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Physical activity and risk of fatty liver in people with different levels of alcohol consumption: a prospective cohort study

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ABSTRACT

Objective: To investigate whether physical activity affects the future incidence of fatty liver in people with never-moderate and heavy alcohol consumption.

Design: Prospective cohort study.

Setting: Health check-up programme at Meiji Yasuda Shinjuku Medical Center in Shinjuku Ward, Tokyo, Japan.

Population: A total of 10 146 people aged 18 years or older without fatty liver enrolled through baseline surveys conducted from 2005 to 2007. They were grouped into never-moderate alcohol drinkers (n=7803) and heavy alcohol drinkers (n=2343) and followed until 2013.

Main outcome measure: Incident fatty liver diagnosed by ultrasound.

Results: During a mean follow-up of 4.4 years (34 648 person-years), 1255 never-moderate alcohol drinkers developed fatty liver; 520 heavy alcohol drinkers developed fatty liver during a mean follow-up of 4.1 years (9596 person-years). For never-moderate alcohol drinkers, engaging in >3×/week of low-intensity (HR=0.82, 95% CI 0.71 to 0.96) and moderate-intensity (HR=0.56, 95% CI 0.39 to 0.81) physical activity significantly reduced incident fatty liver compared with those who engaged in physical activity <1×/week. For vigorous-intensity physical activity, frequencies of 2×/week (HR=0.57, 95% CI 0.38 to 0.86) and >3×/week (HR=0.55, 95% CI 0.38 to 0.79) were significantly associated with lower risk of incident fatty liver. In propensity-adjusted models, these significant associations still remained. By contrast, in heavy alcohol drinkers, there were no significant associations between the type or frequency of physical activity and incident fatty liver.

Conclusions: Physical activity had an independent protective effect on incident fatty liver only in the never-moderate alcohol drinkers, and the preventive effect increased with higher frequencies and intensities of physical activity.

Strengths and limitations of this study

- This study revealed the independent preventive effect of physical activity on incident non-alcoholic fatty liver disease; its strength lies in its prospective cohort design.
- Our large sample size allowed us to show separate HRs according to frequencies and intensities of physical activity.
- Although hepatic ultrasonography is widely used at the population level, it can lead to incorrect diagnoses.

INTRODUCTION

Alcoholic fatty liver disease (AFLD) is a well-known hepatic disorder.[1 2] However, concern is growing over non-AFLD (NAFLD) because NAFLD, as well as AFLD, can progress to hepatitis and fibrosis.[3–5] The incidence of NAFLD has gradually increased[6]; a recent Japanese cohort study[7] has reported that 29.7% of health check-up examinees had NAFLD. Western countries have had a high prevalence of NAFLD for some time,[8] but recently NAFLD has become an urgent issue for the international community including Japan.[6 8 9]

Physical activity (PA) is a well-known way of preventing and improving certain obesity-related diseases such as hypertension,[10] diabetes[11] and dyslipidaemia.[12] Since NAFLD[13 14] and AFLD[15 16] are obesity-related, PA may also have an effect on these diseases. In fact, several cross-sectional[17–21] and retrospective[22] studies already revealed a significant association between higher levels of PA and a lower prevalence of NAFLD. However, a prospective association is still unclear, and evidence from a longitudinal cohort design is needed.[23]

Additionally, recent population studies on PA and fatty liver focused on NAFLD and excluded people with a heavy alcohol intake[17–22]; there are few epidemiological findings on the effect of PA on AFLD. Confirming the preventive effect of PA on fatty liver for light and heavy alcohol drinkers is useful information for all people, but especially for those who cannot cut down or stop drinking.

The purpose of this prospective cohort study was to investigate whether engaging in PA prevents the future incidence of fatty liver diagnosed by ultrasound in two populations: never-moderate alcohol drinkers and heavy alcohol drinkers.

