. By logistic regression analysis, the odds ratio (OR) for MS in women with light alcohol consumption was decreased to < 1.0, but this change was not clear in men. The OR for fatty liver was clearly < 1.0 in men with any level of alcohol consumption and in women with light to moderate consumption.

CONCLUSION: Light to moderate alcohol consumption has a favorable effect for fatty liver, but not for MS in Japanese men and women.

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Key words: Alcoholic hepatitis; Epidemiology; Fatty liver; Metabolic syndrome; Alcohol consumption

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INTRODUCTION

The metabolic syndrome (MS) is defined by abdominal

obesity, hypertension, elevated fasting blood glucose, and dyslipidemia^[1]. Importantly, MS is a risk factor for the development of type 2 diabetes mellitus and coronary artery disease, and is associated with an increased risk of cerebrovascular disease and all-cause mortality^[2]. The favorable effect of alcohol intake enhances insulin sensitivity, increases high-density lipoprotein-cholesterol (HDL-C), and contributes to a lower risk of type 2 diabetes mellitus^[3-6] and cardiovascular disease^[7-10]. Some reports have shown that the prevalence of MS is associated with alcohol consumption, irrespective of the amount consumed^[11-13]. However, several studies have reported beneficial effects of alcohol consumption on MS^[14-16]. Moreover, a study in Korean adults has indicated that light alcohol consumption is associated with a reduced prevalence of MS, whereas substantial alcohol intake leads to a dose-dependent increase in the risk of MS^[17]. The effect of alcohol on MS in the general population has been inconsistent in the literature.

Fatty liver is closely associated with MS, and is considered the hepatic manifestation of MS^[18]. Findings on the relation between alcohol consumption and fatty liver have also been inconsistent in the literature. Although alcohol consumption certainly may be a cause of fatty liver in some cases^[19,20], it potentially plays a protective role against fatty deposition in the liver^[21-25].

Therefore recent studies have implied the possibility that the effect of alcohol is different between fatty liver and MS, although fatty liver is closely associated with MS. However, the discrepancy of alcohol effect among the previous studies may be due to differences in the following cofactors: ethnicity, age, body mass index (BMI), drug usage, and lifestyle, such as alcohol consumption, smoking, and exercise. However, no large epidemiological study has investigated the effect of alcohol on fatty liver and MS at the same time.

We performed a cross-sectional study to investigate the effect of alcohol on fatty liver and MS at the same time. In this study, we separated the subjects according to the grade of alcohol consumption and compared the prevalence of fatty liver and MS in each grade. We focused on the discrepancy in the association between alcohol and MS and between alcohol and fatty liver. Additionally, we checked the impact of prevalence of MS without fatty liver, or fatty liver without MS.

MATERIALS AND METHODS

Study design

We performed a cross-sectional study of participants of a medical health checkup program, including abdominal ultrasonography. The study was approved by the ethics committee of Murakami Memorial Hospital, Gifu, Japan. The program was conducted in the Medical Health Checkup Center at Murakami Memorial Hospital. The purpose of the medical health checkup program was to promote public health through early detection of chronic diseases and the evaluation of their underlying

risk factors. Known as a “human dock”, medical services of this kind are very popular in Japan.

Study population

All of the subjects participating in such health checkup programs at Murakami Memorial Hospital between January 2004 and December 2009 were invited to join this study. Participants who tested positive for hepatitis B antigen or hepatitis C antibody and those who reported a history of known liver disease, including viral, genetic, autoimmune, and drug-induced liver disease, were excluded from the study^[26]. We invited 22 119 participants in the health checkup program to enroll in the study. Of these, a total of 19 016 Japanese participants (11 295 men and 7721 women) were enrolled after giving informed consent. We excluded 123 participants (92 men and 31 women) with hepatitis C virus, 312 (214 men and 98 women) with hepatitis B virus, and nine (7 men and 2 women) who were diagnosed with other liver diseases. As a result, this study consisted ultimately of 18 571 participants (10 982 men and 7589 women). The mean age was 46.5 years (SD: 9.9; range: 18-88 years), and the mean BMI was 22.6 kg/m² (SD: 3.3; range: 14.0-58.3 kg/m²).

Data collection

The health checkup programs that were used for the collection of data included the following tests: eye examinations, urinalysis, blood-cell counts, blood chemistry, electrocardiography, chest radiography, barium examination of the upper gastrointestinal tract, and abdominal ultrasonography. The medical history and lifestyle factors of all participants, including physical activity and habits pertaining to smoking and alcohol consumption, were surveyed by a standardized self-administered questionnaire. When the participants had difficulty completing the questionnaire, trained nurses provided assistance. We undertook blood and urine examinations with MODULAR ANALYTICS (Hitachi High-Technologies Corp. Ltd., Tokyo, Japan).

Standardized questionnaire for lifestyle factors

A standardized questionnaire was administered to all participants by the same trained team of interviewers. Habits regarding alcohol consumption were evaluated by asking the participants about the amount and type of alcoholic beverages consumed per week during the past month, then estimating the mean ethanol intake per week. The validity of information related to alcohol consumption was confirmed previously^[27]. The total amount of alcohol consumed per week was calculated in grams, and then categorized into the following four grades: non or minimal alcohol consumption, < 40 g/wk; light alcohol consumption, 40-140 g/wk; moderate alcohol consumption, 140-280 g/wk; and excess alcohol consumption, > 280 g/wk^[22,24]. Smoking status was also categorized into three groups (never smoker, ex-smoker, and current smoker). On the questionnaire, participants reported the type, duration and frequency of their partici-

pation in sports or recreational activities^[28]. When participants performed any kind of sports at least once a week regularly, we categorized them as regular exercisers^[29].

Definition of fatty liver

The diagnosis of fatty liver was based on the results of abdominal ultrasonography, which was done by trained technicians with Aloka SSD-650CL (Aloka Co., Ltd., Tokyo, Japan). All ultrasonographic images were stored as photocopies. Gastroenterologists reviewed the photocopies and made the diagnosis of fatty liver without reference to any of the participant's other individual data. Of four known criteria (hepatorenal echo contrast, liver brightness, deep attenuation, and vascular blurring), the participants were required to have hepatorenal contrast and liver brightness to be given a diagnosis of fatty liver^[30].

