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Predictive Factors for the Development or Regression of Fatty Liver in Japanese Adults

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Summary **Fatty liver is commonly associated with alcohol or metabolic syndrome. We aimed to examine the longitudinal aspects of fatty liver, and clarify the independent predictors for the development or regression of fatty liver. In the present study, the clinical features of 1578 Japanese adults (1208 men and 370 women; 35 to 69 years of age) who visited our center both in 2000 and 2007–2008 were recorded and compared, including liver status diagnosed by ultrasonography. Of the 1578 participants, 217 (13.8%) showed fatty liver development, and 74 (4.7%) showed fatty liver regression. Logistic regression analysis revealed that body mass index and percentage body fat were strongly associated with the development or regression of fatty liver. Metabolic syndrome-related disorders such as serum levels of total cholesterol, triglyceride, uric acid, and fasting blood glucose were also associated with clinical course to some degree. However, the history of alcohol intake, the presence of metabolic syndrome, blood pressure, and habitual physical exercise were not independent predictors for the development or regression of fatty liver. Our present data suggest that control of body weight in men and the percentage body fat in women are particularly important for the prevention or treatment of fatty liver.**

Key Words**: fatty liver, non-alcoholic fatty liver disease, body mass index, percentage body fat, metabolic syndrome**

Introduction

Fatty liver (steatosis) is defined as an accumulation of fat, mainly triglyceride, in liver cells. This disease is commonly associated with alcohol or metabolic syndrome (diabetes mellitus, hypertension, and dyslipidemia) [*1*]. In particular, non-alcoholic fatty liver diseases (NAFLD) are recognized as the hepatic manifestation of metabolic syndrome and the prevalence of this entity is increasing in many countries [*2–4*]. In Japan, Kojima *et al.* [*5*] reported that the prevalence of fatty liver rose gradually from 12.6% in 1989 to 30.3% in 1998; this was mainly due to an increase in body mass index (BMI). Hamaguchi *et al.* [*6*] reported that

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metabolic syndrome was a risk factor for the development of NAFLD, and conversely, Fan *et al.* [*4*] suggested that the presence of NAFLD might predict the development of metabolic syndrome. Lifestyle changes, including weight loss and physical exercise, have been shown to improve the clinical course in NAFLD [*3*, *7*].

In our previous study, we examined the frequency of fatty liver diagnosed by ultrasonography (USG) in 3432 Japanese adults who visited Health Service Center, Mitsubishi Heavy Industries, Ltd., Nagasaki Shipyard and Machinery Works Hospital, Nagasaki, Japan for a thorough medical examination between January and December 2000 and found that BMI was the most independent predictor for the presence of fatty liver in both sexes [*8*]. We further reported that percentage body fat was a useful index to assess the etiology of fatty liver in non-alcoholic and non-overweight participants, particularly women.

In the present study, we aimed to examine the longitudinal aspects of fatty liver in each participant who visited the same health checkup center. We also clarified the independent predictors for the development or regression of fatty liver in non-alcoholic participants.

Materials and Methods

Study participants

Of the 3432 Japanese participants who visited the Health Service Center, Mitsubishi Heavy Industries, Ltd., Nagasaki Shipyard and Machinery Works Hospital, Nagasaki, Japan for a thorough medical examination between January and December 2000 (in 2000) [*8*], 1589 also visited the same Center between April 2007 and March 2008 (in 2007–2008). The medical examination was performed for subjects who visited the hospital voluntarily (most of them were employees or their families) to promote public health through early detection of chronic diseases. Of these 1589 participants, we excluded 6 participants who turned positive for anti-hepatitis C virus antibody and 5 participants who did not undergo USG in 2007–2008 from the present study. Therefore, the total number of study subjects was 1578 (1208 men and 370 women; mean age, 54.0 ± 4.7 years; range, 35 to 69 years). This study was performed according to the principles of the Declaration of Helsinki. The study protocol was approved by the Ethical Committees of Siebold University of Nagasaki and Mitsubishi Heavy Industries, Ltd., Nagasaki Shipyard and Machinery Works Hospital. Informed consent was obtained from all participants.

Data collection and measurements

The medical examination was performed between 8:00–11:00 am after overnight fasting. The information obtained from the medical records for the present study included sex, age, height, body weight, history of alcohol intake, present physical exercise habit, history of medical treatment for hypertension, dyslipidemia, and/or diabetes mellitus, systolic blood pressure (SBP), diastolic blood pressure (DBP), serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (GGTP), total choresterol (T.Chol.), triglyceride (TG), uric acid (UA), fasting blood glucose (FBG), percentage body fat (% fat volume), and liver status by USG.

The history of alcohol intake, present physical exercise habit and history of medical treatment for hypertension, dyslipidemia and/or diabetes mellitus were determined by questionnaire. The history of alcohol intake was divided into three groups as follows: never drinker, heavy drinker (at least 70 g/day of alcohol intake more than 5 times per week), and moderate drinker (neither never drinker nor heavy drinker). Regarding the present physical exercise habit, participants marked "yes" if they had a habit of physical exercise such as jogging, walking, or playing tennis, golf, or badminton. Regarding the history of medical treatment for hypertension, dyslipidemia and/or diabetes mellitus, participants marked "yes" if they had been receiving medical treatment for such diseases.

The body mass index (BMI) was calculated as body weight (kg) divided by height (m^2). Overweight was defined as a BMI of ≥25 kg/m^2 [*9*]. The percentage body fat measurement was performed using a bipedal bioimpedance instrument (Body Fat Analyzer TBF-202; Tanita, Tokyo, Japan). Obesity was defined for Japanese adults as ≥25% body fat for men and ≥30% body fat for women [*8*].

Abdominal ultrasonography was performed by clinical hepatogastroenterologists or trained technicians without knowledge of the anthropometric and laboratory data. When USG was performed by a trained technician, one hepatogastroenterologist reviewed the stored ultrasonographic images and made the final diagnosis. The diagnosis of fatty liver by USG (Aloka Pro Sound SSD-4000; Aloka, Tokyo, Japan) was based on the findings of "bright liver" (increased echogenicity) with "liver-kidney contrast" (increased echo level of the liver compared with the right kidney). "Vascular blurring" (blurring of the hepatic vein) and "deep attenuation" (attenuation of the echo level in the deep region of the liver) were also seen in many cases, but their absence did not exclude the diagnosis of fatty liver.

