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Article title

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

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Objective: To investigate if physical activity affects future incident fatty liver in people with never-moderate and heavy alcohol consumption.

Design: Prospective cohort study.

Setting: Health check-up program of 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 ≥3x/wk of low-intensity (HR=0.82, 95% CI=0.71 to 0.95) 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 <1x/wk. For vigorous-intensity physical activity, frequencies of both 2x/wk (HR=0.57, 95% CI=0.38 to 0.85) and ≥3x/wk (HR=0.55, 95% CI=0.38 to 0.79) were significantly associated with lower incident risk of fatty liver. In propensity-adjusted models, these significant associations still remained. By contrast, in heavy alcohol drinkers, there were no significant associations between type or frequency of physical activity and incident fatty liver.

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

Key words: exercise; NAFLD; AFLD; hepatic steatosis; obesity

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 hazard ratios 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-alcoholic fatty liver disease (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] 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 more 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 dyslipidemia.[12] Since both 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 both 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 future incident fatty liver diagnosed by ultrasound in two populations: those who are never-moderate alcohol drinkers and those who are 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 to 2007 survey data (n=25,056, aged 18 years or older) as our baseline data. Of these people, 2541 individuals were excluded due to 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 hemangioma, 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 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. This study was approved by the Ethical Committee of Meiji Yasuda Life Foundation of Health and Welfare.

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] The examination and diagnosis of fatty liver were conducted by skilled medical technologists and doctors. The mean diagnosis rate of fatty liver in our surveys from 2005 to 2013 was

23.1±1.0% (range, 22.2 to 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 whiskey, or 0.5 cup of *shochu*. We used a scoring method for frequency of alcohol consumption as follows: 0.5 for an occasional drink, 1.5 for 1–2 days per week, 3.5 for 3–4 days per week, 5.5 for daily with day off drinking, and 7.0 for daily without day off drinking. We set four alcohol categories by calculating average daily alcohol consumption: never, moderate (less than 23.0 g of alcohol per day), heavy (23.0 g to 45.9 g per day), and very heavy (46.0 g per 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 alcohol intake status at baseline, participants were divided into never to moderate alcohol drinkers (n=7803) and heavy alcohol drinkers (n=2343).[27]

Physical activity

A questionnaire assessed leisure-time PA in a typical week by frequency (never, <1x/wk, 1x/wk, 2x/wk, and ≥3x/wk), 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 to 5 metabolic equivalents (METs), moderate-intensity corresponded to 5 to 7 METs, and vigorous-intensity corresponded to 7 or more METs.[29 30]

Since 10 minutes is considered the minimum for a single event activity,[31] we determined a single session of PA to be ≥10 minutes. Each frequency (<1x/wk, 1x/wk, 2x/wk, and ≥3x/wk) of low-, moderate-, 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 two 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 dyslipidemia. A blood sample was drawn from each subject after an overnight fast. The serum triglycerides (TG), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma 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 subject rested at least 15 minutes in a sitting position.

Endpoint determination

In both 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 dyslipidemia. 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 ≥7.0 mmol/L, HbA1c ≥6.5%, there was a diagnosis history or drug usage for diabetes. Dyslipidemia was coded "yes" if LDL-C ≥4.1 mmol/L, HDL ≤1.0 mmol/L, TG ≥2.3 mmol/L, there was a diagnosis history or drug usage for dyslipidemia.

We performed all analyses on both the never-moderate and heavy alcohol drinking groups. To compare baseline characteristics by PA frequencies, we used chi-squared tests for categorical variables and analysis of variance for continuous variables. We used the Cox proportional-hazards analysis to determine prospective associations between 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), AST (continuous), GGT (continuous), hypertension (yes or no), diabetes (yes or no), dyslipidemia (yes or no), and meat and green/yellow vegetable intakes (never or seldom, once every two days, or one or more times per day). 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 ≥3x/wk.[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 <1x/wk and ≥3x/wk, but did not conduct the matching analysis.[32] The areas under the receiver operating curves of

propensity scores were 0.70 to 0.77, 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 version 21.0 (IBM, Inc., Armonk, NY).

