Nonalcoholic fatty liver disease remission in men through regular exercise

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Recent cross-sectional and randomized controlled studies of small sample sizes revealed that regular exercise is effective for improving nonalcoholic fatty liver disease. However, there has been no large-scale longitudinal study addressing the effect of regular exercise on remission of nonalcoholic fatty liver disease. Thus, we investigated the impact of exercise on the natural history of nonalcoholic fatty liver disease. We analyzed 1,010 (860 men and 150 women) Japanese participants who received health checkups repeatedly over 10 years by a historical cohort study and were diagnosed with nonalcoholic fatty liver disease at baseline. Regular exercise was defined as participating in any kind of sports at least once a week. Nonalcoholic fatty liver disease was diagnosed by ultrasonographic images. During 10 years of follow-up, remission of nonalcoholic fatty liver disease was observed in 46.8% (396/860) of men and 48.7% (73/150) of women. In men, the adjusted hazard ratio of regular exercise for remission of nonalcoholic fatty liver disease was 1.46 (95% confidence interval 1.10–1.95, \( p = 0.010 \)). However, this was not significant in women. Exercise at least once a week is implicated in the remission of nonalcoholic fatty liver disease in men.

Key Words: NAFLD, fatty liver, exercise, remission

Nonalcoholic fatty liver disease (NAFLD) is not only a major cause of liver-related morbidity and mortality1,2 but also a risk factor for type 2 diabetes,3,4 chronic kidney disease5,6 and cardiovascular disease.3,7-8 In Japan, its prevalence has increased to 20–30% along with the increased consumption of a high-fat diet and the expansion of a sedentary lifestyle.9,10

Because of the importance of NAFLD, several different strategies have been designed for NAFLD treatment, including pharmacological agents and surgical interventions, but definitive therapy has not been established.11-13 It is well known that body weight reduction leads to remission or improvement of NAFLD.14,15 In addition, there has been increasing interest in lifestyle therapies for NAFLD.14 Several cross-sectional studies have revealed that regular exercise is associated with a lower NAFLD prevalence.13,15-20 However, the impact of regular exercise on the natural history of NAFLD remains to be elucidated, because there is no large longitudinal study addressing the effect size of regular exercise on remission of NAFLD. Therefore, in this study we investigated a longitudinal analysis of the effect of regular exercise on the natural history of NAFLD in a large-scale Japanese population using standardized ultrasonographic diagnosis for fatty liver as well as standardized questionnaires for lifestyle.21

Materials and Methods

Study population. We designed a historical cohort study to investigate the impact of regular exercise on the natural history of NAFLD in participants who underwent a medical health checkup program at Murakami Memorial Hospital, Gifu, Japan. This longitudinal analysis was termed NAGALA (NAFLD in Gifu Area, Longitudinal Analysis). The purpose of the medical health checkup program and the detailed characteristics of participants were described previously.10 In the current study, we included the participants who received the health checkups repeatedly over a decade and who had a fatty liver disease at baseline examination. Exclusion criteria were alcohol intake of more than 20 g/day, known liver disease, or current use of any medication.10,21,22 Participants with known liver disease included those who were positive for hepatitis B antigen or hepatitis C antibody or those with a history of viral, genetic, autoimmune, or drug-induced liver disease.22 The ethics committee of Murakami Memorial Hospital approved the study, and informed consent was obtained from all participants.

Data collection. The following tests were performed for the collection of data: urinalysis, blood cell counts, blood chemistry and abdominal ultrasonography. The medical history and lifestyle factors of all participants were surveyed by a standardized self-administered questionnaire. We undertook blood and urine examinations using MODULAR ANALYTICS (Hitachi HighTechnologies Corp. Ltd., Tokyo, Japan). Body mass index (BMI) was calculated as body weight in kilograms divided by the participant’s height in meters squared.