METHODS

Participants and data collection

We used data from the Meiji Yasuda Longitudinal Study, a prospective cohort study based on annual health check-ups conducted in Meiji Yasuda Shinjuku Medical Center in Shinjuku Ward, Tokyo, Japan. The majority of patients were employees and their spouses, with employers providing financial support for the annual health check-ups. This popular method of providing medical services in Japan is called 'a human dock'. It is also an important source for research participants and data including fatty liver studies.[6 7 14 24] Figure 1 shows the flow of participants through the study. We used 2005–2007 survey data (n=25 056, aged 18 years or older) as our baseline data. Of these people, 2541 individuals were excluded due to the lack of an ultrasound confirming their fatty liver and 2365 due to incomplete data. We further excluded 1328 because they had histories of liver disease, including hepatitis B or C, cirrhosis and hepatic haemangioma, they were using drugs associated with hepatic disease or they had antibodies to hepatitis B or C. We excluded 3832 individuals because they had fatty liver disease at the baseline. Furthermore, 4844 individuals were excluded because they could not be followed for at least 1 year. We had a final tally of 10 146 participants. These participants were followed through their annual health check-ups until fatty liver disease had been diagnosed or until the end of 2013. When a participant we were following did not attend an annual check-up, we used all available follow-up data. All participants provided informed consent.

Assessment of fatty liver and alcohol consumption

Abdominal ultrasonography machines (EUB-2000, Hitachi, Japan; and SSA-340, 550, 580 and 660, Toshiba, Japan) were used to diagnose fatty liver based on known standard criteria, including hepatorenal echo contrast, liver brightness, deep attenuation and vascular blurring.[25 26] A fatty liver appears bright in ultrasound images compared with the kidney; this is the most frequently observed sign of fatty liver.[25] In severe fatty liver, deep attenuation and vascular blurring are also frequently observed.[25] To enhance diagnostic accuracy, we evaluated the ultrasound images in three steps: first, a trained medical technologist performed the ultrasound and provided opinions with images to the doctor; second, the doctor made a diagnosis based on this information and third, a group of medical technologists including the original examiner confirmed the doctor's diagnosis. The mean diagnosis rate of fatty liver in our surveys from 2005 to 2013 was 23.1±1% (range 22.2–24.8%). Ultrasound diagnosis of fatty liver has been validated in a systematic review.[26]

Using a self-administered questionnaire, participants revealed their alcohol intake frequency (never, occasional drink, 1–2 days/week, 3–4 days/week, daily with day off drinking and daily without day off drinking) and the quantity of each type of alcoholic beverage consumed. To determine the quantity of alcohol consumed, participants used information provided on the alcohol/ethanol content of each beverage type equivalent to *sake*. One *go* (a traditional Japanese measurement) of *sake* (23 g of alcohol) is roughly equivalent to 2 glasses of wine, 633 mL of beer, 2.5 single glasses of whisky or 0.5 cup of *shochu*. We used a scoring method for the frequency of alcohol consumption as follows: 0.5 for an occasional drink, 1.5 for 1–2 days/week, 3.5 for 3–4 days/week, 5.5 for daily with day off drinking and 7 for daily without day off drinking. We set four alcohol categories by calculating the average daily alcohol consumption: never, moderate (less than 23 g of alcohol/day), heavy (23–45.9 g/day) and very heavy (46 g/day or more).[27] The validation for this kind of assessment for alcohol consumption was reported in a previous Japanese cohort study.[28] Based on the alcohol intake status at the baseline, participants were divided into never-to-moderate alcohol drinkers (n=7803) and heavy alcohol drinkers (n=2343).[27]

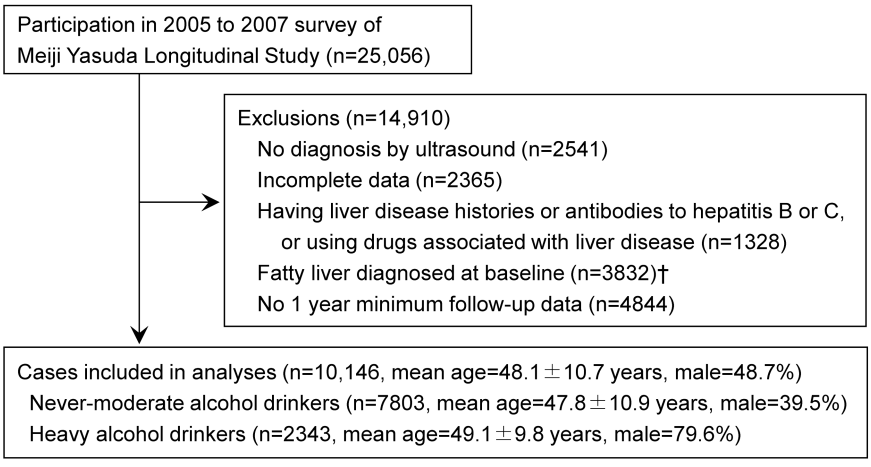

Figure 1 Flow of eligible participants in this study. †At this stage, 3832 of 18 822 examinees (20.4% of total, 29.6% of men, 9.8% of women) were diagnosed with fatty liver. When looking at examinees' levels of alcohol consumption, 2827 of 14 490 never-moderate alcohol drinkers (19.5% of total, 31.1% of men, 10.0% of women) and 1005 of 4332 heavy alcohol drinkers (23.2% of total, 26.8% of men, 7.8% of women) were diagnosed with fatty liver at the baseline.