The standard Japanese criteria for the diagnosis of metabolic syndrome are as follows. The presence of visceral fat accumulation (defined as waist circumference ≥85 cm for men and ≥90 cm for women) is an indispensable factor, with any two or more of the following criteria: (1) a high serum level of triglyceride (≥150 mg/dL or ≥1.7 mmol/L) and/or low serum level of high-density lipoprotein (HDL) cholesterol (<40 mg/dL or <1.03 mmol/L) or receiving specific treatment for these abnormalities; (2) high blood pressure (SBP ≥130 mmHg and/or DBP ≥85 mmHg) or

receiving specific treatment for hypertension; (3) high FBG concentration (≥110 mg/dL or ≥6.11 mmol/L) or receiving specific treatment for glucose abnormality [*10*]. Because waist circumference and serum level of HDL cholesterol were not available in our study subjects, we substituted a BMI ≥25 kg/m^2 for waist circumference, and omitted the HDL cholesterol. Therefore, we defined a "tentative metabolic syndrome" as follows: BMI ≥25 kg/m^2 plus at least two of the following three factors: (1) a high serum level of triglyceride (≥150 mg/dL) or receiving specific treatment for triglyceride abnormality; (2) high blood pressure (SBP ≥130 mmHg and/or DBP ≥85 mmHg) or receiving specific treatment for hypertension; (3) high FBG concentration (≥110 mg/dL) or receiving specific treatment for glucose abnormality. Serum level of low-density lipoprotein (LDL) cholesterol was also unavailable in our study population.

Comparison of data between 2000 and 2007–2008

In the comparison of each individual participant's data between 2000 and 2007–2008, "% change" in BMI and the percentage body fat was calculated as follows: {[(data in 2007–2008) − (data in 2000)] / data in 2000} × 100. "Change" in blood pressures and laboratory data was calculated as follows: (data in 2007–2008) − (data in 2000). Regarding alcohol behavior, participants were divided into following four groups: non-drinker {never drinker or occasional drinker (1–4 times per week) in 2000 [*8*], and never drinker in 2007–2008}; continuous drinker {almost every day drinker (at least 23 g/day of alcohol intake 5–7 times per week) in 2000 [*8*], and heavy drinker or moderate drinker in 2007–2008}, former drinker (almost every day drinker in 2000 and never drinker in 2007–2008); and others (neither non-drinker, continuous drinker, nor former drinker).

Statistical analysis

Data were expressed as mean ± standard deviation (SD) or median (range). Differences between groups were examined for statistical significance using the two-tailed Mann-Whitney *U* test, Wilcoxon signed-rank test, chi-square test, or Fisher's exact probability test. Multivariate analysis for the development or regression of fatty liver was performed for variables that were significant in univariate analyses using logistic regression analysis. Correlations were examined by linear regression analysis using the coefficient of correlation. All data analyses were performed using SPSS statistical package, version 16.0J (SPSS, Inc., Chicago, IL) on a computer with a Windows operating system. A *p*-value less than 0.05 was considered statistically significant.

Results

Clinical and laboratory features of participants in 2007–2008

The participants' age in 2007–2008 was significantly higher in men (54.4 ± 4.7 years; range, 41 to 69 years) than in women (52.7 ± 4.6 years; range, 35 to 65 years) (p<0.001). The number and frequency of participants for each clinical and laboratory feature are shown in Table 1. Of the 1578 participants, fatty liver was diagnosed by USG in 501 (31.7%). Of the 370 women in the study, 247 (66.8%) were obese (≥30% fat volume).

Fatty liver was more frequently seen in men and overweight as well as obese participants. Systolic and diastolic blood pressure, serum levels of AST, ALT, GGTP, T.Chol, TG, UA, and FBG were higher in participants with fatty liver than in those with non-fatty liver. Participants who have "tentative metabolic syndrome" and who had been receiving treatment for hypertension, dyslipidemia and/or diabetes mellitus were more frequently found in the fatty liver group. In contrast, there were no significant differences in age and the proportion of alcohol drinker between the fatty liver and non-fatty liver groups of participants. Physical exercise habit was more common in the non-fatty liver group (Table 2).

Comparison of clinical and laboratory features between 2000 and 2007–2008

The median interval in thorough medical examinations between 2000 and 2007–2008 was 84.0 months (range, 76 to 98 months). Between 2000 and 2007–2008, the change in median body weight, BMI, and percentage body fat was +0.8 kg (range, −16.4 to +19.8 kg), +0.4 kg/m^2 (range, −5.4 to +7.6 kg/m^2), and +0.2% (range, −11.2 to +21.7%), respectively. Body mass index, percentage body fat, serum levels of AST, ALT, GGTP, T.Chol., TG, UA, and FBG were higher in participants in 2007–2008 than in 2000. In contrast, DBP was lower in 2007–2008 than in 2000 (Table 3). In 2000, fatty liver was diagnosed by USG in 358 of the 1578 participants. Of these 358 participants, 284 had fatty liver in 2007–2008. Of the 1220 participants who did not have fatty liver in 2000, 217 had fatty liver in 2007–2008 (Fig. 1).