Results

Description of the sample

The GGT of heavy alcohol drinkers (59.0±64.5 units/L) was remarkably higher than never-moderate alcohol drinkers (27.5±25.8 units/L). Table 1 shows the participants' baseline characteristics by PA frequency in never-moderate and heavy alcohol drinkers. In both groups, participants who engaged in low-intensity PA were less likely to engage in moderate- and vigorous-intensity PA; whereas, participants who engaged in moderate-intensity PA were more likely to engage in vigorous-intensity PA.

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 summarizes 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 0.95) or moderate-intensity PA (HR=0.56, 95% CI=0.39 to 0.81) ≥3x/wk significantly reduced their risks

of incident fatty liver, compared to those who engaged in PA <1x/wk. When participants engaged in vigorous-intensity PA ≥2/wk, they decreased their risk of fatty liver by about half (2x/wk: HR=0.57, 95% CI=0.38 to 0.85; ≥3x: HR=0.55, 95% CI=0.38 to 0.79). All hazard ratios in model 2, including covariates, are shown in Supplementary Table 1. The final propensity-adjusted Cox models (Supplementary Table 2), also confirmed the significant preventive effects of ≥3x/wk of lower-intensity (HR=0.82, 95% CI=0.70 to 0.95), moderate-intensity (HR=0.57, 95% CI=0.39 to 0.82), 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 type or frequency of PA and incident risk of 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 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]

Previous Chinese [33] and Korean [22] cohort studies using an 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 to 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 intensity and frequency increased. When participants engaged in

PA ≥3x/wk, their incident risks of fatty liver decreased significantly regardless of PA intensity. In particular, those who engaged in moderate-intensity PA ≥3x/wk, or vigorous-intensity PA ≥2x/wk had decreased hazard ratios. In a retrospective study,[22] engaging in PA ≥3x/wk 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 occurs with 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 utilization 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 at reducing liver fat and enzymes compared with diet alone. However, that meta-analysis could not incorporate exercise intensity because of the lack of data,[40] which may hide the independent benefit of exercise on NAFLD. Future intervention studies should consider exercise intensity in addition to 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. In heavy alcohol drinkers, increasing BMI, being a smoker, and having dyslipidemia were independent predictors for incident fatty liver (see Supplementary Table 1), which is similar to previous reports.[1 15 16 41] Heavy alcohol drinkers should be especially aware of their weight and smoking habits. Increasing BMI and dyslipidemia 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 both 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 hazard ratios according to PA frequencies and intensities which revealed the advantages of higher frequencies and intensities of PA. PA is a cost-effective and noninvasive 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 diagnose requires liver biopsy. In addition, using several ultrasonography machines during the study may limit the accuracy of diagnoses. However, we believe 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 (e.g. serum iron and ferritin) and fibrosis markers (e.g. 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.[42] Future research on the PA effect on fatty liver should consider inflammation and fibrosis by measuring these markers and performing biopsies.

Third, because PA frequency in our questionnaire only went as high as "≥3x/wk," it was difficult to gauge the total amount of PA at the upper end. Although a more detailed questionnaire would help, to omit recall bias inherent with self-reported assessments, an objective assessment, such as an accelerometer is required. Fourth, 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 generalize our findings. The lack of socioeconomic variables such as education and income was also weakness of the study. Finally, the sample size for heavy drinkers might be inadequate. Although there was no significance, people engaging in ≥3x/wk 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 future risk of incident fatty liver in people with never-moderate or heavy alcohol consumption. In never-moderate alcohol drinkers, PA independently reduced future risk of fatty liver, and hazard ratios decreased as 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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Contributions: KT and YK conceived and designed the study, analyzed and interpreted the data, and drafted the manuscript. KU and TK acquired and interpreted the data and critically revised the manuscript. TN interpreted the data, critically revised the manuscript, and supervised and coordinated the study. All authors read and approved the final manuscript.