Physical activity

A questionnaire assessed leisure-time PA in a typical week by frequency (never, <1×, 1×, 2× and >3×/week), duration (minutes per session) and intensity (low, moderate, vigorous and very vigorous). Low-intensity PA includes activities such as walking, light bicycling, gymnastics, light dancing, golf and Japanese croquet. A moderate-intensity PA includes jogging, bicycling (about 16 km/h), hiking, badminton, tennis and ballroom dancing. A vigorous-intensity PA includes jogging (about 9.6 km/h), swimming, climbing hills and aerobic dancing. A very vigorous PA includes running a marathon, rope jumping and competitive sports such as soccer and rugby. Because few respondents participated in very vigorous PA, we combined the very vigorous and vigorous PA into a single group of vigorous-intensity PA. The low-intensity activities corresponded to about 3–5 metabolic equivalents (METs), moderate-intensity corresponded to 5–7 METs and vigorous-intensity corresponded to 7 or more METs.[29 30]

Since 10 min is considered the minimum for a single event activity,[31] we determined a single session of PA to be >10 min. Each frequency (<1×, 1×, 2× and >3×/week) of low-intensity, moderate-intensity and vigorous-intensity PA was used in our analyses.

Other variables

Demographic variables included age, gender, body mass index (BMI), alcohol consumption (never, moderate, heavy and very heavy), smoking status (never, former and current), meat and green/yellow vegetable intake status (never or seldom, once every 2 days and one or more times per day), family history of liver disease (yes or no) and diagnosis and drug usage histories (yes or no) for hypertension, diabetes and dyslipidaemia. A blood sample was drawn from each participant after an overnight fast. The serum triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, fasting plasma glucose (FPG), glycated haemoglobin (HbA1c), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and γ-glutamyltransferase (GGT) were measured using standard techniques. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were taken from the right arm using a mercury manometer after the participant rested for at least 15 min in a sitting position.

Exposure and outcome

The study's exposure is the PA level at the baseline and the outcome is the future incidence of fatty liver. In never-moderate and heavy alcohol drinkers, incident fatty liver was defined as fatty liver diagnosed by ultrasound.

Statistical analysis

To compose covariates, we set dichotomous variables (yes or no) for hypertension, diabetes and dyslipidaemia. Hypertension was coded 'yes' if SBP ≥140 mm Hg, DBP ≥90 mm Hg, there was a diagnosis history or drug usage for hypertension. Diabetes was coded 'yes' if FPG ≥7 mmol/L, HbA1c ≥6.5%, there was a diagnosis history or drug usage for diabetes. Dyslipidaemia was coded 'yes' if LDL-C ≥4.1 mmol/L, HDL ≤1 mmol/L, TG ≥2.3 mmol/L, there was a diagnosis history or drug usage for dyslipidaemia.

We performed all analyses on the never-moderate and heavy alcohol drinking groups. To compare baseline characteristics with PA frequencies, we used χ^2 tests for categorical variables and analysis of variance for continuous variables. We used the Cox proportional hazard analysis to determine prospective associations between the PA frequency and incident fatty liver. We used two multivariable-adjusted models in this study: covariates of model 1 included age (continuous), gender, BMI (continuous), alcohol consumption (never or moderate for never-moderate alcohol drinkers, and heavy or very heavy for heavy alcohol drinkers), smoking status (never, former or current), family history of liver disease (yes or no), ALT (continuous), GGT (continuous), hypertension (yes or no), diabetes (yes or no), dyslipidaemia (yes or no) and meat and green/yellow vegetable intakes (never or seldom, once every 2 days or one or more times per day). Since there was strong correlation between ALT and AST in both never-moderate (r=0.74) and heavy alcohol drinkers (r=0.76), only ALT was entered into the models to avoid multicollinearity; ALT is closely associated with fatty liver.[7] In model 2, to consider the effect of PA, we incorporated all three PA intensity variables into model 1.