Clinical and laboratory features of participants who were classified as non-drinkers

To determine the clinical and laboratory features of fatty liver and non-fatty liver in non-alcoholic participants, the data from 346 participants who were classified as non-drinkers [never drinker or occasional drinker (1–4 times per week) in 2000 [*8*] and never drinker in 2007–2008] were analyzed. Of these 346 participants, 102 had fatty liver in 2007–2008 and fatty liver was more frequently seen in men, overweight, and obese participants. Systolic and diastolic

Table 1. Number and frequency of participants for each clinical and laboratory feature in 2007–2008 (n = 1578)

Feature	No. of subjects	Frequency (%)
Fatty liver by USG	501	31.7
Alcohol consumption		
Never drinker	365	23.1
Drinker	1098	69.6
Heavy drinker	71	4.5
ND	44	2.8
Physical exercise habit		
Yes	536	34.0
No	1031	65.3
ND	11	0.7
BMI≥25 kg/m^2	414	26.2
% fat volume excess (men and women)	596	37.8
% fat volume≥25% (men)	349	28.9
% fat volume≥30% (women)	247	66.8
SBP≥130 mmHg	505	32.0
DBP≥85 mmHg	194	12.3
AST≥34 IU/L	145	9.2
ALT≥43 IU/L	158	10.0
GGTP≥48 IU/L	558	35.4
T.Chol.≥220 mg/dL	637	40.4
TG≥150 mg/dL	393	24.9
UA≥7.6 mg/dL	167	10.6
FBG≥110 mg/dL	302	19.1
Tentative metabolic syndrome	164	10.4
Receiving treatment for HT, DL, and/or DM	430	27.2

USG, ultrasonography; ND, not described; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGTP, gamma-glutamyl transpeptidase; T.Chol., total cholesterol; TG, triglyceride; UA, uric acid; FBG, fasting blood glucose; HT, hypertension; DL, dyslipidemia; DM, diabetes mellitus.

blood pressures, serum levels of AST, ALT, GGTP, TG, UA, and FBG were higher in participants with fatty liver than in those without fatty liver. Participants who had "tentative metabolic syndrome" and who had been receiving treatment for hypertension, dyslipidemia and/or diabetes mellitus were more frequently found in the fatty liver group. In contrast, there were no significant differences in age and serum level of T.Chol. between participants with and without fatty liver. Physical exercise habit was more common in the non-fatty liver group (Table 4). In 2000, fatty liver was diagnosed in 73 of the 346 participants who were classified as non-drinkers. Of these 73 participants, 12 no longer had evidence of fatty liver in 2007–2008. Of the 273 participants who were classified as non-drinkers and who did not have fatty liver in 2000, 41 had fatty liver in 2007–2008 (Fig. 2).

Comparison of clinical and laboratory features of fatty liver and non-fatty liver in 2007–2008

Men and women were separately analyzed in comparisons of clinical and laboratory features of fatty liver and non-fatty liver in 2007–2008 in participants who did not have fatty liver in 2000 (n = 1220). Body mass index in 2000, % change in BMI, percentage body fat in 2000, % change in percentage body fat, TG in 2000, change in UA, and change in FBG were higher in participants who had fatty liver in 2007–2008 in both sexes. Also, the development of "tentative metabolic syndrome" was more common in participants who had fatty liver in 2007–2008 in both sexes. Systolic blood pressure and T.Chol. in 2000, and change in TG were higher in men who had fatty liver in 2007–2008. Participants who had been receiving specific treatment for hypertension, dyslipidemia and/or diabetes mellitus were more frequent

Table 2. Comparison of clinical and laboratory features of fatty liver and non-fatty liver in 2007–2008 (n = 1578)

Feature	Fatty liver (n = 501)	Non-fatty liver (n = 1077)	p
Men/women	427/74	781/296	<0.001
Age (years)	55 (41–69)	55 (35–69)	0.514
Alcohol (heavy/moderate/never drinker)	22/356/107	49/742/258	0.642
Physical exercise habit (yes/no)	138/359	398/672	0.001
BMI (kg/m^2)	25.1 (17.4–46.0)	22.3 (12.8–32.8)	<0.001
% fat volume (men)	25.7 (14.0–42.0)	20.8 (7.0–35.0)	<0.001
% fat volume (women)	34.3 (22.5–53.8)	26.2 (6.6–41.3)	<0.001
SBP (mmHg)	126 (88–161)	121 (81–177)	<0.001
DBP (mmHg)	76 (54–101)	74 (45–105)	<0.001
AST (IU/L) (NV: 13–33)	25 (9–137)	21 (11–69)	<0.001
ALT (IU/L) (NV: 8–42)	31 (2–169)	19 (5–123)	<0.001
GGTP (IU/L) (NV: 10–47)	50 (12–850)	30 (5–701)	<0.001
T.Chol. (mg/dL) (NV: 130–219)	216 (150–370)	211 (115–319)	0.003
TG (mg/dL) (NV: 46–149)	132 (42–1116)	92 (20–990)	<0.001
UA (mg/dL) (NV: 2.6–7.5)	6.3 (0.7–12.0)	5.5 (1.8–11.8)	<0.001
FBG (mg/dL) (NV: 70–109)	103 (76–295)	97 (66–221)	<0.001
Tentative metabolic syndrome (present/absent)	131/370	33/1044	<0.001
Receiving treatment for HT, DL, and/or DM (yes/no)	185/316	245/832	<0.001

Age, BMI, % fat volume, blood pressure and biochemical data are expressed as median (range).
NV, normal value. Refer to the legend of Table 1 for other abbreviations.

Table 3. Comparison of clinical and laboratory features between 2000 and 2007–2008 (n = 1578)

Feature	2000	2007–2008	p
BMI (kg/m^2)	22.8 (14.8–45.1)	23.1 (12.8–46.0)	<0.001
% fat volume (men)	22.2 (9.2–52.6)	22.4 (7.0–42.0)	0.008
% fat volume (women)	26.9 (11.5–49.8)	27.6 (6.6–53.8)	0.008
SBP (mmHg)	121 (79–199)	123 (81–177)	0.937
DBP (mmHg)	76 (43–121)	75 (45–105)	<0.001
AST (IU/L)	20 (9–153)	22 (9–137)	<0.001
ALT (IU/L)	19 (2–130)	21 (4–169)	<0.001
GGTP (IU/L)	28 (6–438)	36 (5–850)	<0.001
T.Chol. (mg/dL)	207 (106–334)	212 (115–370)	<0.001
TG (mg/dL)	93 (22–1516)	104 (20–1116)	<0.001
UA (mg/dL)	5.5 (1.0–10.0)	5.8 (0.7–12.0)	<0.001
FBG (mg/dL)	94 (65–243)	99 (66–295)	<0.001

Data are expressed as median (range).
Refer to the legend of Table 1 for abbreviations.

in men who had fatty liver in 2007–2008 (Table 5). In participants who had fatty liver in 2000 (n = 358), TG in 2000 and change in FBG were significantly lower in participants whose fatty livers had regressed by 2007–2008 in both sexes. Body mass index in 2000, % change in BMI, percentage body fat in 2000, % change in percentage body fat, and UA in 2000 were lower in men whose fatty livers had regressed by 2007–2008. Also, the development of "tentative metabolic syndrome" was less common in men whose fatty livers had regressed by 2007–2008. Non-drinkers were less common in women whose fatty livers had regressed by 2007–2008 (Table 6).