Standardized questionnaire for lifestyle factors. A standardized questionnaire was administered to all participants by the same trained team of interviewers. Alcohol consumption was evaluated by asking the participants for the amount and type of alcoholic beverages consumed per week during the past month, then estimating the mean ethanol intake per week and the total amount of alcohol consumed per week, in grams.24 The validity of alcohol consumption data was confirmed previously.10 Smoking status was categorized into three groups (never smoker, former smoker and current smoker). On the questionnaire, participants reported the type, duration and frequency of their participation in sports or recreational activities.25 When participants played any sport at least once a week, they were categorized as regular exercisers.26

Definition of fatty liver. Fatty liver was diagnosed based on the results of abdominal ultrasonography, which was performed with the following criteria: the presence of echogenic foci in the liver, the liver-to-skin ratio of more than 1.3, and the liver-to-spleen ratio of more than 1.3.

Definition of regular exercise. Participants were classified as regular exercisers when they reported participating in any kind of exercise at least once a week.
by trained technicians. All ultrasonographic images were stored in the image server as electric images, and gastroenterologists reviewed the images and made the diagnosis of fatty liver without reference to any of the participant’s other individual data. Of the 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.\(^{(23)}\)

**Statistical analysis.** The study participants were divided into two groups based on the persistence or remission of NAFLD, and baseline characteristics were compared between the groups. Continuous variables were expressed as means (SD) and analyzed by Student’s t test. Categorical variables were expressed as numbers (percentages) and analyzed by Pearson’s chi-squared test. The hazard ratio of regular exercise for remission of NAFLD was calculated by Cox hazard model after adjusting for age, BMI, fasting plasma glucose, systolic blood pressure, HDL cholesterol, triglycerides, smoking status, and alcohol consumption at baseline. Initially, the remission rate of NAFLD was higher in the regular exercisers (\(p = 0.015\)) for men but not for women (\(p = 0.430\)) (Fig. 2). Exercise habit as well as BMI were determinates for remission of NAFLD in men, with adjusted hazard ratios of 1.46 [95% confidence interval (95% CI) 1.10–1.95, \(p = 0.010\)] and 0.91 (95% CI 0.87–0.95, \(p < 0.001\)), respectively. However, BMI was the only determinant for remission of NAFLD in women, with an adjusted hazard ratio of 0.86 (95% CI 0.77–0.95, \(p = 0.003\)) (Table 2).

**Discussion**

In this cohort study, we showed clear evidence that regular exercise is associated with remission of NAFLD in men. Several cross-sectional studies revealed that regular exercise is associated with lower NAFLD prevalence.\(^{(15–19)}\) In addition, many randomized controlled trials revealed that exercise intervention is effective for reduction of liver fat.\(^{(27–32)}\) However, the sample sizes in these studies were small. Our study showed that regular exercise is associated with remission of NAFLD in men in a large-scale cohort study. The use of a validated, standardized ultrasonographic diagnosis of fatty liver, standardized questionnaires for lifestyle and the long duration of follow-up of more than a decade are the strengths of this cohort study.

The possible explanations for the effect of regular exercise on remission of NAFLD are as follows. The pathways of fatty acid oxidation and fatty acid synthesis have pivotal roles in hepatic steatosis. Adiponectin and adenosine monophosphate-activated protein kinase (AMPK) are associated with fatty acid oxidation in liver.\(^{(33)}\) AMPK is activated by adiponectin signaling.\(^{(34)}\) However, sterol regulatory element binding protein (SREBP)-1c enhances fatty acid synthesis.\(^{(35)}\) Exercise decreases triglyceride synthesis by increasing adiponectin\(^{(36,37)}\) and AMPK activation.\(^{(38)}\) In addition, exercise also reduces SREBP-1c levels in liver.\(^{(39)}\)
### Table 1. Baseline characteristics of the study participants