We also performed a propensity-adjusted analysis to consider the probability of performing each intensity of PA >3×/week.[32] The propensity scores for the highest frequency of the three PA intensities were calculated by a multivariable logistic regression analysis using all covariates. In propensity-adjusted Cox models, we used full samples of <1× and >3×/week, but did not conduct the matching analysis.[32] The areas under the receiver operating curves of propensity scores were 0.69–0.76, respectively. In all Cox models, we integrated the different hazards for baseline starting years using stratification adjustment. The level of significance for all analyses was set at $p<0.05$. Statistical analyses were performed using SPSS V.21.0 (IBM, Inc, Armonk, New York, USA).

RESULTS

Description of the sample

Table 1 shows the participants' baseline characteristics by PA frequency in never-moderate and heavy alcohol drinkers. The mean age of never-moderate drinkers was 47.8±10.9 years with men representing 39.5% of this group. The heavy drinkers' mean age was 49.1±9.8 years with 79.6% men. In both groups, almost half the people did not engage in any PA. Baseline characteristics for all three intensities of PA are presented in online supplementary tables S1a–c.

Table 1 Baseline characteristics of participants by frequency of physical activity

	Never-moderate alcohol drinkers (n=7803, mean age=47.8±10.9 years, male=39.5%)									Heavy alcohol drinkers (n=2343, mean age=49.1±9.8 years, male=79.6%)								
	Physical activity (times/week)									Physical activity (times/week)								
Baseline variables	**<1×**		**1×**		**2×**		**≥3×**		**p Value**	**<1×**		**1×**		**2×**		**≥3×**		**p Value**
Number of participants	3653		1018		816		2316			1129		322		269		623		
Mean (SD) age (years)	45.4	(9.9)	46.9	(10.6)	49.5	(10.7)	51.3	(11.5)	<0.001	47.1	(9.1)	48.7	(9.1)	49.8	(9.8)	52.6	(10.5)	<0.001
Male gender	1494	(40.9)	416	(40.9)	328	(40.2)	842	(36.4)	0.004	879	(77.9)	269	(83.5)	224	(83.3)	492	(79.0)	0.056
Mean (SD) BMI (kg/m^2)	21.6	(2.7)	21.6	(2.5)	21.6	(2.4)	21.7	(2.6)	0.485	22.4	(2.5)	22.9	(2.5)	22.7	(2.2)	22.6	(2.3)	0.017
Daily alcohol consumption																		
Never	638	(17.5)	168	(16.5)	150	(18.4)	460	(19.9)	0.055	–		–		–		–		
Low-moderate (<23.0 g)	3015	(82.5)	850	(83.5)	666	(81.6)	1856	(80.1)		–		–		–		–		
Heavy (23.0–45.9 g)	–		–		–		–			856	(75.8)	254	(78.9)	193	(71.7)	472	(75.8)	0.254
Very heavy (≥46.0 g)	–		–		–		–			273	(24.2)	68	(21.1)	76	(28.3)	151	(24.2)	
Smoking status									<0.001									<0.001
Never	2070	(56.7)	651	(63.9)	508	(62.3)	1502	(64.9)		263	(23.3)	72	(22.4)	64	(23.8)	173	(27.8)	
Former	620	(17.0)	230	(22.6)	178	(21.8)	539	(23.3)		308	(27.3)	119	(37.0)	117	(43.5)	280	(44.9)	
Current	963	(26.4)	137	(13.5)	130	(15.9)	275	(11.9)		558	(49.4)	131	(40.7)	88	(32.7)	170	(27.3)	
Family history of hepatic disease	203	(5.6)	59	(5.8)	52	(6.4)	144	(6.2)	0.674	69	(6.1)	13	(4.0)	22	(8.2)	41	(6.6)	0.205
Mean (SD) ALT (Units/L)	19.0	(10.4)	18.9	(9.9)	18.9	(8.4)	18.7	(8.6)	0.749	22.1	(12.6)	22.6	(11.5)	22.2	(11.2)	21.4	(12.6)	0.526
Mean (SD) AST (Units/L)	20.1	(5.8)	20.6	(6.0)	21.1	(5.2)	21.3	(5.7)	<0.001	23.1	(8.9)	23.7	(7.1)	23.5	(6.5)	23.7	(7.9)	0.484
Mean (SD) GGT (Units/L)	27.6	(25.2)	28.1	(33.5)	27.9	(24.6)	26.9	(23.2)	0.516	62.1	(74.1)	58.5	(54.3)	59.0	(56.1)	53.4	(52.8)	0.063
Hypertension*	288	(7.9)	78	(7.7)	110	(13.5)	315	(13.6)	<0.001	183	(16.2)	55	(17.1)	63	(23.4)	156	(25.0)	<0.001
Diabetes†	76	(2.1)	28	(2.8)	35	(4.3)	120	(5.2)	<0.001	42	(3.7)	17	(5.3)	21	(7.8)	52	(8.3)	<0.001
Dyslipidaemia‡	705	(19.3)	220	(21.6)	174	(21.3)	540	(23.3)	0.003	236	(20.9)	78	(24.2)	51	(19.0)	142	(22.8)	0.354
Meat intake									<0.001									0.092
Never or seldom	1394	(38.2)	396	(38.9)	348	(42.6)	1043	(45.0)		469	(41.5)	110	(34.2)	114	(42.4)	280	(44.9)	
Once per 2 days	1211	(33.2)	333	(32.7)	260	(31.9)	700	(30.2)		356	(31.5)	119	(37.0)	82	(30.5)	182	(29.2)	
Once a day or more	1048	(28.7)	289	(28.4)	208	(25.5)	573	(24.7)		304	(26.9)	93	(28.9)	73	(27.1)	161	(25.8)	
Vegetable intake									<0.001									<0.001
Never or seldom	949	(26.0)	163	(16.0)	125	(15.3)	294	(12.7)		387	(34.3)	76	(23.6)	63	(23.4)	109	(17.5)	
Once per 2 days	850	(23.3)	231	(22.7)	157	(19.2)	350	(15.1)		297	(26.3)	79	(24.5)	60	(22.3)	123	(19.7)	
Once a day or more	1854	(50.8)	624	(61.3)	534	(65.4)	1672	(72.2)		445	(39.4)	167	(51.9)	146	(54.3)	391	(62.8)	