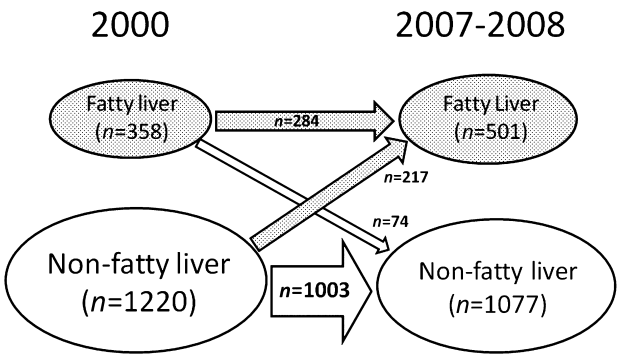

Fig. 1. Number of participants with fatty liver and non-fatty liver in 2000 and 2007–2008 (n = 1578)

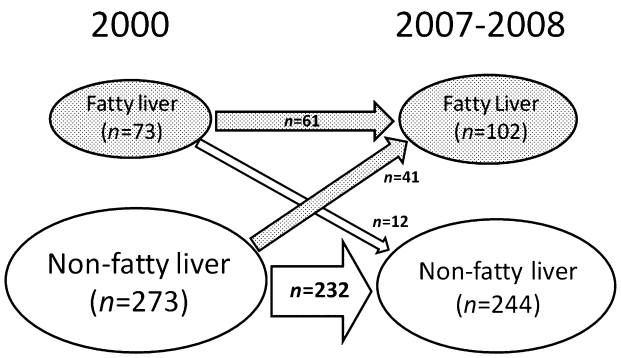

Fig. 2. Number of participants who were classified as non-drinkers with fatty liver and non-fatty liver in 2000 and 2007–2008 (n = 346)

Table 4. Comparison of clinical and laboratory features of fatty liver and non-fatty liver in 2007–2008 in participants who were classified as non-drinkers (n = 346)

Feature	Fatty liver (n = 102)	Non-fatty liver (n = 244)	p
Men/women	59/43	96/148	0.002
Age (years)	55 (42–65)	54 (35–63)	0.359
Physical exercise habit (yes/no)	17/83	72/170	0.034
BMI (kg/m^2)	25.2 (19.4–45.2)	21.6 (16.2–32.8)	<0.001
% fat volume (men)	24.5 (19.0–34.6)	19.8 (10.6–30.7)	<0.001
% fat volume (women)	34.5 (25.3–53.8)	26.5 (14.3–40.6)	<0.001
SBP (mmHg)	123 (91–161)	118 (82–177)	0.002
DBP (mmHg)	73.5 (58–93)	70 (48–103)	0.001
AST (IU/L) (NV: 13–33)	23 (12–91)	20 (11–61)	<0.001
ALT (IU/L) (NV: 8–42)	30 (11–112)	17 (5–69)	<0.001
GGTP (IU/L) (NV: 10–47)	33 (12–140)	19 (9–534)	<0.001
T.Chol. (mg/dL) (NV: 130–219)	216 (163–370)	213.5 (119–319)	0.360
TG (mg/dL) (NV: 46–149)	118 (49–349)	80 (30–484)	<0.001
UA (mg/dL) (NV: 2.6–7.5)	5.5 (3.1–9.3)	4.8 (2.2–8.6)	<0.001
FBG (mg/dL) (NV: 70–109)	102 (76–175)	94 (66–129)	<0.001
Tentative metabolic syndrome (present/absent)	21/81	1/243	<0.001
Receiving treatment for HT, DL, and/or DM (yes/no)	32/70	42/202	0.003

Age, BMI, % fat volume, biochemical and blood pressure data are expressed as median (range).
NV, normal value. Refer to the legend of Table 1 for other abbreviations.

In participants who were classified as non-drinkers and who did not have fatty liver in 2000 (n = 273), body mass index in 2000, % change in BMI, percentage body fat in 2000, and % change in percentage body fat were significantly higher in participants who had fatty liver in 2007–2008 in both sexes. Total cholesterol and TG in 2000 were also higher in men who had fatty liver in 2007–2008. In women, change in TG and UA were higher in participants who had fatty liver in 2007–2008 (Table 7). In participants who were classified as non-drinkers and who had fatty liver in 2000 (n = 73), % change in BMI, % change in percentage body fat, and change in FBG were significantly lower in men whose fatty livers regressed in 2007–2008. Because there were only two women whose fatty livers regressed in 2007–2008, statistical analysis between features of fatty and non-fatty liver participants in 2007–2008 could not sufficiently performed in women (Table 8).

Table 5. Comparison of clinical and laboratory features of fatty liver and non-fatty liver in 2007–2008 in participants who did not have fatty liver in 2000 (n = 1220)

