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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Low alcohol consumption increases the risk of impaired glucose tolerance in patients with non-alcoholic fatty liver disease

Teruki Miyake[1] · Teru Kumagi[1,2] · Masashi Hirooka[1] · Shinya Furukawa[3] · Osamu Yoshida[1] · Mitsuhito Koizumi[1,4] · Shin Yamamoto[1] · Takao Watanabe[1] · Yasunori Yamamoto[1] · Yoshio Tokumoto[1] · Eiji Takeshita[1] · Masanori Abe[1] · Kohichiro Kitai[4] · Bunzo Matsuura[1] · Yoichi Hiasa[1]

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Abstract

Background Fatty liver disease is associated with glucose intolerance and hepatic insulin resistance. However, there are distinct etiologies for alcoholic versus non-alcoholic fatty liver disease (NAFLD), and it is unknown whether alcohol consumption influences the onset of glucose intolerance in fatty liver disease patients. Therefore, we investigated the relationship between fatty liver disease and the onset of impaired fasting glucose (IFG) with respect to alcohol consumption.

Methods The records of 6804 Japanese subjects were reviewed to identify those meeting the criteria for IFG. Male and female subjects were classified into five and four groups, respectively, based on average alcohol consumption (g/week). IFG onset was defined as fasting plasma glucose levels ≥110 mg/dl.

Results In the non-drinker, >0–70 g/week, >70–140 g/week, >140–210 g/week (men only), and >210 g/week (men only) or >140 g/week (women only) groups, 7.3, 6.7, 6.4, 9, and 6.4 % of men and 2, 1.7, 3.1, and 3.2 % of women, respectively, developed IFG. Fatty liver was positively associated with the onset of IFG in men of the >0–70 g/week group (adjusted hazard ratio [aHR], 2.808; 95 % confidence interval [CI] 1.605–5.049, $p < 0.001$) and women of the >70–140 g/week group (aHR, 4.193; 95 % CI, 1.036–14.584, $p = 0.045$) after adjusting for previously reported IFG risk factors. No associations were observed in the other groups.

Conclusions A small amount of alcohol consumption is a significant risk factor for the onset of IFG in NAFLD patients; onset risk differs according to the amount of alcohol consumption.

Keywords Alcohol · Glucose tolerance · Non-alcoholic fatty liver disease · Type 2 diabetes mellitus

Introduction

Metabolic diseases are increasing worldwide due to changes in lifestyles. In particular, it is estimated that the prevalence of type 2 diabetes mellitus (T2DM) in adults is 6.9 %, and will increase to 17 % by 2030 [1]. T2DM is often associated with micro- and macrovascular complications such as diabetic retinopathy, diabetic nephropathy, and cardiovascular disease, negatively impacting both health and life expectancy [2–4]. Therefore, it is important to identify the risk factors for the onset of abnormal glucose tolerance for better intervention and prevention of T2DM [5–8].

Fatty liver is thought to be one of the etiologies of T2DM, and is associated with hepatic insulin resistance [9, 10]. Several studies have shown an association between abnormal glucose tolerance and fatty liver [11–13] or its surrogate markers, such as liver enzymes [14–19] and the fatty liver index [20]. However, fatty liver can be either

✉ Yoichi Hiasa
hiasa@m.ehime-u.ac.jp

1 Department of Gastroenterology and Metabology, Ehime University Graduate School of Medicine, Shitsukawa, Toon, Ehime 791-0295, Japan

2 Department of Community Medicine, Ehime University Graduate School of Medicine, Shitsukawa, Toon, Ehime, Japan

3 Department of Public Health, Ehime University Graduate School of Medicine, Shitsukawa, Toon, Ehime, Japan

4 Ehime General Health Care Association, Misake, Matsuyama, Ehime, Japan

alcohol or non-alcohol related, and no previous studies have explored whether fatty liver predicts the onset of glucose intolerance according to the amount of alcohol consumption.

This large, community-based longitudinal cohort study was designed to allow an epidemiologic assessment of the potential relationship between baseline diagnosis of fatty liver and the development of impaired fasting glucose (IFG), as stratified by the amount of alcohol intake at baseline. Ideally, the results of this study will help clinicians identify those patients who are at greater risk of impaired glucose tolerance.