Values are numbers (percentages) unless stated otherwise.
Baseline characteristics for all three intensities of physical activity are presented in online supplementary tables S1a–c.
*Systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, diagnosis history or drug usage for hypertension.
†Fasting plasma glucose ≥7 mmol/L, HbA1c ≥6.5%, diagnosis history or drug usage for diabetes.
‡Low-density lipoprotein cholesterol ≥4.1 mmol/L, high-density lipoprotein cholesterol ≤1 mmol/L, serum triglycerides ≥2.3 mmol/L, diagnosis history or drug usage for dyslipidaemia.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GGT, γ–glutamyltransferase; HbA1c, glycated haemoglobin.

During a mean follow-up of 4.4 years (34 648 person-years), 1255 of 7803 never-moderate alcohol drinkers (16.1% of total, 24.9% of men, 10.4% of women) developed fatty liver; 520 of 2343 heavy alcohol drinkers (22.2% of total, 25.4% of men, 9.6% of women) developed fatty liver during a mean follow-up of 4.1 years (9596 person-years). In total, 1775 of 10 146 participants (17.5% of total, 25.1% of men, 10.3% of women) were newly diagnosed with fatty liver during a mean follow-up of 4.4 years (44 244 person-years).

Incident fatty liver and PA in never-moderate alcohol drinkers

Table 2 summarises the Cox models in never-moderate alcohol drinkers. In model 2, participants who engaged in low-intensity PA (HR=0.82, 95% CI 0.71 to 0.96) or moderate-intensity PA (HR=0.56, 95% CI 0.39 to 0.81) >3×/week significantly reduced their risks of incident fatty liver, compared with those who engaged in PA <1×/week. When participants engaged in vigorous-intensity PA >2×/week, they decreased their risk of fatty liver by about half (2×/week: HR=0.57, 95% CI 0.38 to 0.86; >3×: HR=0.55, 95% CI 0.38 to 0.79). All HRs in model 2, including covariates, are shown in online supplementary table S2. The final propensity-adjusted Cox models (see online supplementary table S3) also confirmed the significant preventive effects of >3×/week of lower-intensity (HR=0.82, 95% CI 0.71 to 0.96), moderate-intensity (HR=0.57, 95% CI 0.40 to 0.83) and vigorous-intensity PA (HR=0.55, 95% CI 0.38 to 0.79) on fatty liver.

Incident fatty liver and PA in heavy alcohol drinkers

There were no significant associations between the type or frequency of PA and the risk of incident fatty liver in heavy alcohol drinkers (table 3).