Feature	Men (n = 891)			Women (n = 329)		
	Fatty liver in 2007–2008 (n = 177)	Non-fatty liver in 2007–2008 (n = 714)	p	Fatty liver in 2007–2008 (n = 40)	Non-fatty liver in 2007–2008 (n = 289)	p
Age (years) in 2000	48 (34–61)	48 (34–62)	0.121	47 (36–53)	46 (29–58)	0.367
Alcohol in 2000 (drinker/non-drinker)	119/58	508/206	0.307	4/36	30/259	0.941
Alcohol behavior (non-drinker/continuous/former drinker/others)	19/115/1/36	86/482/11/117	0.552	22/3/1/13	146/28/2/108	0.751
Physical exercise habit (yes/no)	59/116	278/430	0.375	11/29	102/186	0.572
BMI (kg/m^2) in 2000	23.4 (18.5–32.8)	22.3 (16.5–28.3)	<0.001	22.9 (18.4–28.8)	21.0 (14.8–28.6)	<0.001
% change in BMI*	+4.6 (−10.3–+18.9)	+1.0 (−14.2–+22.6)	<0.001	+6.8 (−9.2–+38.8)	+0.5 (−17.7–+19.9)	<0.001
% fat volume in 2000	22.6 (14.0–32.0)	20.7 (9.2–35.6)	<0.001	30.5 (22.2–39.3)	25.7 (11.5–41.0)	<0.001
% change in % fat volume*	+7.7 (−38.1–+66.2)	−0.5 (−47.1–+75.4)	<0.001	+9.0 (−18.5–+84.2)	+0.3 (−42.6–+106.0)	<0.001
SBP (mmHg) in 2000	124 (88–199)	121 (83–165)	0.003	120 (85–176)	115 (79–163)	0.085
Change in SBP (mmHg)**	+1 (−53–+43)	+1 (−48–+49)	0.655	−1 (−42–+58)	+2 (−38–+42)	0.440
DBP (mmHg) in 2000	77 (56–121)	77 (47–100)	0.061	74.5 (53–114)	71 (43–100)	0.213
Change in DBP (mmHg)**	−1 (−32–+27)	−2 (−40–+26)	0.436	−1.5 (−20–+16)	−1 (−28–+25)	0.435
T.Chol. (mg/dL) in 2000	212 (142–298)	202 (123–334)	0.003	205 (159–314)	205 (106–321)	0.669
Change in T.Chol. (mg/dL)**	+10 (−107–+87)	+6 (−159–+91)	0.065	+26 (−103–+112)	+19 (−109–+98)	0.202
TG (mg/dL) in 2000	119 (42–656)	88.5 (26–1516)	<0.001	76 (40–166)	63 (22–236)	0.002
Change in TG (mg/dL)**	+20 (−425–+323)	+7 (−535–+831)	<0.001	+20.5 (−58–+167)	+14 (−73–+192)	0.065
UA (mg/dL) in 2000	5.7 (2.8–8.7)	5.7 (1.7–9.5)	0.146	4.2 (2.0–7.4)	4.1 (1.7–7.5)	0.713
Change in UA (mg/dL)**	+0.6 (−3.7–+3.2)	+0.3 (−3.4–+4.0)	<0.001	+0.8 (−1.1–+2.1)	+0.3 (−1.5–+2.3)	<0.001
FBG (mg/dL) in 2000	94 (65–158)	94 (75–203)	0.550	90 (78–132)	90 (65–120)	0.788
Change in FBG (mg/dL)**	+8 (−12–+80)	+5 (−58–+82)	<0.001	+7 (−13–+42)	+2 (−19–+76)	0.014
Tentative metabolic syndrome in 2000 (present/absent)	2/175	13/701	0.523	1/39	2/287	0.323
Change in tentative metabolic syndrome between 2000 and 2007–2008 (present-present/present-absent/absent-present/absent-absent)	2/0/26/149	6/7/17/684	<0.001	1/0/3/36	2/0/0/287	<0.001
Receiving treatment for HT, DL, and/or DM (yes/no)	59/118	181/533	0.032	10/30	39/250	0.055

* % change was calculated as follows: {[(data in 2007–2008) – (data in 2000)] / data in 2000} × 100.
** Change was calculated as follows: (data in 2007–2008) – (data in 2000).
Age, BMI, % fat volume, biochemical and blood pressure data are expressed as median (range).
Refer to the legend of Table 1 for abbreviations.

Independent predictors for the development or regression of fatty liver in 2007–2008 by logistic regression analysis

The logistic regression analysis showed that high percentage body fat in 2000, increase in UA, and positive % change in percentage body fat were independent predictors for the development of fatty liver in 2007–2008 in both sexes. In addition, positive % change in BMI, increase in FBG, and high serum levels of T.Chol. and TG were independent predictors for the development of fatty liver in 2007–2008 in men. Negative % change in BMI and low BMI in 2000 were independent predictors for the regression of fatty liver in 2007–2008 in men, and a decrease in FBG was an independent predictor for the regression of fatty liver in 2007–2008 in women (Table 9).

In participants who were classified as non-drinkers, positive % change in BMI and high percentage body fat in 2000 were independent predictors for the development of fatty liver in 2007–2008 in men and women, respectively. Negative % change in BMI and decrease in FBG were independent predictors for the regression of fatty liver in 2007–2008 in men (Table 9).

Discussion

The relation between fatty liver and metabolic syndrome-related disorders such as obesity is well known, but data from longitudinal observation (with sufficient duration) of individuals in a large population are hitherto sparse. Kojima *et al.* [*5*] reported that 5088 (14.3%) of 35519 participants developed fatty liver, and that fatty liver resolved in 1248 (3.5%) of those participants during the follow-up period from 1989 to 2000. They further reported that BMI, as well as the relative change in BMI in each individual, was related to the onset of fatty liver, followed by serum levels of TG

Table 6. Comparison of clinical and laboratory features of fatty liver and non-fatty liver in 2007–2008 in participants who had fatty liver in 2000 (n = 358)