Patients and methods

This retrospective, community-based, longitudinal cohort study reviewed the medical records of 7905 Japanese subjects (3863 men and 4042 women) who had undergone annual health check-ups at the Ehime General Health Care Association more than twice between April 2003 and August 2013. Their ages ranged from 18 to 80 years. The annual health check-up included a review of the patient's medical history and prescription medications, the administration of a questionnaire that assessed the frequencies and quantities of alcohol and cigarette consumption, and second-degree family history of diabetes. A physical examination was also performed, and anthropometric and routine biochemical variables were measured. Body weight and height were measured while the subjects were clothed in light gowns without shoes; these measurements were used to calculate body mass index (BMI). Blood pressure measurements were obtained with an automated sphygmomanometer while the subjects were seated. Blood samples were collected in the morning, after the subjects had been fasting for $\geq$10 h, and were used to measure (a) fasting plasma glucose levels; (b) the lipid profile, including triacylglycerols (TG) and high-density lipoprotein cholesterol (HDL-c) levels; (c) creatinine levels; and (d) other blood chemistry variables, including uric acid (UA), hepatitis B surface antigen (HBs-Ag), and hepatitis C antibody (anti-HCV) levels. Fatty liver was diagnosed using abdominal ultrasonography (Hitachi EUB-2000 or Hitachi Avius, Tokyo, Japan) by experienced technicians who were blinded to the subjects' individual data. Two gastroenterologists (M. K. and K. K.) reviewed all ultrasonography images to diagnose fatty liver disease. Of the four known criteria for fatty liver that can be identified from ultrasonography (hepatorenal echo contrast, liver brightness, deep attenuation, and vascular blurring) [21], evidence of hepatorenal contrast and liver brightness were required for diagnosis. A priori approval for the study was obtained from the Ehime University Hospital Research Ethics Board (Approval ID #110405, University Hospital Medical Information Network ID: UMIN000011953) according to the 1975 Declaration of Helsinki, and all study procedures were conducted in accordance with guidelines on good clinical practices, as well as local ethical and legal requirements.

After laboratory data and medical histories were assessed at the first check-up, 1101 subjects were excluded from this study because they met at least one of the following exclusion criteria: (1) fasting plasma glucose $\geq$110 mg/dl [22, 23] ($n = 634$); (2) currently being on anti-diabetic ($n = 132$), anti-hypertensive ($n = 366$), or lipid-lowering ($n = 170$) regimens; and/or (3) testing positive for HBs-Ag ($n = 115$) or anti-HCV ($n = 79$). Ultimately, 6804 subjects (3089 men and 3715 women) were analyzed. The observation period lasted 4.37 ± 2.52 years (4.27 ± 2.51 years for men and 4.46 ± 2.52 years for women), with a median of 4.05 years (range, 0.44–10.13 years). The median interval between visits was 1.05 years (range, 0.44–9.05 years), with only 0.36 % being under 6 months and 18.4 % being over 2 years. Male subjects were classified into five groups based on average alcohol consumption: Non-drinkers, >0–70 g/week, >70–140 g/week, >140–210 g/week, and >210 g/week; female subjects were classified into four groups: non-drinkers, >0–70 g/week, >70–140 g/week, and >140 g/week. The alcohol consumption threshold for NAFLD patients was defined as <30 g/days (210 g/week) for men and <20 g/days (140 g/week) for women [24]. The onset of IFG during the observation period was defined as a fasting plasma glucose level $\geq$110 mg/dl observed during any health check-up [22, 23].

All subjects were assigned a numerical code that was used throughout the study, and all data were stored in a secure database to maintain anonymity. Statistical analyses were performed using JMP version 11 software (SAS Institute Japan, Tokyo, Japan). One-way analysis of variance was used to analyze between-group differences in baseline characteristics, such as age, results of the physical examinations, and anthropometric and routine biochemical variables. The Chi-square test was used to analyze the presence or absence of fatty liver, family history, and smoking history. To identify factors independently associated with the rate of onset of IFG, we performed univariate and multivariate Cox proportional hazards regression analyses using forward likelihood ratio tests. The assumption of proportional hazards was assessed by including time-dependent covariates in the models; no indication of a violation was found. The following variables are known to affect glucose intolerance [25–30], and were included in the multivariate Cox regression models (from which we obtained adjusted hazard ratios (aHRs) for the incidence of IFG onset): age, BMI, systolic blood

pressure, TG, HDL-c, creatinine, fatty liver, family history of diabetes, and current smoking status (Model 1). The remaining model (Model 2) included factors that were significant in the univariate analyses ($p < 0.05$). All data are expressed as mean ± standard deviation, all p values were two-tailed, and p values <0.05 were considered statistically significant.