MS

There are several differing criteria for the MS worldwide^[1,31-34]. In this study, we used the following two definitions: (1) the revised National Cholesterol Education Program Adult Treatment Panel III (rATP III) definition^[34]; and (2) the new International Diabetes Federation (IDF) definition^[32].

According to the rATP III definition^[1], subjects who had three or more of the following criteria were identified as having MS: (1) triglycerides ≥ 150 mg/100 mL; (2) HDL-C < 40 mg/100 mL for men, and < 50 mg/100 mL for women; (3) elevated blood pressure (systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg); (4) fasting glucose ≥ 100 mg/100 mL instead of ≥ 110 mg/100 mL; or (5) abdominal-obesity-modified waist circumference cutoffs (≥ 90 cm for men and ≥ 80 cm for women) were used instead of the waist circumference cutoffs (≥ 102 cm for men and ≥ 88 cm for women) proposed in the existing definition.

According to the new IDF definition, Japanese people were defined as having MS if the subjects had abdominal obesity (waist circumference cutoffs ≥ 90 cm for men and ≥ 80 cm for women) plus two or more of the following risk factors: (1) elevated triglyceride level ≥ 150 mg/100 mL or on treatment; (2) low HDL-C < 40 mg/100 mL for men and < 50 mg/100 mL for women or on treatment; (3) elevated blood pressure (systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg); and (4) high fasting glucose ≥ 100 mg/100 mL^[32].

Sample size

Because preliminary studies indicated that the number in the excess alcohol consumption group was small ($n = 22$ and 24), we invited as many subjects as possible. Practically, we collected data for waist circumference from 2004. Then, we set the study period from 2004 to 2009.

Statistical analysis

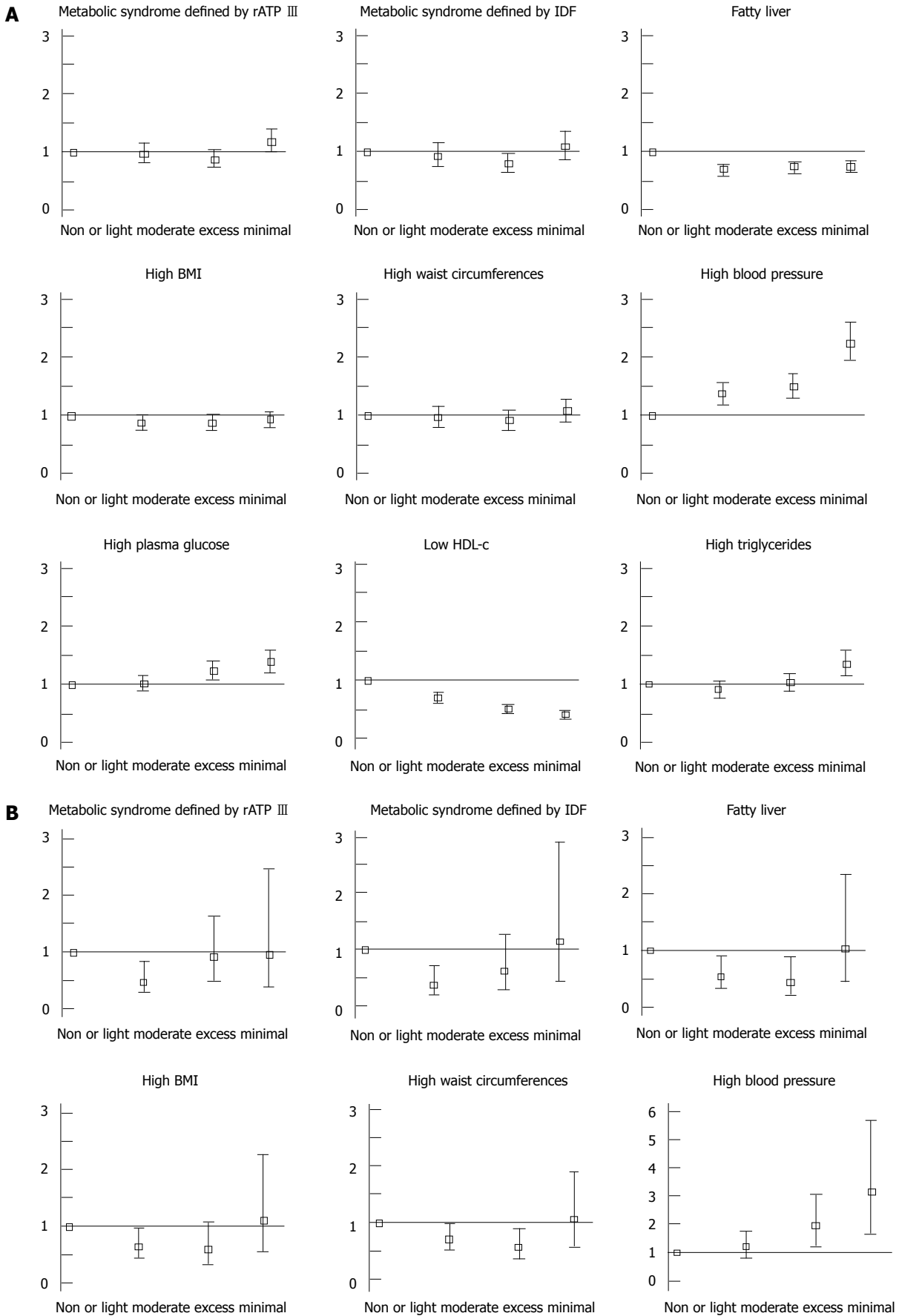
The R version 2.4.1 (available from <http://www.r-project.org/>) was used for statistical analyses. Data was expressed

as mean (SD). Two groups of subjects were compared by χ^2 test. The significance of differences between non or minimal alcohol consumption and the others was determined by two-tailed, multiple χ^2 tests with Bonferroni correction ($P < 0.016$ for three comparisons in four groups). The linear association of alcohol consumption with several parameters associated with MS was evaluated by Spearman's rank correlation, and a P value < 0.05 was accepted as significant. We assessed the odds ratio (OR) of the alcohol consumption grade for MS and fatty liver using a multivariate logistic model while controlling for potential covariates. In a multivariate logistic model, we selected age, use of drugs that potentially affect MS, and lifestyle, such as alcohol consumption, regular exercise, and smoking as the potential covariates. The adjusted OR and 95% CIs were calculated.