DISCUSSION

This prospective study investigated the association between PA engagement and incident fatty liver in two populations, those with never-moderate or heavy alcohol consumption. We found that PA had an independent effect against incident fatty liver in never-moderate alcohol drinkers, whereas there was no association in heavy alcohol drinkers. Our results suggest that PA is an effective tool for preventing NAFLD as well as other obesity-related diseases.[10–12]

Table 2 HRs of incident fatty liver by frequency of physical activity in never-moderate alcohol drinkers

	Frequency of engaging in physical activity (times/week)			
	HR (95% CI)			
	<1×	1×	2×	≥3×
Low-intensity physical activity				
Number of participants	4900	728	516	1659
Number of person-years	21 679	3278	2269	7422
Number of fatty liver cases	804	108	88	255
Incidence rates per 1000 person-years	37	33	39	34
Unadjusted	1.00	0.89 (0.73 to 1.09)	1.05 (0.84 to 1.31)	0.93 (0.81 to 1.07)
Adjusted for age and gender	1.00	0.87 (0.71 to 1.07)	0.98 (0.78 to 1.22)	*0.86 (0.74 to 0.99)*
Model 1*	1.00	0.95 (0.78 to 1.17)	1.00 (0.80 to 1.24)	0.87 (0.75 to 1.01)
Model 2†	1.00	0.91 (0.74 to 1.12)	0.96 (0.77 to 1.20)	*0.82 (0.71 to 0.96)*
Moderate-intensity physical activity				
Number of participants	6699	478	318	308
Number of person-years	29 579	2200	1441	1428
Number of fatty liver cases	1117	67	41	30
Incidence rates per 1000 person-years	38	30	28	21
Unadjusted	1.00	0.81 (0.63 to 1.04)	0.76 (0.55 to 1.03)	*0.56 (0.39 to 0.81)*
Adjusted for age and gender	1.00	0.81 (0.63 to 1.03)	*0.71 (0.52 to 0.97)*	*0.52 (0.36 to 0.75)*
Model 1*	1.00	0.88 (0.69 to 1.13)	*0.74 (0.54 to 1.01)*	*0.56 (0.39 to 0.81)*
Model 2†	1.00	0.87 (0.68 to 1.12)	0.74 (0.54 to 1.01)	*0.56 (0.39 to 0.81)*
Vigorous-intensity physical activity				
Number of participants	6935	328	254	286
Number of person-years	30 641	1484	1181	1342
Number of fatty liver cases	1153	48	24	30
Incidence rates per 1000 person-years	38	32	20	22
Unadjusted	1.00	0.86 (0.64 to 1.15)	*0.54 (0.36 to 0.82)*	*0.60 (0.42 to 0.86)*
Adjusted for age and gender	1.00	0.84 (0.63 to 1.12)	*0.54 (0.36 to 0.82)*	*0.55 (0.38 to 0.79)*
Model 1*	1.00	0.87 (0.65 to 1.16)	*0.58 (0.39 to 0.88)*	*0.54 (0.38 to 0.78)*
Model 2†	1.00	0.86 (0.64 to 1.15)	*0.57 (0.38 to 0.86)*	*0.55 (0.38 to 0.79)*

The HRs of all covariates in model 2 are presented in online supplementary table S2. Italic numbers indicate p<0.05.
*Adjusted for age, gender, body mass index, alcohol consumption (never or low-moderate), smoking, family history of liver disease, alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase, hypertension, diabetes, dyslipidaemia and meat and vegetable intakes.
†Additional adjustment of model 1 for other intensity types of physical activity.

Table 3 HRs of incident fatty liver by frequency of physical activity in heavy alcohol drinkers