Results

Baseline characteristics and prevalence of IFG onset according to the average amount of consumed alcohol

The baseline characteristics of the study subjects are presented in Tables 1 and 2. For each subject, complete data were available for all of the examined variables, with the exception of the BMI of one subject (0.015 %). Compared to the >210 g/week group, men in the other four groups had higher levels of creatinine, lower levels of many metabolic markers (including systolic blood pressure, TG, HDL-c, and UA), and a lower ratio of current smokers. Subjects of the bottom three alcohol consumption groups were also younger than those in the >210 g/week group and had a higher proportion of subjects with fatty livers (Table 1). Compared to the >140 g/week group, women in the >0–70 g/week group were younger, while those of the non-drinking group were older; women who were non-drinkers and those in the >0–70 g/week and >70–140 g/week groups had lower systolic blood pressure, TG, HDL-c, and UA, and these groups also contained a lower ratio of subjects who were current smokers (Table 2). The non-drinking group contained a higher ratio of subjects who had fatty liver, while the >70–140 g/week group subjects had a lower ratio of fatty liver (Table 2). The incidence rates of IFG in men and women were not significantly different between each group (Tables 1, 2).

The change in the average weekly alcohol consumption between baseline and endpoint

The changes in average weekly alcohol consumption between baseline and endpoint are shown in Table 3. In men, 2047 of 3089 subjects (66.2 %) maintained the same amount of alcohol consumption between baseline and endpoint, while 921 subjects (29.8 %) switched to an immediately adjacent alcohol consumption group (one group up or down). In women, 2772 of 3715 subjects (74.6 %) maintained the same amount of alcohol consumption between baseline and endpoint, while 899

Table 1 Men: baseline characteristics and the onset of impaired fasting glucose according to alcohol consumption

Total ($n = 3089$)	Amount of alcohol	Non-drinker ($n = 303$)	>0–70 g/week ($n = 1145$)	>70–140 g/week ($n = 776$)	>140 g–210 g/week ($n = 536$)	>210 g/week ($n = 329$)	p value
Age	(years)	42.9 ± 8.9	40.1 ± 8.6	42.3 ± 8.5	45.1 ± 8.7	44.6 ± 8.1	<0.001
Body mass index	(kg/m^2)	23.6 ± 3.3	23.6 ± 3.2	23.5 ± 3	23.4 ± 2.7	23.3 ± 2.8	0.639
Systolic blood pressure	(mmHg)	113.4 ± 14.6	113.6 ± 14	115.5 ± 14.3	118.1 ± 14.7	121.7 ± 14.3	<0.001
Creatinine	(mg/dl)	0.87 ± 0.11	0.88 ± 0.12	0.88 ± 0.11	0.87 ± 0.11	0.84 ± 0.12	<0.001
Triacylglycerols	(mg/dl)	130.7 ± 71.3	125.8 ± 86.2	127.5 ± 82.2	143.8 ± 110.8	154.9 ± 180	<0.001
High-density lipoprotein cholesterol	(mg/dl)	55.1 ± 13.4	57.1 ± 13.8	60.3 ± 14.5	62.5 ± 15.8	65.5 ± 17.3	<0.001
Uric acid	(mg/dl)	6.16 ± 1.18	6.1 ± 1.13	6.24 ± 1.18	6.29 ± 1.3	6.34 ± 1.29	0.003
Fatty liver	(%)	111/303 (36.6 %)	412/1145 (36 %)	215/776 (27.7 %)	130/536 (24.3 %)	86/329 (26.1 %)	<0.001
Family history of diabetes	(%)	56/303 (18.5 %)	191/1145 (16.7 %)	115/776 (14.8 %)	79/536 (14.7 %)	66/329 (20.1 %)	0.151
Current smoker	(%)	122/303 (40.3 %)	425/1145 (37.1 %)	297/776 (38.3 %)	241/536 (45 %)	195/329 (59.3 %)	<0.001
Onset of impaired fasting glucose[a]	(%)	22/303 (7.3 %)	77/1145 (6.7 %)	50/776 (6.4 %)	48/536 (9 %)	21/329 (6.4 %)	0.621

Values are expressed as mean ± standard deviation

For continuous values, differences among groups were assessed using one-way analysis of variance. The Chi-square test was employed for comparisons of prevalence

[a] Onset of impaired fasting glucose was defined as a fasting plasma glucose level ≥110 mg/dl

Table 2 Women: baseline characteristics and the onset of impaired fasting glucose according to alcohol consumption