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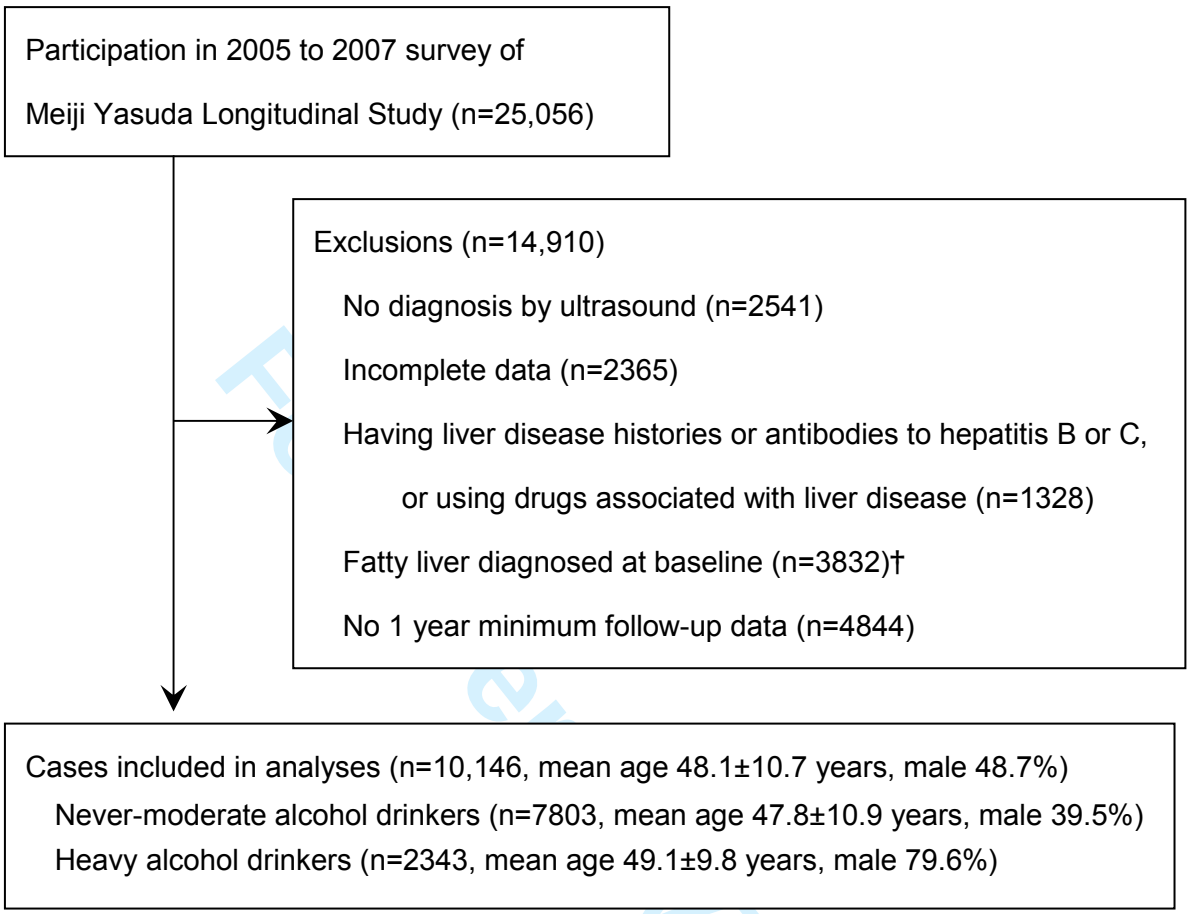

Figure 1. Flow of eligible participants in this study

†At this stage, 3832 of 18,822 examinees (20.4%) were diagnosed with fatty liver. When looking at examinees' levels of alcohol consumption, 2827 of 14,490 never-moderate alcohol drinkers (19.5%) and 1005 of 4332 heavy alcohol drinkers (23.2%) were diagnosed with fatty liver at baseline.