Feature	Men (n = 317)			Women (n = 41)		
	Fatty liver in 2007–2008 (n = 250)	Non-fatty liver in 2007–2008 (n = 67)	p	Fatty liver in 2007–2008 (n = 34)	Non-fatty liver in 2007–2008 (n = 7)	p
Age (years) in 2000	47 (34–58)	47 (35–54)	0.889	47 (35–56)	46 (39–50)	0.282
Alcohol in 2000 (drinker/non-drinker)	158/92	50/17	0.080	1/33	3/4	0.012
Alcohol behavior (non-drinker/continuous/former drinker/others)	40/149/3/49	10/44/1/7	0.321	12/0/1/21	2/0/3/2	0.005
Physical exercise habit (yes/no)	66/182	16/51	0.689	2/32	2/5	0.128
BMI (kg/m^2) in 2000	25.4 (19.1–45.1)	24.6 (19.1–29.8)	0.002	26.1 (21.5–41.3)	24.7 (21.1–27.6)	0.198
% change in BMI*	+2.3 (−20.0–+18.7)	−1.8 (−14.1–+9.6)	<0.001	+3.0 (−10.4–+14.0)	−0.1 (−9.1–+5.8)	0.125
% fat volume in 2000	25.8 (14.8–52.6)	24.2 (17.1–33.0)	0.012	35.8 (18.4–49.8)	31.6 (26.2–38.9)	0.144
% change in % fat volume*	+1.5 (−41.4–+63.6)	−4.7 (−32.5–+66.3)	<0.001	+2.2 (−25.7–+84.8)	+5.2 (−25.3–+9.3)	0.879
SBP (mmHg) in 2000	128 (79–171)	124 (79–161)	0.608	127 (98–162)	129 (105–153)	0.879
Change in SBP (mmHg)**	−1 (−58–+43)	−3 (−55–+24)	0.326	−4 (−50–+25)	−7 (−39–+6)	0.672
DBP (mmHg) in 2000	80 (43–107)	80 (51–107)	0.691	79 (58–100)	77 (67–93)	0.906
Change in DBP (mmHg)**	−4 (−38–+30)	−5 (−32–+21)	0.900	−5.5 (−28–+13)	−3 (−30–+2)	0.959
T.Chol. (mg/dL) in 2000	214 (140–320)	209 (142–317)	0.635	221 (136–271)	211 (178–248)	0.599
Change in T.Chol. (mg/dL)**	±0 (−107–+87)	−7 (−79–+54)	0.241	+9 (−90–+73)	+7 (−28–+76)	0.959
TG (mg/dL) in 2000	154 (36–586)	110 (48–753)	0.009	128 (49–336)	73 (40–132)	0.041
Change in TG (mg/dL)**	±0 (−378–+713)	−6 (−545–+279)	0.400	+1.5 (−210–+193)	±0 (−6–+18)	0.826
UA (mg/dL) in 2000	6.4 (0.7–10.1)	6.0 (2.9–8.3)	0.017	4.9 (3.1–6.2)	4.2 (3.4–6.2)	0.799
Change in UA (mg/dL)**	+0.2 (−5.8–+4.1)	±0 (−1.8–+1.8)	0.201	+0.4 (−1.2–+2.6)	+0.5 (−0.2–+1.5)	0.826
FBG (mg/dL) in 2000	98.5 (76–243)	99 (80–197)	0.208	96.5 (77–128)	96 (88–111)	0.747
Change in FBG (mg/dL)**	+8 (−125–+87)	+3 (−32–+31)	0.001	+7 (−10–+63)	−1 (−16–+4)	0.003
Tentative metabolic syndrome in 2000 (present/absent)	53/197	11/56	0.387	2/32	0/7	1.000
Change in tentative metabolic syndrome between 2000 and 2007–2008 (present-present/present-absent/absent-present/absent-absent)	43/10/47/150	5/6/3/53	0.001	2/0/7/25	0/0/0/7	0.305
Receiving treatment for HT, DL, and/or DM (yes/no)	102/148	23/44	0.336	14/20	2/5	0.534

Refer to the legends of Table 1 and 5 for abbreviations.

and FBG in both sexes, and that alcohol intake did not have any relation to the onset of fatty liver, in contrast with the data from the Dionysos study [*11*]. Our present results were partly in line with these findings, because 217 (13.8%) of 1578 participants developed fatty liver, which resolved in 74 (4.7%) participants, and the logistic regression analysis revealed that alcohol consumption was not a predictor for the development of fatty liver as previously reported [*8*, *12*]. However, in contrast with the results by Kojima *et al.* [*5*], not BMI but high percentage body fat in 2000 and increased % change in percentage body fat during the follow-up period in each participant were independent predictors for the development of fatty liver in both sexes in the present study. Eguchi *et al.* [*13*] reported that hepatic fat infiltration in NAFLD might be influenced by visceral fat accumulation regardless of BMI. Imamura *et al.* [*14*] also reported that altered body composition, particularly increased percentage body fat without an increase in BMI, was strongly associated with the increasing prevalence of fatty liver.

Indeed, the change in BMI between 2000 and 2007–2008 was constantly associated with the development and regression of fatty liver in men regardless of the history of alcohol intake in the present study. In contrast, in women, a high percentage body fat in 2000 was associated with the development of fatty liver in 2007–2008 regardless of alcohol consumption. The BMI is chosen as a measure of overall adiposity and elevated percentage body fat with normal BMI can be presumed to reflect central body fat distribution [*8*]. Lonardo *et al.* [*12*] reported that women with fatty liver had a more central fat distribution, which reflects visceral fat, than women without fatty liver, and concluded that this central-type body fat distribution predicted fatty liver only in women. Our results support these data and sex differences in the pathogenesis and treatment of fatty liver, particularly NAFLD, should be further determined.

Metabolic syndrome-related disorders with abnormal serum levels of T.Chol., TG, UA, and FBG were associated with the development or regression of fatty liver in men and women with or without alcohol intake in the present study.

Table 7. Comparison of clinical and laboratory features of fatty liver and non-fatty liver in 2007–2008 in participants who were classified as non-drinkers and who did not have fatty liver in 2000 (n = 273)