Total ($n = 3715$)	Amount of alcohol	Non-drinker ($n = 1068$)	>0–70 g/week ($n = 1983$)	>70–140 g/week ($n = 479$)	>140 g/week ($n = 185$)	p value
Age	(years)	43 ± 9	39.4 ± 8.6	41.9 ± 8.1	42.8 ± 7.6	<0.001
Body mass index	(kg/m^2)	21.3 ± 3.2	21.4 ± 3.1	21.1 ± 2.8	21.6 ± 2.9	0.201
Systolic blood pressure	(mmHg)	108.2 ± 15.7	105.8 ± 14.2	107.3 ± 14.2	112.6 ± 15.6	<0.001
Creatinine	(mg/dl)	0.63 ± 0.1	0.64 ± 0.09	0.64 ± 0.9	0.64 ± 0.1	0.336
Triacylglycerols	(mg/dl)	81.3 ± 45.9	72.4 ± 37.2	76.9 ± 61.2	89.3 ± 59	<0.001
High-density lipoprotein cholesterol	(mg/dl)	73.9 ± 16.1	72.4 ± 37.2	77.8 ± 16.4	83.1 ± 18.9	<0.001
Uric acid	(mg/dl)	4.24 ± 0.89	4.23 ± 0.87	4.31 ± 0.88	4.72 ± 0.99	<0.001
Fatty liver	(%)	135/1068 (12.6 %)	201/1983 (10.1 %)	36/479 (7.5 %)	19/185 (10.2 %)	0.019
Family history of diabetes	(%)	220/1068 (20.6 %)	435/1983 (21.9 %)	113/479 (23.5 %)	39/185 (21.1 %)	0.599
Current smoker	(%)	34/1068 (3.2 %)	99/1983 (5 %)	38/479 (7.9 %)	37/185 (20 %)	<0.001
Onset of impaired fasting glucose[a]		21/1068 (2 %)	33/1983 (1.7 %)	15/479 (3.1 %)	6/185 (3.2 %)	0.129

Values are expressed as mean ± standard deviation

Body mass index value unavailable for one subject

For continuous values, differences among groups were assessed using one-way analysis of variance. The Chi-square test was employed for comparisons of prevalence

[a] Onset of impaired fasting glucose was defined as a fasting plasma glucose level ≥110 mg/dl

Table 3 The change in the average weekly alcohol consumption between baseline and endpoint

Average alcohol consumption	Number of cases at baseline	Number of cases in each drinking category at endpoint				
		Non-drinker	>0–70 g/week	>70–140 g/week	>140–210 g/week	>210 g/week
Men						
Non-drinker	303	232 (76.6)	64 (21.1)	6 (2)	1 (0.3)	0 (0)
>0–70 g/week	1145	76 (6.6)	878 (76.7)	158 (13.8)	26 (2.3)	7 (0.6)
>70–140 g/week	776	6 (0.8)	190 (24.5)	433 (55.8)	131 (16.9)	16 (2.1)
>140–210 g/week	536	0 (0)	26 (4.9)	147 (27.4)	301 (56.2)	62 (11.6)
>210 g/week	329	0 (0)	6 (1.8)	27 (8.2)	93 (28.3)	203 (61.7)
Women						
Non-drinker	1068	859 (80.4)	203 (19)	4 (0.4)	2 (0.2)	
>0–70 g/week	1983	278 (14)	1533 (77.3)	156 (7.9)	16 (0.8)	
>70–140 g/week	479	7 (1.5)	172 (36)	246 (51.5)	53 (11.1)	
>140 g/week	185	4 (2.2)	12 (6.5)	36 (19.5)	133 (71.9)	

[a] Because of rounding, not all percentages total 100 %

subjects (24.2 %) switched to an immediately adjacent alcohol consumption group (one group up or down).

Risk factors for the onset of IFG according to average amount of consumed alcohol