	Frequency of engaging in physical activity (times/week)			
	HR (95% CI)			
	<1×	1×	2×	≥3×
Low-intensity physical activity				
Number of participants	1554	230	142	417
Number of person-years	6412	901	597	1686
Number of fatty liver cases	338	47	33	102
Incidence rates per 1000 person-years	53	52	55	60
Unadjusted	1.00	0.98 (0.72 to 1.33)	1.07 (0.75 to 1.53)	1.14 (0.91 to 1.42)
Adjusted for age and gender	1.00	0.93 (0.69 to 1.27)	1.03 (0.72 to 1.47)	1.09 (0.87 to 1.37)
Model 1*	1.00	0.97 (0.71 to 1.32)	0.97 (0.68 to 1.40)	1.18 (0.93 to 1.49)
Model 2†	1.00	0.98 (0.72 to 1.33)	0.96 (0.67 to 1.38)	1.18 (0.93 to 1.50)
Moderate-intensity physical activity				
Number of participants	2002	154	101	86
Number of person-years	8149	666	457	324
Number of fatty liver cases	442	30	27	21
Incidence rates per 1000 person-years	54	45	59	65
Unadjusted	1.00	0.83 (0.58 to 1.21)	1.09 (0.74 to 1.61)	1.17 (0.75 to 1.81)
Adjusted for age and gender	1.00	0.81 (0.56 to 1.17)	1.02 (0.69 to 1.50)	1.05 (0.68 to 1.64)
Model 1*	1.00	0.82 (0.56 to 1.18)	1.14 (0.77 to 1.69)	1.06 (0.68 to 1.66)
Model 2†	1.00	0.81 (0.56 to 1.18)	1.15 (0.77 to 1.71)	1.13 (0.72 to 1.78)
Vigorous-intensity physical activity				
Number of participants	2055	115	77	96
Number of person-years	8377	488	312	419
Number of fatty liver cases	456	24	21	19
Incidence rates per 1000 person-years	54	49	67	45
Unadjusted	1.00	0.91 (0.61 to 1.38)	1.20 (0.78 to 1.86)	0.82 (0.52 to 1.31)
Adjusted for age and gender	1.00	0.92 (0.61 to 1.39)	1.25 (0.81 to 1.94)	0.79 (0.50 to 1.25)
Model 1*	1.00	0.86 (0.56 to 1.31)	1.27 (0.81 to 1.97)	0.76 (0.47 to 1.22)
Model 2†	1.00	0.88 (0.57 to 1.34)	1.32 (0.85 to 2.07)	0.77 (0.48 to 1.25)

The HRs of all covariates in model 2 are presented in online supplementary table S2. Italic numbers indicate p<0.05.
*Adjusted for age, gender, body mass index, alcohol consumption (heavy or very heavy), smoking, family history of liver disease, alanine aminotransferase, γ-glutamyltransferase, hypertension, diabetes, dyslipidaemia and meat and vegetable intakes.
†Additional adjustment of model 1 for other intensity types of physical activity.

Previous Chinese[33] and Korean[22] cohort studies using ultrasound for diagnosis reported that, after 5 years, 11.6% and 19.3% of participants, respectively, developed fatty liver. Similarly, in our study during 6–8 years of follow-up (mean 4.4 years), 17.5% of participants developed fatty liver, which is a feasible rate for Asian populations.

In the never-moderate alcohol drinkers, engaging in PA significantly reduced incident fatty liver, and the effect increased as the intensity and frequency increased. When participants engaged in PA >3×/week, the risks of incident fatty liver decreased significantly regardless of the PA intensity. In particular, those who engaged in moderate-intensity PA >3×/week, or vigorous-intensity PA >2×/week had decreased HRs. In a retrospective study,[22] engaging in PA >3×/week was associated with a lower prevalence of NAFLD. Our prospective findings confirm that study's results, and in addition, show the advantage of higher intensity levels of PA for preventing NAFLD.

Our results might reflect a dose–response relationship between increasing the total amount of PA and decreasing the risk of incident NAFLD; however they may also reflect a special effect of higher intensity levels of PA on NAFLD prevention. Similar to our current findings, a cross-sectional study using biopsy assessment of non-alcoholic steatohepatitis (NASH)[21] found a significant association between vigorous-intensity PA and a lower prevalence of NASH, but this was not true for moderate-intensity PA, which was of a similar intensity to our study's low-intensity PA. Intervention studies on PA intensities and abdominal fat also reported that vigorous-intensity PA more strongly reduced abdominal fat than low-intensity PA, even with the same energy expenditure.[34 35] Kistler *et al*[21] suggested that vigorous-intensity PA may be better at preventing NAFLD, because of the effect that PA has on AMP-activated protein kinase (AMP-kinase). The activation of AMP-kinase increases ATP production through fatty acid oxidation and glucose transport, and AMP-kinase is activated by depletion of ATP such as in the case of vigorous-intensity PA.[21 36] We also put forward the possible influence of the *liver–brain–adipose neurocircuitry* recently discovered by Izumida *et al*,[37] whereby depletion of liver glycogen triggers the promotion of fat consumption. Higher intensity PA typically promotes liver glycogen catabolism[38 39] which may promote fat utilisation via this liver–brain–adipose neurocircuitry.

A meta-analysis by Keating *et al*[40] on exercise and NAFLD showed that exercise with diet intervention was not more effective in reducing liver fat and enzymes compared with diet alone. However, this meta-analysis could not incorporate the exercise intensity because of the lack of data,[40] which may hide the independent benefit of exercise on NAFLD. Future intervention studies should consider the exercise intensity in addition to the duration and frequency.

