Research Article

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Roles of alcohol consumption in fatty liver: A longitudinal study

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Background & Aims: Roles of alcohol consumption in non-alcoholic fatty liver disease are still controversial, although several cross-sectional studies have suggested the beneficial effect of light to moderate drinking on fatty liver. We analyzed the longitudinal relationship between drinking pattern and fatty liver.

Methods: We included 5297 Japanese individuals (3773 men and 1524 women) who underwent a baseline study in 2003 and follow-up at least once from 2004 to 2006. Generalized estimating equation was used to estimate any association between drinking pattern and fatty liver assessed by ultrasonography.

Results: At baseline, 1179 men (31.2%) and 235 women (15.4%) had fatty liver; 2802 men (74.2%) and 436 women (28.6%) reported alcohol consumption. At the latest follow-up, 348 of 2594 men (13.4%) and 101 of 1289 women (7.8%) had newly developed fatty liver; 285 of 1179 men (24.2%) and 70 of 235 women (29.8%) demonstrated a remission of fatty liver. In men, drinking 0.1–69.9 g/week (odds ratio, 0.79 [95% confidence interval, 0.68–0.90]), drinking 70.0–139.9 g/week (0.73 [0.63–0.84]), drinking 140.0–279.9 g/week (0.69 [0.60–0.79]), and drinking $\geqslant$280.0 g/week (0.68 [0.58–0.79]) were inversely associated with fatty liver after adjusting for obesity, exercise, and smoking. In women, drinking 0.1–69.9 g/week (0.71 [0.52–0.96]) and drinking 70.0–139.9 g/week (0.67 [0.45–0.98]) were inversely associated with fatty liver after the adjustment.

Conclusions: Light to moderate alcohol consumption, or even somewhat excessive amounts especially in men, was likely to protect most individuals against fatty liver over time.

Keywords: Non-alcoholic fatty liver disease; Drinking pattern; Generalized estimating equation; Ultrasonography.

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Abbreviations: NAFLD, non-alcoholic fatty liver disease; ALDH2, aldehyde dehydrogenase 2.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease not only in the Western world [1,2] but also in Asia [3,4]. NAFLD is strongly associated with obesity and other metabolic syndrome-related conditions [2,3] and can progress to the severe form of NAFLD, i.e., non-alcoholic steatohepatitis, resulting in the development of liver cirrhosis, liver failure, and hepatocellular carcinoma [5–7]. A recent report indicated that insulin resistance and weight gain are predictors of NAFLD incidence, whereas weight reduction is a predictor of NAFLD remission [8].

NAFLD is considered to be a phenotype of metabolic syndrome in the liver [9–14]. As many studies have demonstrated that moderate alcohol consumption reduces the risk of metabolic syndrome-related diseases and mortality [15–19], a number of recent studies have also demonstrated that light to moderate alcohol consumption is inversely associated with an elevation of the serum alanine aminotransferase levels [20,21], the presence of NAFLD [22–26], or severity of NAFLD [27,28]. Although excessive alcohol consumption is well known to cause alcoholic liver diseases, i.e., alcoholic fatty liver and alcoholic liver cirrhosis [29,30], light to moderate alcohol consumption appears to protect against NAFLD. However, it remains unanswered whether the influence of alcohol consumption against NAFLD is preventive, therapeutic, or both. In addition, there is another possibility that alcohol consumption is simply associated with NAFLD via the effects of various confounders. Furthermore, no studies have assessed the association between ongoing alcohol consumption and the disease severity or natural history of NAFLD and/or non-alcoholic steatohepatitis; therefore, no recommendations concerning non-heavy alcohol consumption for individuals with NAFLD have been made to date [31].

In a previous study [25], we demonstrated that the prevalence of fatty liver in drinkers is directly associated with the amount of alcohol consumed and inversely associated with the alcohol consumption frequency. We hypothesized that drinking pattern might also influence the development and/or remission of fatty liver and aimed to test it in the present study.

Materials and methods

Study population

This was a longitudinal study of the association between drinking patterns and the prevalence of fatty liver, based on the analyses of the data obtained from systemic health checkups at Junpukai Health Maintenance Center. The health checkups are annually organized by employers of various workplaces for the welfare of their employees and are conducted in a standardized manner. Any employee can undergo the health checkup voluntarily in order to obtain advice to improve their lifestyle, as well as to detect the presence of diseases. Employers bear a large part of the cost for the health checkup. Data regarding the clinical and demographic characteristics (age, sex, height, body weight, and blood pressure) and laboratory parameters (aspartate aminotransferase, alanine aminotransferase, γ-glutamyltransferase, total cholesterol, triglyceride, high-density lipoprotein, fasting plasma glucose, and uric acid levels) are measured and recorded during the health checkups. The data related to alcohol consumption, smoking history, physical exercise, and medical history are obtained by means of a questionnaire. The questionnaire employed in the present study has been described in detail elsewhere [25]. Experienced technicians perform real-time ultrasonography to screen for abdominal diseases, and specialist physicians subsequently confirm the validity of the findings.