RESULTS

We investigated the OR of alcohol consumption for MS defined by rATP III and fatty liver using a logistic regression model (Figure 1). The OR for MS was decreased to < 1.0 in women with light alcohol consumption, but it was not clear in men. The OR for fatty liver was clearly < 1.0 in men with any level of alcohol consumption and in women with light to moderate consumption. In men and women, the ORs for high blood pressure and high fasting plasma glucose were increased as the level of alcohol consumption increased. Conversely, the OR for low HDL-C was decreased to < 1.0 in men and women. However, the OR for high triglycerides was increased to > 1.0 in men with excess alcohol consumption, and decreased to < 1.0 in women with light consumption. Moreover, the OR for high waist circumference was not significant, and was the same as the OR for high BMI. The actual adjusted ORs are shown in Table 1.

Table 2 indicates the basic characteristics of men and women in the four grades. And liner association between alcohol consumption and several factors associated with MetS were evaluated by Spearman's rank correlation (Table 3). BMI and waist circumferences were lowest in light consumption (Table 2), but Spearman's rank correlation coefficients were not significant (Table 3). Systolic blood pressure, diastolic blood pressure, and fasting plasma glucose were increased as the alcohol consumption increased (Tables 2 and 3). On the other hand, the associations of consumption with diastolic blood pressure, and that with fasting plasma glucose were not statistically significant in women, while systolic blood pressure was also increased as the consumption increased in women. In men and women, low-density lipoprotein (LDL) cholesterol, non HDL cholesterol, and LDL cholesterol/HDL cholesterol ratio were decreased and HDL cholesterol were increased as the consumption increased (Tables 2 and 3). Triglycerides were lower in light consumption and were higher in moderate and excess than those in non or minimal (Table 2). Over all, the trend of the associations between alcohol consumption and MetS



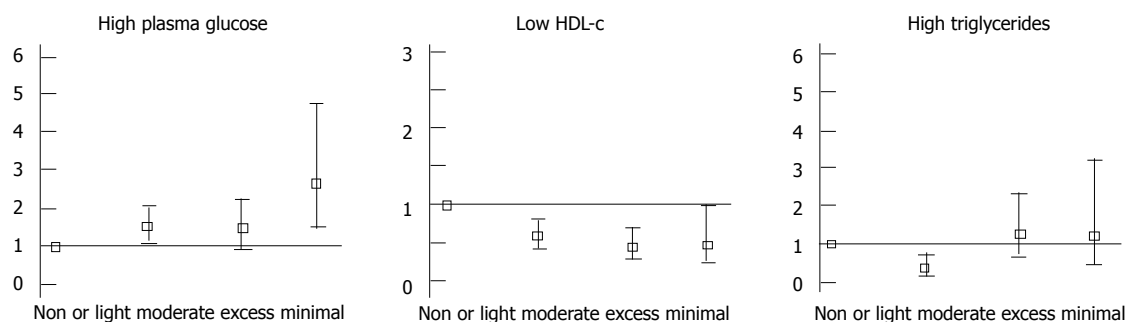


Figure 1 Adjusted odds ratio of the level of alcohol consumption for metabolic syndrome and fatty liver in men (A) and women (B). We assessed the odds ratio (OR) of the level of alcohol consumption for metabolic syndrome (MS) and fatty liver using a multivariate logistic model while controlling for potential covariates. In a multivariate logistic model, we selected age, usage of drugs that potentially affected MS, and lifestyle factors such as wine consumption, regular exercise, and smoking status, as the potential covariates. Bars mean the adjusted OR and 95% CIs. HDL-c: High-density lipoprotein-cholesterol; rATP III: Revised National Cholesterol Education Program Adult Treatment Panel III; IDF: International Diabetes Federation; BMI: Body mass index.

Table 1 The adjusted odds ratio (95% CI) for the metabolic syndrome and fatty liver

	Men odds ratio (95% CI)	P value	Women odds ratio (95% CI)	P value
For MetS defined by rATP III				
The grade of alcohol consumption				
Light	0.98 (0.83-1.15)	0.77	0.48 (0.27-0.82)	0.008
Moderate	0.88 (0.75-1.04)	0.14	0.9 (0.5-1.65)	0.74
Excess	1.18 (1.01-1.39)	0.043	0.96 (0.37-2.48)	0.93
Age	1.01 (1-1.02)	< 0.001	1.08 (1.05-1.1)	< 0.001
The usage of drugs	4.95 (4.3-5.69)	< 0.001	7.46 (4.96-11.24)	< 0.001
Wine consumers	1.13 (0.67-1.9)	0.66	0.52 (0.24-1.15)	0.11
Regular exercisers	0.6 (0.51-0.71)	< 0.001	0.6 (0.38-0.94)	0.027
Smoking states				
Ex smoker/non smoker	1.21 (1.03-1.41)	0.017	0.89 (0.48-1.65)	0.72
Current smoker/non smoker	1.13 (0.97-1.33)	0.12	1.07 (0.58-1.98)	0.83
For MetS defined by IDF				
The grade of alcohol consumption				
Light	0.93 (0.75-1.14)	0.46	0.36 (0.19-0.69)	< 0.001
Moderate	0.78 (0.63-0.97)	0.029	0.61 (0.3-1.25)	0.18
Excess	1.08 (0.87-1.33)	0.48	1.14 (0.45-2.9)	0.78
Age	1 (0.99-1.01)	0.66	1.08 (1.05-1.1)	< 0.001
Age	3.64 (3.05-4.34)	< 0.001	4.85 (3.09-7.63)	< 0.001
The usage of drugs	0.78 (0.37-1.65)	0.52	0.6 (0.26-1.35)	0.22
Wine consumers	0.64 (0.51-0.79)	< 0.001	0.55 (0.34-0.92)	0.021
Regular exercisers				
Smoking states	1.3 (1.06-1.59)	0.01	1.03 (0.54-1.97)	0.93
Ex smoker/non smoker	1.09 (0.89-1.35)	0.39	1.07 (0.54-2.1)	0.85
Current smoker/non smoker				
For fatty liver				
The grade of alcohol consumption				
Light	0.69 (0.6-0.79)	< 0.001	0.54 (0.34-0.88)	0.012
Moderate	0.72 (0.63-0.83)	< 0.001	0.43 (0.21-0.88)	0.021
Excess	0.74 (0.64-0.85)	< 0.001	1.02 (0.44-2.35)	0.97
Age	1 (0.99-1)	0.21	1.06 (1.04-1.08)	< 0.001
The usage of drugs	2.09 (1.83-2.38)	< 0.001	2.17 (1.4-3.38)	< 0.001
Wine consumers	0.85 (0.53-1.35)	0.48	0.59 (0.3-1.15)	0.12
Regular exercisers	0.67 (0.59-0.77)	< 0.001	0.76 (0.52-1.13)	0.17
Smoking states				
Ex smoker/non smoker	1.24 (1.09-1.41)	< 0.001	0.38 (0.18-0.79)	0.01
Current smoker/non smoker	0.92 (0.81-1.05)	0.21	1 (0.57-1.74)	1
For high BMI				
The grade of alcohol consumption				
Light	0.86 (0.75-0.99)	0.034	0.64 (0.43-0.97)	0.036
Moderate	0.85 (0.73-0.98)	0.026	0.59 (0.33-1.06)	0.077
Excess	0.9 (0.78-1.05)	0.18	1.1 (0.53-2.31)	0.8
Age	0.99 (0.98-0.99)	< 0.001	1.04 (1.02-1.06)	< 0.001
The usage of drugs	2.19 (1.91-2.51)	< 0.001	1.77 (1.15-2.74)	0.01
Wine consumers	0.79 (0.48-1.29)	0.34	0.68 (0.39-1.21)	0.19
Regular exercisers	0.93 (0.81-1.06)	0.29	0.69 (0.48-0.99)	0.047
Smoking states				
Ex smoker/non smoker	1.19 (1.04-1.36)	0.013	0.56 (0.32-0.97)	0.037