|                          | Remission of NAFLD | Persistent of NAFLD | *p*   | Remission of NAFLD | Persistent of NAFLD | *p*   |
|--------------------------|--------------------|--------------------|-------|--------------------|--------------------|-------|
| **Total number**         | 396 (46.0)         | 464 (54.0)         | —     | 73 (48.6)          | 77 (51.4)          | —     |
| **Age (years)**          | 42.7 (7.1)         | 41.7 (7.0)         | 0.034 | 44.7 (7.6)         | 46.4 (6.8)         | 0.148 |
| **Body mass index (kg/m²)** | 24.8 (2.5)        | 26.0 (3.1)         | <0.001 | 25.1 (2.7)        | 26.3 (3.1)         | 0.019 |
| **Systolic blood pressure (mmHg)** | 123.4 (15.1)    | 126.6 (14.6)       | 0.002 | 124.8 (17.2)       | 126.5 (18.8)       | 0.565 |
| **Diastolic blood pressure (mmHg)** | 77.9 (9.9)       | 79.6 (9.8)         | 0.012 | 77.2 (11.4)        | 78.0 (11.5)        | 0.687 |
| **Aspartate Aminotransferase (IU/L)** | 21.5 (6.5)       | 24.8 (10.6)        | <0.001 | 18.2 (5.9)        | 20.0 (10.2)        | 0.187 |
| **Alanine aminotransferase (IU/L)** | 33.2 (16.8)      | 43.1 (24.4)        | <0.001 | 21.7 (11.1)       | 27.3 (19.7)        | 0.035 |
| **γ-glutamyl-transferase (IU/L)** | 32.2 (26.4)      | 34.8 (24.2)        | <0.001 | 18.6 (16.0)       | 24.5 (28.4)        | 0.123 |
| **Fasting plasma glucose (mmol/L)** | 5.7 (1.1)         | 5.7 (1.1)          | 0.522 | 5.7 (1.6)         | 5.5 (0.8)          | 0.327 |
| **HDL cholesterol (mmol/L)** | 1.1 (0.3)         | 1.0 (0.2)          | 0.356 | 1.3 (0.3)         | 1.3 (0.2)          | 0.384 |
| **Triglycerides (mmol/L)** | 1.9 (1.2)         | 1.9 (1.1)          | 0.624 | 1.5 (1.3)         | 1.4 (0.8)          | 0.549 |
| **Alcohol consumption (g/week)** | 42.7 (42.2)       | 37.8 (42.2)        | 0.114 | 15.2 (32.4)       | 11.8 (27.1)        | 0.512 |
| **Smoking states**       |                    |                    |       |                    |                    |       |
| Never smoker             | 133 (33.3)         | 162 (34.7)         | 0.795 | 66 (90.4)         | 69 (89.5)          | 0.97  |
| Former smoker            | 119 (30.2)         | 130 (28.1)         | 0.984 | 2 (2.7)           | 2 (2.6)            |       |
| Current smoker           | 144 (36.5)         | 172 (37.2)         | 0.984 | 5 (6.9)           | 6 (7.9)            |       |
| **Physical activities**  |                    |                    |       |                    |                    |       |
| Regular exerciser        | 68 (17.2)          | 52 (11.2)          | 0.012 | 9 (12.3)          | 6 (7.8)            | 0.355 |

Data are given as numbers (percentages), mean (SD). NAFLD, non-alcoholic fatty liver disease. HDL, high density lipoprotein. *p* value = remission of NAFLD vs persistent of NAFLD in men. **p** value = remission of NAFLD vs persistent of NAFLD in women. †,‡ Student’s t test, Pearson’s qui-squared test were performed.

### Fig. 2. Hazard ratio of the effect of regular exercise on remission of NAFLD. The vertical axis is cumulative incidence of fatty liver and the horizontal axis is time as days. The black line represents regular exercisers. The gray line represents non-regular exercisers.