Feature	Men (n = 105)			Women (n = 168)		
	Fatty liver in 2007–2008 (n = 19)	Non-fatty liver in 2007–2008 (n = 86)	p	Fatty liver in 2007–2008 (n = 22)	Non-fatty liver in 2007–2008 (n = 146)	p
Age (years) in 2000	49 (34–55)	48 (34–56)	0.809	47 (36–53)	46 (29–55)	0.409
Physical exercise habit (yes/no)	3/15	32/53	0.120	6/16	40/105	0.927
BMI (kg/m^2) in 2000	23.2 (19.9–25.7)	21.4 (16.5–26.2)	0.003	22.5 (19.8–26.4)	21.4 (16.5–28.6)	0.001
% change in BMI*	+4.3 (−1.9–+17.4)	+1.0 (−8.4–+22.6)	0.006	+6.8 (−2.7–+19.6)	±0 (−17.7–+19.9)	<0.001
% fat volume in 2000	20.9 (17.7–31.3)	18.7 (9.6–35.6)	0.006	30.4 (23.6–37.6)	25.9 (16.7–35.6)	<0.001
% change in % fat volume*	+8.5 (−6.4–+30.9)	−0.5 (−29.7–+61.1)	0.016	+10.4 (−5.9–+38.0)	−0.8 (−33.9–+106.0)	<0.001
SBP (mmHg) in 2000	117 (100–140)	114 (83–149)	0.206	119.5 (85–158)	115 (79–163)	0.342
Change in SBP (mmHg)**	+4 (−15–+23)	+2 (−32–+32)	0.963	−1 (−42–+58)	+2 (−38–+38)	0.457
DBP (mmHg) in 2000	73 (57–89)	72 (47–94)	0.405	72.5 (53–88)	71 (43–100)	0.544
Change in DBP (mmHg)**	−3 (−19–+8)	−1 (−17–+22)	0.191	−1.5 (−20–+16)	−2 (−28–+20)	0.432
T.Chol. (mg/dL) in 2000	212 (183–255)	196.5 (133–328)	0.021	208 (162–307)	204.5 (106–309)	0.485
Change in T.Chol. (mg/dL)**	+10 (−42–+33)	+4 (−159–+77)	0.191	+26 (−67–+112)	+19 (−44–+97)	0.231
TG (mg/dL) in 2000	116 (47–242)	81 (26–545)	0.001	67.5 (48–166)	63.5 (27–221)	0.210
Change in TG (mg/dL)**	+13 (−54–+117)	+10 (−382–+181)	0.606	+29.5 (−42–+167)	+12.5 (−63–+192)	0.035
UA (mg/dL) in 2000	5.8 (2.8–8.7)	5.3 (2.1–7.8)	0.053	4.2 (2.0–6.6)	4.1 (2.3–7.5)	0.974
Change in UA (mg/dL)**	+0.6 (−0.2–+1.6)	+0.2 (−2.3–+2.8)	0.058	+1.1 (−0.6–+1.8)	+0.4 (−1.1–+2.3)	0.004
FBG (mg/dL) in 2000	95 (79–102)	90 (78–108)	0.141	90 (78–132)	91 (65–120)	0.693
Change in FBG (mg/dL)**	+6 (−5–+22)	+4 (−14–+24)	0.431	+5.5 (−9–+42)	+2 (−19–+76)	0.073
Tentative metabolic syndrome in 2000 (present/absent)	0/19	0/86	—	1/21	0/146	0.131
Change in tentative metabolic syndrome between 2000 and 2007–2008 (present-present/present-absent/absent-present/absent-absent)	0/0/2/17	0/0/1/85	0.084	1/0/0/21	0/0/0/146	0.131
Receiving treatment for HT, DL, and/or DM (yes/no)	2/17	17/69	0.515	6/16	23/123	0.183

Refer to the legends of Table 1 and 5 for abbreviations.

However, the presence of "tentative metabolic syndrome" was not an independent predictor for the development or regression of fatty liver. Hamaguchi *et al.* [*6*] studied 4401 Japanese adults, and 308 (7.0%) of those participants developed fatty liver, which resolved in 113 (2.6%) participants during the mean follow-up period of 414 days. In their study population, the presence of metabolic syndrome at baseline was one of the independent predictors for the development and regression of fatty liver in both sexes. One possible explanation for these discrepant results may be the difference in diagnostic criteria of the metabolic syndromes. In contrast with the ATP III criteria [*15*], which were adopted by Hamaguchi *et al.* [*6*], the Japanese criteria for the diagnosis of metabolic syndrome adopted in the present study defined the presence of central obesity (waist circumference) as a pre-requisite and indispensable factor [*10*]. Because waist circumference was not available in our study subjects, we followed the method used by Hamaguchi *et al.* [*6*] and substituted a BMI ≥25 kg/m^2 instead of waist circumference. However, if the participants were not overweight as judged by BMI, they failed to be included in the group of subjects with "tentative metabolic syndrome". Since International Diabetes Federation also proposed central obesity (waist circumference) as an indispensable factor for the diagnosis of metabolic syndrome [*16*], detailed evaluation of metabolic syndrome including the measurement of waist circumference should be performed in the near future.

Blood pressures, both SBP and DBP, and physical activity were not independent predictors for the development or regression of fatty liver in our study population. Donati *et al.* [*17*] reported that insulin resistance, a factor independently associated with fatty liver, was predicted by the presence of arterial hypertension in non-obese, non-diabetic, non-heavy alcohol drinking patients with arterial hypertensive and normal liver enzymes. Akahoshi *et al.* [*18*] also reported that non-obese male participants with fatty liver had the highest odds ratio for hypertension. Unfortunately, we did not perform such analysis, and the discrepancy between these results and ours is unclear. The association between arterial hypertension or physical activity and fatty liver remains uncertain and requires further investigation. Physical activity may also reduce the associated risk factors and prevent the progression of fatty liver, especially NAFLD, but the independent contribution on variations in liver fat is so far

Table 8. Comparison of clinical and laboratory features of fatty liver and non-fatty liver in 2007–2008 in participants who were classified as non-drinkers and who had fatty liver in 2000 (n = 73)