Table 1-a. Baseline characteristics of participants by frequency of *low-intensity* physical activity

	Never-moderate alcohol drinkers (n=7803)					Heavy alcohol drinkers (n=2343)				
	Low-intensity physical activity (times/week)					Low-intensity physical activity (times/week)				
Baseline variables	<1x	1x	2x	≥3x	*P* value	<1x	1x	2x	≥3x	*P* value
Number	4900	728	516	1659		1544	230	142	417	
Mean (SD) age (years)	46.1 (10.3)	47.8 (10.8)	50.9 (10.8)	51.7 (11.5)	< 0.001	47.6 (9.3)	50.2 (9.4)	51.0 (9.4)	53.3 (10.5)	< 0.001
Male Gender	41.0	37.8	39.3	35.7	0.002	79.3	83.5	83.1	77.2	0.191
Mean (SD) BMI (kg/m^2)	21.6 (2.6)	21.5 (2.5)	21.6 (2.5)	21.6 (2.6)	0.761	22.5 (2.5)	22.7 (2.5)	22.8 (2.4)	22.5 (2.4)	0.482
Daily alcohol consumption										
Never	17.4	18.4	18.0	20.4	0.056	–	–	–	–	
Low-moderate (<23.0 g)	82.6	81.6	82.0	79.6		–	–	–	–	
Heavy (23.0–45.9 g)	–	–	–	–		74.5	82.2	73.2	77.7	0.050
Very heavy (≥46.0 g)	–	–	–	–		25.5	17.8	26.8	22.3	
Smoking status					< 0.001					< 0.001
Never	58.7	62.1	61.2	65.6		24.4	21.3	25.4	25.9	
Former	18.3	23.4	23.3	22.9		31.5	41.7	43.7	42.4	
Current	23.0	14.6	15.5	11.5		44.1	37.0	31.0	31.7	
Family history of hepatic disease	5.8	5.5	6.2	6.2	0.870	6.1	4.3	9.9	6.2	0.199
Mean (SD) ALT (units/L)	19.4 (9.0)	19.2 (9.3)	19.7 (8.4)	19.2 (8.4)	0.737	22.7 (12.5)	21.6 (9.2)	23.5 (10.0)	21.8 (11.0)	0.264
Mean (SD) AST (units/L)	20.0 (7.3)	20.0 (6.7)	21.3 (6.7)	20.4 (6.0)	< 0.001	23.0 (9.3)	22.8 (7.0)	23.6 (8.2)	22.9 (8.1)	0.819
Mean (SD) GGT (units/L)	27.5 (24.2)	28.0 (37.2)	29.5 (29.9)	26.7 (22.9)	0.172	60.8 (71.2)	54.9 (40.3)	63.1 (59.3)	52.8 (48.6)	0.084
Hypertension†	8.4	7.1	15.3	14.9	< 0.001	16.5	19.6	27.5	27.8	< 0.001
Diabetes‡	2.3	3.3	5.4	5.5	< 0.001	4.2	6.5	9.2	9.4	< 0.001
Dyslipidemia¶	19.1	21.7	26.0	24.8	< 0.001	19.9	23.9	23.9	26.1	0.030
Meat intake					< 0.001					0.105
Never or seldom	38.7	39.7	46.7	45.6		40.3	37.4	45.8	47.0	
Once per 2 days	32.9	32.7	32.8	29.2		31.7	33.5	32.4	29.7	
Once a day or more	28.4	27.6	20.5	25.3		28.1	29.1	21.8	23.3	
Vegetable intake					< 0.001					< 0.001
Never or seldom	23.6	14.1	15.9	11.5		30.7	23.0	23.9	17.0	
Once per 2 days	22.9	20.2	17.2	13.7		25.4	24.3	22.5	18.2	
Once a day or more	53.5	65.7	66.9	74.8		43.9	52.6	53.5	64.7	
Moderate-intensity PA					< 0.001					0.088
<1x/wk	84.1	88.7	88.2	89.0		84.1	88.3	86.6	88.5	
1x/wk	6.6	6.0	5.4	4.9		6.7	7.0	7.7	5.5	
2x/wk	4.5	3.4	3.9	3.3		4.8	3.5	4.9	2.9	
≥3x/wk	4.8	1.8	2.5	2.9		4.4	1.3	0.7	3.1	
Vigorous-intensity PA					< 0.001					< 0.001
<1x/wk	87.7	90.0	89.1	91.7		86.0	87.4	91.5	93.0	
1x/wk	4.1	4.8	4.7	4.0		5.1	7.4	1.4	4.1	
2x/wk	3.7	2.7	3.1	2.2		3.9	2.6	4.2	1.2	
≥3x/wk	4.4	2.5	3.1	2.0		5.1	2.6	2.8	1.7	