We enrolled Japanese subjects who underwent ultrasonography as a part of the systemic health checkup in 2003 (n = 8509) and analyzed those who underwent follow-up studies at least once during 2004 to 2006, excluding those who had any missing components of data or reported liver diseases under treatment or follow-up except for alcoholic liver diseases and NAFLD.

The institutional review board of Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences and that of Junpukai Health Maintenance Center approved the study protocol, which conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Each participant provided written informed consent.

Variables

We defined a drinker as an individual who reported current alcohol consumption of at least once a week. The amount of beverages consumed per drinking day was converted into grams of alcohol and multiplied by the number of drinking days a week in order to calculate the total amount of alcohol consumed per week. The average weekly alcohol consumption was classified into five categories: none, 0.1–69.9 g/week, 70.0–139.9 g/week, 140.0–279.9 g/week, and ⩾280.0 g/week. We classified alcohol consumption frequencies into four categories: none, drinking 1–3 days/week, drinking 4–6 days/week, and drinking on a daily basis.

According to the findings of a recent study [32], we considered the presence of any of the following factors to be indicative of fatty liver: vessel blurring, deep attenuation, and increased hepatorenal echo contrast. Obesity was defined as a body mass index of ⩾25 kg/m^2 according to the Japanese criterion for obesity [33]. Atherogenic dyslipidemia was defined as a triglyceride level of ⩾150 mg/dl, high-density lipoprotein level of <40 mg/dl, or the use of antidyslipidemic medications. Glucose intolerance was defined as a fasting plasma glucose level of ⩾100 mg/dl or the use of medications for diabetes mellitus. The smoking status was divided into either current smoking or current non-smoking. Regular exercise was defined as exercise undertaken at least once per week, regardless of the duration. The parameters mentioned above were treated as dichotomous variables.

Statistical analysis

Continuous variables were expressed as the mean ± standard deviation and were compared using Student's *t*-test. Categorical variables were compared using Fisher's exact test. Generalized estimating equation with binomial distribution was used to provide risk estimates [34]. We applied an exchangeable correlation structure for the within-individual correlation matrix. We analyzed the influence of alcohol consumption (the average weekly alcohol consumption and alcohol consumption frequency) on fatty liver adjusting for obesity, smoking status, and regular exercise in the primary analysis; we also adjusted for atherogenic dyslipidemia and glucose intolerance besides those factors mentioned above in the secondary analysis. A p <0.05 was considered to indicate statistically significant. The statistical analyses were performed with R version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria) [35].

Results

Subject description at baseline and follow-up study

As illustrated in Fig. 1, we enrolled 8509 individuals (5960 men and 2549 women) who underwent a baseline study in 2003 and excluded 831 ineligibles. Out of the 7678 eligible individuals,

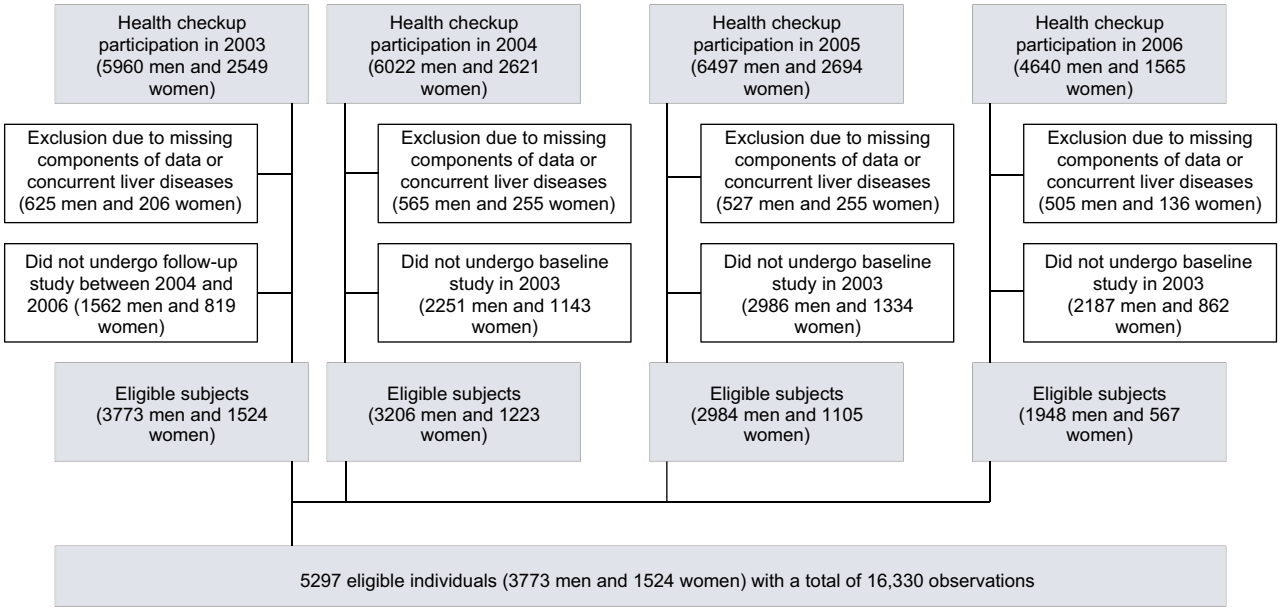

Fig. 1. Inclusion and exclusion flow chart.