### Table 2. Hazard ratio of baseline characteristics for the remission of NAFLD

|                          | Men        | Women      |
|--------------------------|------------|------------|
|                          | HR with 95% CI | *p*   | HR with 95% CI | *p*   |
| **Age (years)**          | 1.01 (0.99–1.03) | 0.201 | 0.97 (0.94–1.01) | 0.177 |
| **BMI (kg/m²)**          | 0.91 (0.87–0.95) | <0.001 | 0.86 (0.77–0.95) | 0.003 |
| **Alcohol consumption**  | 1.00 (1.00–1.00) | 0.215 | 1.01 (1.00–1.01) | 0.134 |
| **Former smoker**        | 0.98 (0.74–1.29) | 0.984 | 0.77 (0.18–3.28) | 0.464 |
| **Current smoker**       | 0.98 (0.87–1.28) | 0.984 | 0.57 (0.22–1.51) | 0.464 |
| **Regular exerciser**    | 1.46 (1.10–1.95) | 0.010 | 1.45 (0.66–3.16) | 0.369 |
| **Fasting plasma glucose (mmol/L)** | 1.00 (0.98–1.02) | 0.766 | 1.00 (0.98–1.02) | 0.482 |
| **Systolic blood pressure (mmHg)** | 0.99 (0.98–1.00) | 0.073 | 1.00 (0.99–1.02) | 0.584 |
| **HDL cholesterol (mmol/L)** | 1.47 (1.02–2.15) | 0.215 | 1.47 (0.46–3.14) | 0.526 |
| **Triglycerides (mmol/L)** | 1.00 (0.84–1.09) | 0.598 | 1.00 (0.86–1.11) | 0.629 |

NAFLD, non-alcoholic fatty liver disease; HR, hazard ratio; CI, confidence interval; BMI, body mass index; HDL, high density lipoprotein. Hazard ratio of the regular exercise for the remission of NAFLD was calculated by Cox hazard model after adjusting by age, BMI, systolic blood pressure, fasting plasma glucose, HDL cholesterol, triglycerides, smoking status and alcohol consumption at baseline.
Thus, exercise has a protective effect on fatty liver via activating the AMPK pathway and/or repressing the SREBP-1c pathway. Moreover it has been reported that exercise induced anti-oxidant enzymes via SIRT3.(40)

Our study revealed that the association between regular exercise and remission of NAFLD was observed in men but not in women. This might be because NAFLD was more common in men than in women, which is consistent with past reports.(41) Therefore, the number of participants with NAFLD at baseline examination might be not enough to evaluate the effect of regular exercise on the natural history of NAFLD in women, because hazard ratios for regular exercise on remission of NAFLD were almost the same between men and women.

Some limitations of our study should be noted. First, ultrasonography may give an incorrect diagnosis compared to liver biopsy, although it has been validated for diagnosing fatty liver.(29) However, it is impossible to perform liver biopsy in such a large number of healthy participants. Moreover, ultrasonography is a reasonable noninvasive surrogate measure for use in clinical settings and has a high sensitivity and specificity for diagnosing fatty liver.(42) Second, self-reported information regarding exercise is frequently subject to misreporting, which could be a source of bias. Moreover, we did not measure the intensity of physical activity or the type of exercise, such as resistance training, aerobic training, or both. However, the purpose of this study was to determine the effect of regular exercise on remission of NAFLD. Third, this was a historical cohort study. Thus, we cannot exclude the possibility that our sample contained more health-concerned people than the general population of Japan. Forth, we don’t consider the influence of participant’s dietary.(43,44) Lastly, the generalizability of our study to non-Japanese populations is uncertain.

To the best of our knowledge, this is the first study to investigate the association of remission of NAFLD and regular exercise with the natural history of NAFLD in a large-scale Japanese population. We suggest that regular exercise can remit NAFLD.

In conclusion, exercise at least once a week is implicated in the remission of NAFLD in men.

Specific Author Contributions
Takafumi Osaka researched data, wrote manuscript and has approved the final draft submitted; Yoshitaka Hashimoto and Masahide Hamaguchi researched data, reviewed and edited the manuscript and has approved the final draft submitted; Takao Kojima and Akihiro Obora researched data and have approved the final draft submitted. Michiaki Fukui researched data, reviewed the manuscript and has approved the final draft submitted.

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Conflict of Interest
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