Current smoker/non smoker	0.99 (0.87-1.14)	0.92	0.95 (0.58-1.57)	0.85
For high waist circumferences				
The grade of alcohol consumption				
Light	0.96 (0.81-1.13)	0.61	0.71 (0.51-0.97)	0.03
Moderate	0.89 (0.75-1.06)	0.21	0.57 (0.36-0.9)	0.016
Excess	1.06 (0.89-1.27)	0.5	1.06 (0.58-1.93)	0.85
Age	1 (0.99-1.01)	0.85	1.07 (1.06-1.09)	< 0.001
The usage of drugs	2.35 (2.01-2.74)	< 0.001	1.64 (1.14-2.36)	0.007
Wine consumers	0.63 (0.32-1.23)	0.18	0.68 (0.43-1.07)	0.095
Regular exercisers	0.71 (0.6-0.84)	< 0.001	0.69 (0.52-0.92)	0.012
Smoking states				
Ex smoker/non smoker	1.26 (1.07-1.49)	0.005	0.93 (0.64-1.35)	0.69
Current smoker/non smoker	1.04 (0.88-1.23)	0.67	0.91 (0.6-1.37)	0.64
For high blood pressure				
The grade of alcohol consumption				
Light	1.33 (1.16-1.53)	< 0.001	1.22 (0.85-1.75)	0.27
Moderate	1.47 (1.27-1.7)	< 0.001	1.97 (1.26-3.07)	< 0.001
Excess	2.24 (1.93-2.59)	< 0.001	3.13 (1.71-5.72)	< 0.001
Age	1.04 (1.03-1.05)	< 0.001	1.07 (1.06-1.09)	< 0.001
The usage of drugs	6.16 (5.33-7.13)	< 0.001	16.09 (10.87-23.83)	< 0.001
Wine consumers	1.09 (0.68-1.73)	0.73	0.72 (0.42-1.23)	0.23
Regular exercisers	0.81 (0.71-0.93)	< 0.001	0.8 (0.57-1.12)	0.19
Smoking states				
Ex smoker/non smoker	1.01 (0.88-1.15)	0.93	0.78 (0.5-1.23)	0.28
Current smoker/non smoker	0.67 (0.59-0.77)	< 0.001	0.73 (0.45-1.18)	0.2
For high plasma glucose				
The grade of alcohol consumption				
Light	1 (0.88-1.13)	0.94	1.52 (1.11-2.08)	0.009
Moderate	1.23 (1.08-1.4)	< 0.001	1.46 (0.95-2.25)	0.085
Excess	1.38 (1.2-1.58)	< 0.001	2.66 (1.49-4.76)	< 0.001
Age	1.03 (1.03-1.04)	< 0.001	1.07 (1.06-1.09)	< 0.001
The usage of drugs	2.05 (1.79-2.33)	< 0.001	1.88 (1.29-2.72)	< 0.001
Wine consumers	1.78 (1.17-2.72)	0.007	0.56 (0.33-0.96)	0.034
Regular exercisers	0.76 (0.68-0.86)	< 0.001	0.92 (0.68-1.24)	0.58
Smoking states				
Ex smoker/non smoker	1.22 (1.08-1.38)	< 0.001	0.68 (0.44-1.05)	0.083
Current smoker/non smoker	0.94 (0.83-1.06)	0.31	0.67 (0.42-1.06)	0.087
For low HDL-c				
The grade of alcohol consumption				
Light	0.7 (0.61-0.8)	< 0.001	0.58 (0.42-0.79)	< 0.001
Moderate	0.49 (0.42-0.57)	< 0.001	0.43 (0.27-0.69)	< 0.001
Excess	0.41 (0.35-0.48)	< 0.001	0.48 (0.24-0.96)	0.039
Age	1.01 (1-1.01)	0.082	1.01 (1-1.02)	0.055
The usage of drugs	3.4 (2.96-3.9)	< 0.001	4.24 (2.97-6.03)	< 0.001
Wine consumers	0.79 (0.47-1.32)	0.37	0.9 (0.6-1.35)	0.61
Regular exercisers	0.71 (0.62-0.82)	< 0.001	0.68 (0.52-0.91)	0.009
Smoking states				
Ex smoker/non smoker	1.06 (0.92-1.22)	0.45	0.64 (0.43-0.95)	0.027
Current smoker/non smoker	1.65 (1.44-1.9)	< 0.001	1.47 (1.03-2.11)	0.036
For high triglycerides				
The grade of alcohol consumption				
Light	0.89 (0.76-1.03)	0.11	0.37 (0.19-0.74)	0.005
Moderate	1.01 (0.87-1.18)	0.88	1.27 (0.68-2.35)	0.45
Excess	1.34 (1.16-1.56)	< 0.001	1.2 (0.45-3.2)	0.72
Age	1 (0.99-1)	0.19	1.06 (1.04-1.09)	< 0.001
The usage of drugs	3.06 (2.67-3.51)	< 0.001	11.13 (7.07-17.53)	< 0.001
Wine consumers	0.83 (0.49-1.4)	0.48	0.92 (0.43-1.99)	0.83
Regular exercisers	0.68 (0.59-0.79)	< 0.001	0.73 (0.44-1.21)	0.22
Smoking states				
Ex smoker/Non smoker	1.26 (1.09-1.46)	< 0.001	0.99 (0.49-2.01)	0.98
Current smoker/Non smoker	1.44 (1.24-1.66)	< 0.001	1.91 (1.02-3.55)	0.042