Univariate analyses revealed that several variables were significantly and positively associated with IFG onset in men. In the NAFLD (non-drinker—210 g/week) group, fatty liver, age, BMI, systolic blood pressure, TG, UA, family history of diabetes, and being a current smoker were correlated with IFG onset; there was also a negative association with creatinine and HDL-c. In the non-drinker group, fatty liver and BMI were correlated with IFG onset; in the >0–70 g/week group, fatty liver, age, BMI, systolic blood pressure, TG, UA, and being a current smoker were

correlated with IFG onset; there was a negative association with creatinine and HDL-c. In the >70–140 g/week group, fatty liver, age, BMI, systolic blood pressure, TG, HDL-c, UA, and being a current smoker were correlated with IFG onset; there was a negative association with HDL-c. In the >140–210 g/week group, fatty liver, age, BMI, systolic blood pressure, TG, and being a current smoker were correlated with IFG onset; there was a negative association with HDL-c and creatinine. In the >210 g/week group, fatty liver, age, BMI, and TG were correlated with IFG onset (Table 4). Risk factors for the onset of IFG in women were the same as those observed in men, as follows: in the NAFLD (non-drinker—140 g/week) group, fatty liver, age, BMI, systolic blood pressure, UA, and family history of diabetes (there was a negative association with HDL-c); in the non-drinker group, fatty liver, age, BMI, TG, UA, and family history of diabetes; in the >0–70 g/week group, fatty liver, age, BMI, systolic blood pressure, TG, HDL-c, and UA; and in the >70–140 g/week group, age, systolic blood pressure, and HDL-c. In the >140 g/week group, creatinine showed a negative association (Table 5).

Effect of fatty liver on the risk of IFG onset in relation to alcohol consumption

Among men, the aHR from Model 1 indicated a significant positive association between fatty liver and the onset of IFG in the NAFLD group and the >0–70 g/week group (Table 6). Model 2 included adjustments for variables found to be significant on univariate analyses, revealing a significant association between fatty liver and IFG onset in the NAFLD group and the >0–70 g/week group. However, there were no significant associations in the other groups (Table 6). Among women, the aHR from Model 1 indicated a significant positive association between fatty liver and the onset of IFG in the NAFLD group and the >70–140 g/week group (Table 6). Model 2 analyses revealed a significant association between fatty liver and IFG onset in the NAFLD group and the >70–140 g/week group; there were no significant associations in the other groups (Table 6).

Effect of fatty liver on the risk of IFG onset in relation to alcohol consumption compared to non-drinkers without fatty liver

Among men, the aHRs for age and BMI indicated a significant positive association between fatty liver and the onset of IFG in the >0–70 g/week group compared to non-drinkers without fatty liver (Table 7). Among women, the aHRs indicated a significant positive association between fatty liver and the onset of IFG in the >0–70 g/week and >70–140 g/week groups compared to non-drinkers without fatty liver (Table 7).

Discussion

We conducted this large, community-based longitudinal cohort study to examine the associations between fatty liver and the onset of IFG, as stratified by the amount of alcohol intake. Our findings indicate that a small amount of alcohol consumption in non-alcoholic fatty liver disease (NAFLD) patients is a significant risk factor for the onset of IFG in both sexes. The association remained significant after adjusting for potential confounders.

Recently, several studies have examined the associations between fatty liver and the onsets of pre-diabetes and T2DM [11–13]. Kim et al. investigated whether fatty liver is an independent risk factor of T2DM incidence in 5372 non-diabetic Koreans [11]. Subjects underwent voluntary medical check-ups in 2000 and follow-up examinations in 2005. In multiple logistic regression models after adjusting for age, sex, BMI, triglycerides, HDL-c, fasting plasma glucose, alanine aminotransferase, ultrasonography operator, alcohol consumption, and smoking, subjects with fatty liver were at a significantly higher risk of developing T2DM compared to those without fatty liver [11]. Yamada et al. examined whether fatty liver predicted IFG and T2DM in a longitudinal study among 12,375 Japanese subjects undergoing health checkups [12]. They reported that fatty liver was a risk factor for IFG and/or T2DM in both sexes by multiple logistic regression analyses adjusted for age, BMI, hypertension, family history of diabetes mellitus, alcohol consumption, and smoking [12]. Moreover, Sung et al. examined 12,853 subjects without diabetes from a South Korean occupational cohort, and they quantified the risk of incident diabetes with different combinations including insulin resistance, obesity, and fatty liver at baseline to determine whether each was an independent risk factor for diabetes [13]. Fatty liver, insulin resistance, and obesity increased the risk of T2DM incidence by multiple logistic regression models after adjusting for age, sex, alcohol, smoking status, exercise, educational status, triglycerides, and alanine aminotransferase. Moreover, the clustering of fatty liver, insulin resistance, and obesity markedly increased the odds of developing T2DM [13]. However, these researchers did not consider the effect of alcohol on fatty liver; that is, they did not stratify patients by the amounts of their alcohol intake at baseline, which was the primary aim of our study. Additionally, they only collected data at two time points during the observation period (in 2000 and 2005, or in 2003 and 2008), even though participants may have undergone