Feature	Men (n = 50)			Women (n = 23)		
	Fatty liver in 2007–2008 (n = 40)	Non-fatty liver in 2007–2008 (n = 10)	p	Fatty liver in 2007–2008 (n = 21)	Non-fatty liver in 2007–2008 (n = 2)	p
Age (years) in 2000	47 (35–57)	47.5 (35–54)	0.747	47 (35–56)	48.5 (47–50)	0.711
Physical exercise habit (yes/no)	6/33	0/10	0.362	2/19	0/2	1.000
BMI (kg/m^2) in 2000	25.6 (22.2–31.6)	24.7 (21.6–27.7)	0.511	24.3 (21.7–41.3)	23.6 (21.5–25.7)	0.332
% change in BMI*	+3.0 (−7.9–+18.4)	−1.5 (−14.1–+2.8)	0.004	+2.1 (−10.4–+14.0)	+2.3 (−0.1–+4.7)	0.870
% fat volume in 2000	24.3 (17.8–34.2)	23.9 (18.4–32.7)	0.839	36.1 (28.8–49.1)	31.1 (26.2–36.0)	0.285
% change in % fat volume*	+4.5 (−20.2–+63.6)	−4.3 (−22.0–+20.7)	0.020	+0.2 (−25.7–+21.5)	+2.2 (−3.1–+7.5)	0.711
SBP (mmHg) in 2000	122.5 (93–160)	120 (112–156)	0.896	125 (98–159)	148 (143–153)	0.198
Change in SBP (mmHg)**	+3.5 (−41–+31)	−1.5 (−27–+24)	0.296	−7 (−46–+25)	−14.5 (−32–+3)	0.640
DBP (mmHg) in 2000	77 (63–102)	77 (56–87)	0.711	77 (58–100)	85 (77–93)	0.569
Change in DBP (mmHg)**	−1.5 (−17–+17)	−5 (−19–+21)	0.693	−5 (−28–+13)	−8.5 (−9—8)	0.387
T.Chol. (mg/dL) in 2000	211 (152–302)	198.5 (181–257)	0.465	204 (136–271)	233 (218–248)	0.640
Change in T.Chol. (mg/dL)**	+9 (−107–+68)	+2 (−40–+54)	0.896	+9 (−90–+61)	−5.5 (−22–+11)	0.569
TG (mg/dL) in 2000	128.5 (46–414)	104 (48–271)	0.319	128 (49–336)	68 (40–96)	0.198
Change in TG (mg/dL)**	+7.5 (−214–+251)	+1 (−75–+213)	0.933	−5 (−210–+53)	+12.5 (+7–+18)	0.387
UA (mg/dL) in 2000	6.2 (3.5–8.5)	5.8 (3.8–7.3)	0.465	4.8 (3.1–6.2)	3.85 (3.5–4.2)	0.237
Change in UA (mg/dL)**	+0.2 (−3.6–+3.0)	−0.1 (−0.9–+1.3)	0.711	+0.3 (−1.2–+1.2)	+1.2 (+0.9–+1.5)	0.071
FBG (mg/dL) in 2000	98.5 (81–140)	97 (87–161)	0.877	98 (83–122)	96 (96–96)	0.870
Change in FBG (mg/dL)**	+10 (−14–+70)	−1.5 (−32–+12)	0.001	+7 (−10–+40)	−2 (−4–±0)	0.158
Tentative metabolic syndrome in 2000 (present/absent)	8/32	1/9	0.665	0/21	0/2	—
Change in tentative metabolic syndrome between 2000 and 2007–2008 (present-present/present-absent/absent-present/absent-absent)	6/2/8/24	0/1/0/9	0.177	0/0/4/17	0/0/0/2	1.000
Receiving treatment for HT, DL, and/or DM (yes/no)	15/25	1/9	0.138	9/12	1/1	1.000

Refer to the legends of Table 1 and 5 for abbreviations.

unknown [*19*, *20*]. In our study, there was a limitation because self-reported information regarding habitual physical activity, as well as alcohol consumption, can lead to under- or over-reporting. A direct interview by trained medical staff should have been performed to get accurate information from individuals.

In conclusion, BMI and percentage body fat were strongly associated with the development or regression of fatty liver regardless of the history of alcohol intake in the present study. Metabolic syndrome-related disorders such as serum levels of T.Chol., TG, UA, and FBG were also associated with such clinical features in some degree. Although most patients with NAFLD have a benign clinical course [*21*], the presence of multiple metabolic disorders can be associated with potentially progressive and severe liver diseases such as non-alcoholic steatohepatitis [*22*, *23*]. Our present data suggest that control of body weight in men and the percentage body fat in women are particularly important for the prevention or treatment of fatty liver, followed by the control of dyslipidemia, hyperuricemia, and hyperglycemia.

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Table 9. Independent predictors for the development or regression of fatty liver in 2007–2008 by logistic regression analysis

Variables	Regression coefficient	Standard error	*p*	Adjusted odds ratio	95% CI
For the development of fatty liver in participants who did not have fatty liver in 2000 (*n* = 1220)					
Men (*n* = 891)					
% fat volume in 2000	0.144	0.036	<0.001	1.155	1.076–1.239
% change in BMI*	0.127	0.028	<0.001	1.135	1.074–1.199
Change in FBG (mg/dL)**	0.030	0.009	0.001	1.030	1.012–1.049
T.Chol. (mg/dL) in 2000	0.009	0.003	0.005	1.009	1.003–1.015
Change in UA (mg/dL)**	0.243	0.103	0.018	1.276	1.042–1.560
TG (mg/dL) in 2000	0.003	0.001	0.021	1.003	1.001–1.005
% change in % fat volume*	0.020	0.010	0.035	1.020	1.000–1.040
Women (*n* = 329)					
% fat volume in 2000	0.314	0.090	<0.001	1.369	1.148–1.633
Change in UA (mg/dL)**	0.788	0.313	0.012	2.199	1.191–4.061
% change in % fat volume*	0.041	0.017	0.018	1.042	1.008–1.077
For the regression of fatty liver in participants who had non-fatty liver in 2000 (*n* = 358)					
Men (*n* = 317)					
% change in BMI*	−0.170	0.042	<0.001	0.844	0.777–0.916
BMI (kg/m^2) in 2000	−0.255	0.099	0.010	0.775	0.638–0.941
Women (*n* = 41)					
Change in FBG (mg/dL)**	−0.290	0.139	0.036	0.748	0.570–0.983
For the development of fatty liver in participants who were classified as non-drinkers and who did not have fatty liver in 2000 (*n* = 273)					
Men (*n* = 105)					
% change in BMI*	0.209	0.098	0.034	1.232	1.017–1.493
Women (*n* = 168)					
% fat volume in 2000	0.421	0.139	0.002	1.523	1.160–2.001
For the regression of fatty liver in participants who were classified as non-drinkers and who had fatty liver in 2000 (*n* = 73)					
Men (*n* = 50)					
Change in FBG (mg/dL)**	−0.186	0.071	0.009	0.830	0.722–0.954
% change in BMI*	−0.351	0.174	0.044	0.704	0.501–0.990
Women (*n* = 23)					
Nil					

CI, confidence interval. Refer to the legends of Table 1 and 5 for other abbreviations.

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