BMI: Body mass index; HDL-c: High density lipoprotein cholesterol; rATP III: Revised National Cholesterol Education Program Adult Treatment Panel III; IDF: International Diabetes Federation.

were not so changed between men and women.

This observed inverse association between alcohol consumption and fatty liver might be due to changed habits of alcohol use after previous detection of fatty

liver. We analyzed the study population according to previous data. Among 10 981 men, 6547 were new participants and 4434 were repeat participants. Among 7573 women, 5138 were new participants and 2435 were

Table 2 The correlation between components for the metabolic syndrome, liver associated enzymes and alcohol consumptions in participants free from drugs

	Men				Women			
	Non or minimal	Light	Moderate	Excess	Non or minimal	Light	Moderate	Excess
No. of subjects	6154	1734	1616	1478	6893	406	207	84
Age, yr	46.3 (10)	47.5 (9.4)	49.3 (9.4)	49.4 (8.9)	45.1 (9.9)	45.2 (8.8)	45.5 (8.5)	45 (9.3)
Aspartate aminotransferase, IU/L	20.2 (8.7)	19.6 (7.1)	20.8 (10.2)	23.2 (11.6)	17.2 (9)	17.1 (4.9)	17.5 (5.8)	19 (6.2)
Alanine aminotransferase, IU/L	26.1 (16.9)	23.7 (13.3)	23.8 (14.1)	25.5 (14.7)	15.9 (13.1)	15.2 (6.7)	15.6 (6.7)	16 (7)
Gamma-glutamyltransferase, IU/L	24.3 (21.9)	28.9 (24.6)	36 (34.5)	48.8 (51)	13.8 (9.5)	15.8 (12.1)	17.1 (10.6)	22.6 (21.8)
BMI, kg/m ²	23.5 (3.3)	23.2 (2.9)	23.3 (2.7)	23.4 (2.9)	21.4 (3.2)	20.9 (2.7)	20.9 (3.1)	21.3 (3.2)
Waist circumference, cm	81.8 (8.6)	81.5 (7.7)	82.2 (7.5)	82.9 (7.7)	72.3 (8.8)	71.5 (7.9)	71.5 (8.6)	73.9 (9.4)
Systolic blood pressure, mmHg	120.1 (15.6)	121.7 (15.8)	123.9 (15.8)	127.4 (16.1)	111.2 (16.2)	111.2 (15.6)	114.3 (19.4)	116.7 (17)
Diastolic blood pressure, mmHg	75.9 (10.3)	77.2 (10.2)	79 (10.4)	81.3 (10.1)	69.1 (10.3)	69.6 (10.6)	72.2 (11.9)	72.9 (10.9)
Fasting plasma glucose, mg/dL	100.5 (19.3)	100 (16.4)	102.4 (19.9)	103.5 (19.1)	91.3 (12.7)	91.8 (10.1)	91.5 (9.8)	96.1 (18.7)
HDL-c, mg/dL	46 (11.4)	49.6 (12.5)	52 (13.4)	53.3 (14.2)	59.9 (13.3)	65.7 (14.1)	69 (14.9)	68.6 (14)
LDL-c, mg/dL	128 (30)	122.8 (29.6)	121.5 (29.5)	116.6 (31.6)	118.1 (31.1)	108.4 (29.6)	105.6 (27.7)	102 (26.5)
nonHDL-c, mg/dL	155.4 (33.9)	150.1 (33.4)	150.6 (33)	149.2 (34.7)	139.3 (34.8)	129 (32.2)	127.3 (31.8)	124.4 (28.1)
LDL-c/HDL-c ratio	3 (1)	2.6 (0.9)	2.5 (0.9)	2.4 (0.9)	2.1 (0.8)	1.7 (0.7)	1.6 (0.6)	1.6 (0.6)
Triglycerides, mg/dL	109.5 (83)	108.6 (100.2)	117.7 (107.7)	135.5 (116.7)	64.6 (44.5)	60 (31.9)	69 (53.4)	67.2 (42.2)

Among 18 571 participants (10 982 men and 7589 women), we separate men and women into the following four grades: non or minimal alcohol consumption, < 40 g/wk; light alcohol consumption, 40-140 g/wk; moderate alcohol consumption, 140-280 g/wk; and excess alcohol consumption. Data was expressed as mean (SD). BMI: Body mass index; HDL-c: High density lipoprotein cholesterol; LDL-c: Low density lipoprotein cholesterol.

Table 3 The linear association between the amount of alcohol consumption and several parameters associated with the metabolic syndrome

	Men		Women	
	ρ	<i>P</i> value	ρ	<i>P</i> value
Age, yr	0.11	< 0.001	-0.09	< 0.001
Aspartate aminotransferase, IU/L	0.09	< 0.001	0	0.77
Alanine aminotransferase, IU/L	-0.02	0.08	-0.02	0.05
Gamma-glutamyltransferase, IU/L	0.34	< 0.001	0.08	< 0.001
BMI, kg/m ²	-0.01	0.16	-0.02	0.1
Waist circumference, cm	0.04	< 0.001	-0.01	0.32
Systolic blood pressure, mmHg	0.14	< 0.001	-0.04	< 0.001
Diastolic blood pressure, mmHg	0.17	< 0.001	-0.02	0.18
Fasting plasma glucose, mg/dL	0.08	< 0.001	-0.01	0.28
HDL-c, mg/dL	0.23	< 0.001	0.13	< 0.001
LDL-c, mg/dL	-0.13	< 0.001	-0.13	< 0.001
nonHDL-c, mg/dL	-0.08	< 0.001	-0.13	< 0.001
LDL-c/HDL-c ratio	-0.25	< 0.001	-0.17	< 0.001
Triglycerides, mg/dL	0.06	< 0.001	-0.06	< 0.001