Table 4 Men: results of univariate analysis of risk factors for the onset of impaired fasting glucose according to alcohol consumption

	NAFLD		Non-drinker		>0–70 g/week		>70–140 g/week		>140–210 g/week		>210 g/week	
	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value
Age (years)	1.064 (1.048–1.079)	<0.001	1.044 (0.999–1.091)	0.057	1.061 (1.035–1.086)	<0.001	1.077 (1.046–1.109)	<0.001	1.063 (1.029–1.099)	<0.001	1.083 (1.024–1.148)	0.005
Body mass index (kg/m^2)	1.144 (1.103–1.183)	<0.001	1.135 (1.035–1.224)	0.009	1.135 (1.075–1.191)	<0.001	1.183 (1.083–1.287)	<0.001	1.153 (1.046–1.266)	0.004	1.195 (1.038–1.364)	0.014
Systolic blood pressure (mmHg)	1.026 (1.017–1.035)	<0.001	1.022 (0.997–1.043)	0.083	1.022 (1.007–1.036)	0.005	1.031 (1.011–1.05)	0.002	1.028 (1.009–1.046)	0.003	1.015 (0.985–1.045)	0.33
Creatinine (mg/dl)	0.194 (0.053–0.692)	0.011	1.396 (0.032–50.676)	0.86	0.131 (0.016–0.981)	0.049	1.042 (0.074–13.55)	0.975	0.03 (0.002–0.405)	0.008	0.344 (0.008–12.465)	0.569
Triacylglycerols (mg/dl)	1.0036 (1.0027–1.0044)	<0.001	1.004 (0.999–1.009)	0.126	1.003 (1.002–1.005)	<0.001	1.003 (1.00006–1.004)	0.045	1.004 (1.003–1.005)	<0.001	1.002 (1.001–1.003)	0.005
High-density lipoprotein cholesterol (mg/dl)	0.961 (0.95–0.972)	<0.001	0.984 (0.95–1.016)	0.34	0.944 (0.925–0.963)	<0.001	0.962 (0.94–0.983)	<0.001	0.966 (0.944–0.987)	0.001	0.976 (0.947–1.003)	0.085
Uric acid (mg/dl)	1.297 (1.154–1.455)	<0.001	1.257 (0.901–1.719)	0.174	1.363 (1.119–1.657)	0.002	1.344 (1.058–1.702)	0.016	1.182 (0.947–1.474)	0.139	1.187 (0.852–1.654)	0.311
Fatty liver (%)	2.956 (2.233–3.926)	<0.001	2.482 (1.07–6.016)	0.034	4.897 (3.031–8.194)	<0.001	2.25 (1.279–3.926)	0.005	2.323 (1.291–4.102)	0.006	3.433 (1.441–8.281)	0.006
Family history of diabetes (%)	2.956 (2.233–3.926)	<0.001	2.47 (0.986–5.768)	0.053	1.478 (0.848–2.452)	0.162	1.791 (0.896–3.325)	0.096	1.07 (0.438–2.239)	0.869	0.798 (0.228–2.174)	0.68
Current smoker (%)	1.538 (1.091–2.126)	0.0148	1.333 (0.562–3.092)	0.505	1.604 (1.024–2.511)	0.039	1.686 (0.961–2.948)	0.069	1.193 (0.675–2.109)	0.541	0.753 (0.317–1.809)	0.518

Onset of impaired fasting glucose was defined as a fasting plasma glucose level ≥110 mg/dl

HR hazard ratio, *CI* confidence interval

Table 5 Women: results of univariate analysis of risk factors for the onset of impaired fasting glucose according to alcohol consumption