The present study investigated the association between PA and incident fatty liver in a population with a high rate of alcohol consumption. Contrary to never-moderate alcohol drinkers, in heavy alcohol drinkers, the intensity and frequency of PA did not contribute a protective effect on incident fatty liver. Since positive[41 42] and negative[43 44] associations have been reported between alcohol consumption and fatty liver disease, the influence of alcohol on the liver is not yet certain. Although the effect that large amounts of alcohol have on the liver may be the reason that we found no association between PA and incident fatty liver in heavy alcohol drinkers, we did not have the details or data to determine this. Further epidemiological and physiological studies are needed. In heavy alcohol drinkers, increasing BMI, being a smoker and having dyslipidaemia were independent predictors for incident fatty liver (see online supplementary table S2), which is similar to previous reports.[1 15 16 45] Heavy alcohol drinkers should be especially aware of their weight and smoking habits. Increasing BMI and dyslipidaemia were also independent predictors in never-moderate alcohol drinkers, similar to other studies.[13 14] Hence, avoiding obesity is an important aspect in preventing fatty liver for never-moderate and heavy alcohol drinkers.

This study is the first to reveal the independent preventive effect of PA on incident NAFLD; its strength lies in its prospective cohort design. Additionally, our large sample size allowed us to show separate HRs according to PA frequencies and intensities which revealed the advantages of higher frequencies and intensities of PA. PA is a cost-effective and non-invasive prescription for good health[31]; and this study reinforces the importance of PA in the prevention of NAFLD.

There were several limitations in this study. First, although hepatic ultrasonography is widely used at the population level, it can lead to incorrect diagnoses.[26] More precise diagnosis requires liver biopsy. In addition, using several ultrasonography machines during the study may limit the accuracy of diagnoses. However, we believe that this did not seriously affect our results because (1) the similar fatty liver rates obtained at all annual surveys support the reliability of ultrasound diagnosis in the check-ups and (2) all participants randomly/equally shared this error. Second, we did not measure inflammation (eg, serum iron and ferritin) and fibrosis markers (eg, hyaluronic acid and type IV collagen).[3] A recent intervention study reported that exercise intervention reduced ferritin and thiobarbituric acid reactive substances more than diet therapy in fatty liver patients.[46] Future research on the effect that PA may have on fatty liver should consider inflammation and fibrosis by measuring these markers and performing biopsies. Third, to maintain an adequate sample size, we did not divide the sample by gender. Women's incidence rate of fatty liver is lower than men's, and alcohol's effect on fatty liver may differ by gender. If we could obtain an adequate sample size for each gender group, a gender difference might be observed. Fourth, because the PA frequency in our questionnaire only went as high as '>3×/week', it was difficult to gauge the total amount of PA at the upper end. Although a more detailed questionnaire would help with this problem, to omit recall bias inherent with self-reported assessments, an objective assessment, such as an accelerometer, is required. Fifth, we focused only on the levels of PA and alcohol consumption at the baseline; the study did not examine the possibility of changing the pattern of PA and alcohol consumption during a follow-up period. To be sure of the effect of PA on fatty liver in never-moderate and heavy drinkers, an intervention study is needed. Sixth, we cannot deny the influence of selection bias; the majority of participants were employees and their spouses in Tokyo, and they might have a higher social status than a rural population. Thus, we may not be able to generalise our findings. The lack of socioeconomic variables such as education and income was also a weakness of the study. Finally, the sample size for heavy drinkers might be inadequate. Although there was no significance, people engaging in >3×/week of vigorous-intensity PA were likely to have a lower incident risk of fatty liver, but we cannot determine if this trend reflects the effect of vigorous-intensity PA or just chance with our current data. A larger sample size of heavy alcohol drinkers is needed.

CONCLUSIONS

This study investigated whether PA reduces the future risk of incident fatty liver in people with never-moderate or heavy alcohol consumption. In never-moderate alcohol drinkers, PA independently reduced the future risk of fatty liver, and HRs decreased as the PA intensity and frequency increased. In contrast, the type or frequency of PA was not significantly associated with incident fatty liver in heavy alcohol drinkers.

PA is a novel tool for preventing NAFLD, along with its well-known effect on other obesity-related diseases. Our prospective cohort findings on fatty liver are currently limited, and more prospective studies are needed to build sound evidence.

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