The linear association between alcohol consumption and several factors associated with the metabolic syndrome were evaluated by Spearman's rank correlation in 10 982 men and 7589 women, respectively, and a *P* value of < 0.05 was accepted as a significant level. BMI: Body mass index; HDL-c: High density lipoprotein cholesterol; LDL-c: Low density lipoprotein cholesterol.

repeat participants. The alcohol consumption of repeat participants with fatty liver was the same as that of new participants with fatty liver (Table 4). Next, we analyzed repeat participants and separated them into four groups according to previous and present fatty liver. We assessed the changed habit of alcohol consumption. At first, the change in alcohol consumption was small in each group (Table 5). Moreover, the level of change was no different among the four groups of men and women.

We calculated the number of subjects with both MS and fatty liver, those who had only MS, and those who had only fatty liver (Table 6). Unexpectedly, more

Table 4 Alcohol consumptions of new and repeat participants

	<i>n</i>	Men		<i>P</i> value	<i>n</i>	Women		<i>P</i> value
		Alcohol consumption (g/wk)				Alcohol consumption (g/wk)		
New participants without fatty liver	4417	113.02 (161.03)	< 0.001 ²	4662	21.37 (67.57)	0.092 ²		
New participants with fatty liver	2130	96.14 (157.95)	0.7 ¹	476	13.99 (68.47)	0.841 ¹		
Repeat participants without fatty liver	2986	125.79 (157.24)	< 0.001 ³	2154	21.48 (58.33)	0.853 ³		
Repeat participants with fatty liver	1448	102.02 (155.3)		281	18.09 (75.15)			

¹New participants with fatty liver *vs* repeat participants with fatty liver;

²New participants with fatty liver *vs* new participants without fatty liver;

³Repeat participants with fatty liver *vs* repeat participants without fatty liver.

than half of the participants with fatty liver were not diagnosed with MS, even if the definition was changed. 42.5% or 25.5% of men with fatty liver were diagnosed with MS defined by τ ATP III or IDF, respectively. Conversely, 66.0% or 78.8% of men with MS defined by τ ATP III or IDF were diagnosed with fatty liver. The result was similar in women: 43.7% or 38.6% of women with fatty liver were diagnosed with MS defined by τ ATP III or IDF, respectively. Conversely, 49.1% or 55.9% of women with MS defined by τ ATP III or IDF were diagnosed with fatty liver. The prevalence of fatty liver among men with MS decreased along with level of alcohol consumption and prevalence of fatty liver among women with MS decreased in those with light or moderate consumption (Table 6).

DISCUSSION

As far as we know, the present study is the first to investigate the association of alcohol with ultrasonography-

Table 5 Changed alcohol consumption habits among four groups

Previous fatty liver	Present fatty liver	Men		Women	
		<i>n</i>	Change of alcohol consumption (g/wk)	<i>n</i>	Change of alcohol consumption (g/wk)
Negative	Negative	2784	-1.69 (109.95)	2112	-5.38 (48.13)
Negative	Positive	269	4.07 (116.14)	75	-20.69 (142.71)
Positive	Negative	202	6.07 (104.09)	42	-20.9 (56.96)
Positive	Positive	1179	-4.45 (100.32)	206	-5.56 (31.87)

Change in alcohol consumption (g/wk) was calculated by present alcohol consumption minus previous alcohol consumption, and expressed as mean (SD). We performed a Tukey test to investigate the statistical significance of the difference between two groups. No significant difference was identified.

Table 6 Positive prevalence of parameters for four levels of alcohol consumption *n* (%)