	NAFLD		Non-drinker		>0–70 g/week		>70–140 g/week		>140 g/week	
	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value
Age (years)	1.088 (1.058–1.118)	<0.001	1.07 (1.018–1.127)	0.008	1.094 (1.052–1.138)	<0.001	1.091 (1.025–1.165)	0.006	1.063 (0.959–1.178)	0.241
Body mass index (kg/m^2)	1.259 (1.198–1.318)	<0.001	1.364 (1.234–1.503)	<0.001	1.276 (1.193–1.355)	<0.001	1.094 (0.932–1.243)	0.251	1.193 (0.947–1.429)	0.123
Systolic blood pressure (mmHg)	1.027 (1.013–1.04)	<0.001	1.001 (0.973–1.027)	0.921	1.037 (1.019–1.053)	<0.001	1.034 (1.003–1.059)	0.032	1.018 (0.968–1.064)	0.462
Creatinine (mg/dl)	0.231 (0.016–3.181)	0.278	0.354 (0.003–35.445)	0.664	0.165 (0.003–7.258)	0.362	0383 (0.001–119.762)	0.748	0.0000012 (15×10^{-12}–0.027)	0.006
Triacylglycerols (mg/dl)	0.231 (0.016–3.181)	0.278	1.009 (1.004–1.014)	0.003	1.011 (1.006–1.014)	<0.001	1.003 (0.999–1.005)	0.123	1.006 (0.996–1.014)	0.2
High-density lipoprotein cholesterol (mg/dl)	0.964 (0.947–0.979)	<0.001	0.985 (0.956–1.013)	0.291	0.948 (0.923–0.971)	<0.001	0.963 (0.928–0.997)	0.033	0.962 (0.912–1.008)	0.106
Uric acid (mg/dl)	2.06 (1.606–2.623)	<0.001	2.04 (1.287–3.163)	0.003	2.422 (1.684–3.434)	<0.001	1.434 (0.835–2.391)	0.189	1.371 (0.611–3.011)	0.44
Fatty liver (%)	7.092 (4.373–11.389)	<0.001	5.591 (2.28–13.224)	<0.001	9.159 (4.584–18.213)	<0.001	6.36 (1.98–17.913)	0.003	4.36 (0.604–22.39)	0.128
Family history of diabetes (%)	1.855 (1.106–3.026)	0.02	2.553 (1.009–6.069)	0.048	1.401 (0.616–2.911)	0.401	1.911 (0.64–5.306)	0.233	3.584 (0.663–19.382)	0.13
Current smoker (%)	1.279 (0.389–3.094)	0.645	Not calculated		2.662 (0.79–6.766)	0.104	Not calculated		0.922 (0.481–5.743)	0.94

Onset of impaired fasting glucose was defined as a fasting plasma glucose level ≥110 mg/dl

HR hazard ratio, *CI* confidence interval

Table 6 Associations between fatty liver and the onset of impaired fasting glucose according to average alcohol consumption

	NAFLD		Non-drinker		>0–70 g/week		>70–140 g/week		>140–210 g/week		>210 g/week	
	aHR (95 % CI)	*p* value	aHR (95 % CI)	*p* value	aHR (95 % CI)	*p* value	aHR (95 % CI)	*p* value	aHR (95 % CI)	*p* value	aHR (95 % CI)	*p* value
Men												
Model 1	1.739 (1.26–2.406)	<0.001	1.294 (0.438–3.842)	0.638	2.808 (1.605–5.049)	<0.001	1.311 (0.684–2.501)	0.412	1.53 (0.769–2.978)	0.222	1.928 (0.662–5.501)	0.224
Model 2	1.739 (1.26–2.406)	<0.001	1.648 (0.619–4.441)	0.314	2.737 (1.569–4.906)	<0.001	1.303 (0.682–2.475)	0.419	1.611 (0.817–3.101)	0.166	1.946 (0.701–5.34)	0.198
Women												
Model 1	2.092 (1.131–3.816)	0.019	1.864 (0.64–5.252)	0.248	2.11 (0.831–5.246)	0.115	4.193 (1.036–14.584)	0.045				
Model 2	2.276 (1.245–4.109)	0.008	1.569 (0545–4.365)	0.396	2.174 (0.848–5.466)	0.105	4.697 (1.402–13.87)	0.014				

Model 1 was adjusted for all variables that were previously reported to be associated with metabolic disease or risk factors for the onset of glucose intolerance: age (years), BMI (kg/m^2), systolic blood pressure (mmHg), triacylglycerols (mg/dl), high-density lipoprotein cholesterol (mg/dl), creatinine (mg/dl), uric acid (mg/dl), fatty liver, family history of diabetes, alcohol drinking status, and current smoking status

Model 2 was adjusted for all factors that were significant on univariate analyses

Onset of impaired fasting glucose was defined as a fasting plasma glucose level ≥110 mg/dl

aHR adjusted hazard ratio, *CI* confidence interval, *BMI* body mass index

Table 7 Adjusted hazard ratios for the onset of impaired fasting glucose in fatty liver patients compared to non-drinkers without fatty livers in each category of alcohol consumption