	Non or minimal	Light	Moderate	Excess	Non or minimal vs light	Light vs moderate	Moderate vs excess
Men							
Fatty liver	2248 (36.5)	457 (26.4)	449 (27.8)	424 (28.7)	< 0.001	< 0.001	< 0.001
MS defined by rATP III	1282 (20.8)	331 (19.1)	317 (19.6)	373 (25.2)	0.12	0.33	< 0.001
MS defined by IDF	668 (10.9)	165 (9.5)	143 (8.8)	182 (12.3)	0.12	0.04	0.15
Fatty liver among men with MS defined by rATP III	923 (72)	204 (61.6)	188 (59.3)	206 (55.2)	< 0.001	< 0.001	< 0.001
Fatty liver among men with MS defined by IDF	568 (85)	118 (71.5)	100 (69.9)	127 (69.8)	< 0.001	< 0.001	< 0.001
MS defined by rATP III among men with fatty liver	923 (41.1)	204 (44.6)	188 (41.9)	206 (48.6)	0.17	0.79	0.005
MS defined by IDF among men with fatty liver	568 (25.3)	118 (25.8)	100 (22.3)	127 (30)	0.85	0.22	0.058
Components of MS							
High waist circumference	968 (15.7)	257 (14.8)	236 (14.6)	257 (17.4)	0.38	0.32	0.15
High blood pressure	1766 (28.7)	591 (34.1)	626 (38.7)	707 (47.8)	< 0.001	< 0.001	< 0.001
High fasting plasma glucose	2332 (37.9)	681 (39.3)	749 (46.3)	729 (49.3)	0.31	< 0.001	< 0.001
Low HDL-C	2133 (34.7)	425 (24.5)	333 (20.6)	284 (19.2)	< 0.001	< 0.001	< 0.001
High triglycerides	1385 (22.5)	360 (20.8)	394 (24.4)	459 (31.1)	0.13	0.14	< 0.001
High BMI (> 25 kg/m ²)	1731 (28.1)	417 (24)	388 (24)	379 (25.6)	< 0.001	< 0.001	0.07
Smoking status							
Current smoker	2012 (32.7)	602 (34.7)	657 (40.7)	740 (50.1)	0.12	< 0.001	< 0.001
Never smoker	2220 (36.1)	446 (25.7)	308 (19.1)	180 (12.2)	< 0.001	< 0.001	< 0.001
Ex smoker	3933 (63.9)	1288 (74.3)	1308 (80.9)	1298 (87.8)	< 0.001	< 0.001	< 0.001
Usage of drugs							
Regular exerciser	1096 (17.9)	361 (20.9)	326 (20.3)	272 (18.5)	0.01	0.04	0.64
Wine consumer	45 (0.7)	18 (1)	17 (1.1)	14 (0.9)	0.26	0.30	0.52
Women							
Fatty liver	719 (10.5)	22 (5.4)	9 (4.3)	7 (8.3)	< 0.001	0.01	0.65
MS defined by rATP III	632 (9.2)	19 (4.7)	17 (8.2)	6 (7.1)	< 0.001	0.73	0.65
MS defined by IDF	494 (7.2)	12 (3)	10 (4.8)	6 (7.1)	< 0.001	0.25	0.84
Fatty liver among women with MS defined by rATP III	322 (50.9)	4 (21.1)	3 (17.6)	2 (33.3)	0.020	0.013	0.65
Fatty liver among women with MS defined by IDF	284 (57.5)	3 (25)	3 (30)	2 (33.3)	0.051	0.16	0.44
MS defined by rATP III among women with fatty liver	322 (44.8)	4 (18.2)	3 (33.3)	2 (28.6)	0.024	0.73	0.63
MS defined by IDF among women with fatty liver	284 (39.5)	3 (13.6)	3 (33.3)	2 (28.6)	0.026	0.97	0.84
Components of MS							
High waist circumference	1257 (18.2)	61 (15)	26 (12.6)	16 (19)	0.12	0.05	0.96
High blood pressure	1026 (14.9)	65 (16)	45 (21.7)	22 (26.2)	0.58	0.01	0.01
High fasting plasma glucose	906 (13.1)	70 (17.2)	33 (15.9)	19 (22.6)	0.02	0.29	0.02
Low HDL-C	1772 (25.7)	58 (14.3)	25 (12.1)	10 (11.9)	< 0.001	< 0.001	0.01
High triglycerides	507 (7.4)	12 (3)	18 (8.7)	6 (7.1)	0.00	0.56	0.89
High BMI (> 25 kg/m ²)	792 (11.5)	30 (7.4)	14 (6.8)	9 (10.7)	0.01	0.05	0.96
Smoking status							
Current smoker	372 (5.4)	50 (12.3)	57 (27.5)	25 (29.8)	< 0.001	< 0.001	< 0.001
Never smoker	6086 (88.3)	291 (71.7)	106 (51.2)	37 (44)	< 0.001	< 0.001	< 0.001
Ex smoker	804 (11.7)	115 (28.3)	101 (48.8)	47 (56)	< 0.001	< 0.001	< 0.001
Usage of drugs							
Regular exerciser	1179 (17.2)	82 (20.3)	34 (16.7)	19 (22.6)	0.13	0.91	0.25
Wine consumer	140 (2)	30 (7.4)	17 (8.2)	11 (13.1)	< 0.001	< 0.001	< 0.001

This table indicates the positive prevalence of parameters for four levels of alcohol consumption: non or minimal, < 40 g/wk; light, 40-140 g/wk; moderate, 140-280 g/wk; and excess, > 280 g/wk. Two groups of subjects were compared by using the unpaired *t* test and χ^2 test. The significance of differences between two side-by-side groups among the four groups was determined by two-tailed, multiple χ^2 tests with Bonferroni correction ($P < 0.016$ for three comparisons in four groups). Smoking status was also categorized into three groups; never smoker, ex smoker and current smoker. Regular exercisers were defined as participants who performed any kind of sports at least once a week. Usage of drugs was defined as participants who receive any drugs that potentially affected metabolic syndrome (MS). HDL-c: High-density lipoprotein-cholesterol; rATP III: Revised National Cholesterol Education Program Adult Treatment Panel III; IDF: International Diabetes Federation; BMI: Body mass index.

proven fatty liver and MS at the same time in a general population. Our study clearly indicated that the effect of alcohol was different between fatty liver and MS, although they are correlated closely. The effect of alcohol consumption on MS was not consistent, because it differed among components of MS. Alcohol consumption was associated with lower risk for HDL-C, but was associated with higher risk for high blood pressure and high fasting plasma glucose. Waist circumferences were not affected by level of alcohol consumption. Moreover, these results were similar when we used the Japan Society for The Study of Obesity definition for MS^[33]. Our study clearly indicated that light to moderate alcohol consumption was associated with lower risk of fatty liver. Moreover, any level of alcohol consumption could have a protective effect on fatty liver in men. Our study was cross-sectional, therefore, the findings might be due to changed alcohol consumption after previous detection of fatty liver. However, our sub-analysis indicated that changes in alcohol consumption were small and were not due to previous detection of fatty liver.

Previous studies have indicated that the presence of fatty liver is a strong predictor of MS^[36], and fatty liver correlates with all the components of MS^[37]. Among populations with no or light alcohol consumption, liver fat content in participants with MS is significantly increased up to fourfold higher than those without MS^[37], and the incidence of fatty liver has been shown to be increased fourfold in men and 11-fold in women with MS^[27]. Although fatty liver is considered to be a hepatic manifestation of MS, more than half of Japanese men and women with fatty liver were not diagnosed with MS.

Interpretations

Alcohol consumption is a lifestyle factor, and its effects on health range from beneficial to detrimental. The dose-response relationship between alcohol and all-cause mortality follows a J- or U-shaped curve, which points to lower all-cause mortality among those with light to moderate alcohol consumption compared to excess consumption^[38]. This effect is thought to be due mainly to a reduction in cardiovascular disease^[7]. This reduction in cardiovascular disease has been attributed to the beneficial impact of alcohol on plasma lipid levels, hemostatic factors^[8], and insulin sensitivity^[3,6]. Some studies have suggested that as much as half of the cardiovascular benefit attributable to alcohol consumption may be because it increases HDL-C level^[7-10]. We found that HDL-C was increased as the quantity of alcohol consumption increased, which was consistent with previous reports^[7-10]. On the other hand, alcohol consumption contributes to elevated blood pressure^[39,40]. Then, we also found that blood pressure was increased as the quantity of alcohol consumption increased.