	Non-drinker		>0–70 g/week		>70–140 g/week		>140–210 g/week		>210 g/week	
	aHR (95 % CI)	*p* value	aHR (95 % CI)	*p* value	aHR (95 % CI)	*p* value	aHR (95 % CI)	*p* value	aHR (95 % CI)	*p* value
Men	1.488 (0.567–3.996)	0.418	2.603 (1.283–5.867)	0.007	1.637 (0.698–4.098)	0.262	1.648 (0.967–2.791)	0.066	1.794 (0.9–3.594)	0.097
	Non-drinker		>0–70 g/week		>70–140 g/week		>140 g/week			
Women	1.693 (0.609–4.546)	0.305	2.855 (1.122–7.263)	0.028	5.768 (1.465–18.951)	0.014	1.995 (0.242–10.381)	0.478		

aHR was adjusted for age (years) and BMI (kg/m^2)

Onset of impaired fasting glucose was defined as a fasting plasma glucose level ≥110 mg/dl

aHR adjusted hazard ratio, *CI* confidence interval, *BMI* body mass index

health checkups annually during which they may have received interventions.

With respect to an association between NAFLD and abnormal glucose tolerance, there are several reports [27, 31–34]. Shibata et al. conducted an observational cohort study in 3189 male workers ≥40 years old in a Japanese company between 1997 and 2005 [31]. They reported that NAFLD significantly increases the risk of diabetes on multivariate Cox proportional hazards analysis adjusted for age and BMI [31]. Yamazaki et al. enrolled 3074 subjects, who underwent a health checkup twice with a >10-year interval in between, and examined the long-term effects of NAFLD on T2DM incidence and the association between NAFLD improvement and T2DM incidence reduction [32]. They reported that NAFLD at baseline was associated with T2DM incidence, and NAFLD improvement was associated with reduced T2DM incidence by logistic regression models adjusted for age, sex, BMI, IFG, family history of diabetes, dyslipidemia, hypertension, and physical exercise [32]. However, these studies had some limitations, such as including only men, insufficient time points, or small cohort numbers.

The mechanisms that may explain why NAFLD patients who consume small amount of alcohols are at risk for the onset of IFG remain unclear. Many epidemiologic and experimental studies revealed a protective effect of light or moderate alcohol consumption on fatty liver [35, 36] and glucose intolerance [37] by improving insulin sensitivity [38, 39], increasing adiponectin levels [35, 39, 40], and enhancing hepatic blood flow [41]. Despite this evidence, light or moderate alcohol consumption may nevertheless make one susceptible to T2DM. On the other hand, several other studies did not indicate a beneficial effect of small amounts of alcohol on NAFLD. Ekstedt et al. reported that moderate alcohol consumption with heavy episodic drinking is associated with NAFLD progression in 71 patients diagnosed with biopsy-confirmed disease [42]. Moreover, in an experimental NAFLD rodent model, a combination high fat diet and moderate alcohol intake exacerbated hepatic inflammation and apoptosis by inhibiting sirtuin 1 deacetylase activity or enhancing Toll-like receptor 4 signaling [43–45]. Therefore, a combination of NAFLD and small amounts of alcohol appear to affect NAFLD progression, including hepatic inflammation; this may exacerbate insulin sensitivity and induce the onset of abnormal glucose tolerance. However, further research is required to clarify these potential associations.

The primary strengths of our study were its investigation of the general population, and the completeness of the data for all relevant variables; there was only one missing data point. On the other hand, our study had several limitations. First, only 293 subjects (218 men and 75 women) showed IFG onset out of 6804 participants (3089 men and 3715 women). This relatively low rate may explain the lack of a significant association between fatty liver and IFG onset in the non-drinker and >140 g/week groups. Additionally, we were unable to determine the proportion of subjects in the >210 g/week group in men and the >140 g/week group in women who were high alcohol consumers, because the sizes of these groups were too small. Second, we were only able to collect data annually; therefore, data collection was not truly continuous. Third, our study relied on self-reported information for several of the investigated factors. Therefore, misreported data could have skewed our findings. Finally, we only examined a Japanese population, which could limit the generalizability of our results to other populations. Despite these limitations, our study showed several noteworthy results. In particular, our findings suggest that NAFLD with a small amount of alcohol consumption is a significant risk factor for the onset of IFG. These results showed that the risk of fatty liver on glucose tolerance differed according to the amount of alcohol consumption. To help prevent the onset of IFG and the development of further complications, clinicians should take note of the amount of their alcohol consumption in fatty liver patients, and recommend that NAFLD patients refrain from alcohol even if they consume small amounts.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

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