In fact, studies about the association between alcohol consumption and obesity have not been consistent. Waist-to-hip ratio increases as the quantity of alcohol consumption increases^[41,42], and waist circumference in-

creases with excess alcohol consumption (> 40 g/d)^[43]. Alcohol consumption of 30 g/d or more significantly increases BMI and the risk of weight gain^[44]. In contrast, another study has reported that light-to-moderate alcohol consumption reduces waist circumference^[16]. Moreover, some studies have found no significant association between alcohol consumption and obesity^[45,46]. We also found no significant association between alcohol consumption and high waist circumference and BMI (BMI > 25 kg/m²).

Alcohol consumption may increase triglyceride concentrations^[8]. Triglycerides have been reported to be higher in individuals with excess alcohol consumption, but lower in those with light to moderate consumption^[8]. Similar results were found in our study, which indicated that the OR for high triglyceride levels was increased to > 1.0 in men with excess alcohol consumption, and was decreased to < 1.0 in women with light consumption. The favorable effect of alcohol consumption contributing to enhance insulin sensitivity has been reported^[3-6]. However, another study has provided different evidence that insulin resistance is related to alcohol consumption in a U-shaped manner^[47]. In our study, the OR for high fasting plasma glucose was increased as the level of alcohol consumption increased.

Overall, the present study proved that the effect of alcohol consumption for MS was not significant in the Japanese general population. In fact, studies regarding the association between alcohol consumption and MS have not been consistent^[11-17], because the relationship heavily depends on the individual components of MS. Moreover, previous studies have claimed that the type of alcohol is important for the association of alcohol consumption and MS^[23,48,49]. Modest wine consumption has been reported to be associated with reduced all-cause mortality^[48,49] and fatty liver^[23]. In our study, however, the association between wine consumption and MS and fatty liver was not significant. Similarly, Djousse *et al.*^[15] have reported that the association between alcohol consumption and MS is unrelated to the type of alcoholic beverage.

Findings on the relation between alcohol consumption and fatty liver have also been inconsistent^[19-25]. Fat deposition in the liver has been shown to be primarily due to an increased influx of fatty acids to the liver; most likely as a result of the increased lipolysis associated with obesity and insulin resistance, and as a result of increased hepatic *de novo* lipogenesis^[50]. Reduced fatty acid oxidation and mitochondrial dysfunction and decreased export of fat further contribute to the accumulation of liver fat^[51,52]. Alcohol-dehydrogenase-mediated ethanol metabolism generates a reduced form of nicotinamide adenine dinucleotide, which promotes steatosis by stimulating the synthesis of fatty acids and opposing their oxidation^[53]. The hepatic lipogenic pathway is activated after the consumption of 24 g/d ethanol^[53]. Sterol regulatory element binding protein 1c (SREBP1c)^[54] and peroxisome proliferator activated receptor (PPAR) α ^[55], are altered with alcohol consumption. The involvement

of AMP-activated protein kinase activity in the action of ethanol on the liver has been demonstrated in experimental models of ethanol-induced steatosis^[56].

SREBP1c is upregulated, which potentially results in increased conversion of glucose to fatty acids and triglycerides in experimental models of obesity^[52]. PPAR α is a nuclear receptor that is important in fatty acid uptake and oxidation, and has been shown to be underexpressed in experimental models of non-alcoholic steatosis^[57]. In addition, the administration of adiponectin reverses non-alcoholic steatosis in experimental models^[57,58].

Thus, several pivotal factors in the pathogenesis of fatty liver may be common in both alcoholic and non-alcoholic subjects. Therefore, the possible mechanism by which alcohol has a protective effect against fatty deposition in the liver remains unclear. Our study also provides clear evidence that light to moderate alcohol consumption has a favorable effect on fatty liver.

Some limitations of our study should be noted. First, although ultrasonography has been validated for detecting fatty liver, it may give an incorrect diagnosis compared to liver biopsy^[30]. Second, self-reported information regarding alcohol intake is frequently subject to underreporting, and misreporting could be a source of bias. However, the self-reported information regarding alcohol intake in our study was validated previously^[27]. Third, the generalizability of our study to non-Japanese populations is uncertain.

In conclusion, the effect of alcohol consumption was different between MS and fatty liver. The relationship between alcohol consumption and MS depends on the individual components of MS given the inconsistency of the association between alcohol consumption and MS. Light to moderate alcohol consumption has a favorable effect on fatty liver in Japanese men and women. Moreover, any level of alcohol consumption may have a protective effect against fatty liver in men. Unexpectedly, more than half of Japanese men and women with fatty liver were not diagnosed with MS, although fatty liver is considered to be a hepatic manifestation of MS. However, our previous studies have implied that the risk of fatty liver for cardiovascular disease is independent of MS^[59]. Thus, fatty liver without MS is an important disease in the general population.

A future longitudinal study is needed to clarify that alcohol consumption has true hepatoprotective effects. Furthermore, the protective mechanism of alcohol against fatty deposition in the liver remains unclear. Thus, basic research is also needed to clarify the mechanisms that underlie modest alcohol consumption and fatty liver.

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COMMENTS

Background

The effects of alcohol on the metabolic syndrome (MS) have been inconsistent in previous studies. Fatty liver is closely associated with MS, and is considered to be the hepatic manifestation of MS. Findings on the relation between alcohol consumption and fatty liver have also been inconsistent.

Research frontiers

The favorable effect of alcohol intake enhances insulin sensitivity, and increases high-density lipoprotein-cholesterol, which contributes to a lower risk of type 2 diabetes mellitus, and cardiovascular disease. Moreover, alcohol consumption plays a protective role against fatty deposition in the liver, although alcohol consumption certainly could be a cause of fatty liver in some cases.

Innovations and breakthroughs

The authors investigated the association of alcohol consumption with ultrasonography-proven fatty liver and the MS at the same time in a general population, and clearly indicated that light to moderate alcohol consumption has favorable and unfavorable effects for components of MS, but has a protective effect for fatty liver.

Applications

Light to moderate alcohol consumption has a favorable effect on fatty liver in Japanese men and women. Moreover, any level of alcohol consumption may have a protective effect in men. A future longitudinal study is needed to clarify that alcohol consumption has true hepatoprotective effects. Furthermore, the mechanism of alcohol protection against fatty deposition in the liver remains unclear. Thus, basic research is also needed to clarify the mechanisms that underlie the effect of modest alcohol consumption on fatty liver.

Peer review

The strengths of the study include its large sample size and validated questionnaire.

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