Values are percentages unless stated otherwise.

ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, GGT: gamma glutamyltransferase, PA: physical activity.

†Systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, diagnosis history or drug usage for hypertension.

‡Fasting plasma glucose ≥7.0 mmol/L, HbA1c ≥6.5%, diagnosis history or drug usage for diabetes.

¶Low-density lipoprotein-cholesterol ≥4.1 mmol/L, high-density lipoprotein-cholesterol ≤1.0 mmol/L, serum triglycerides ≥2.3 mmol/L, diagnosis history or drug usage for dyslipidemia.

Table 1-b. Baseline characteristics of participants by frequency of *moderate-intensity* physical activity

	Never-moderate alcohol drinkers (n=7803)					Heavy alcohol drinkers (n=2343)				
	Moderate-intensity physical activity (times/week)					Moderate-intensity physical activity (times/week)				
Baseline variables	<1x	1x	2x	≥3x	*P* value	<1x	1x	2x	≥3x	*P* value
Number	6699	478	318	308		2002	154	101	86	
Mean (SD) age (years)	47.4 (10.8)	48.3 (11.0)	50.1 (10.9)	52.5 (11.7)	< 0.001	48.7 (9.8)	49.1 (8.8)	52.1 (9.1)	53.9 (10.6)	< 0.001
Male Gender	39.7	36.0	40.6	39.3	0.437	78.9	83.8	82.2	83.7	0.318
Mean (SD) BMI (kg/m^2)	21.6 (2.6)	21.5 (2.4)	21.8 (2.5)	21.7 (2.4)	0.436	22.5 (2.5)	22.8 (2.3)	22.7 (2.1)	22.6 (2.3)	0.425
Daily alcohol consumption										
Never	18.4	13.0	17.9	21.4	0.011	–	–	–	–	
Low-moderate (<23.0 g)	81.6	87.0	82.1	78.6		–	–	–	–	
Heavy (23.0–45.9 g)	–	–	–	–		76.2	72.1	71.3	77.9	0.451
Very heavy (≥46.0 g)	–	–	–	–		23.8	27.9	28.7	22.1	
Smoking status					< 0.001					< 0.001
Never	59.7	68.8	65.1	64.3		24.1	22.7	26.7	31.4	
Former	19.7	22.0	22.6	23.1		33.4	40.3	47.5	52.3	
Current	20.6	9.2	12.3	12.7		42.5	37.0	25.7	16.3	
Family history of hepatic disease	5.7	8.4	5.7	6.2	0.118	6.1	5.2	6.9	8.1	0.819
Mean (SD) ALT (units/L)	19.4 (9.1)	18.8 (8.0)	19.3 (7.0)	18.4 (7.3)	0.117	22.3 (11.7)	23.9 (12.6)	22.8 (13.0)	22.7 (12.0)	0.419
Mean (SD) AST (units/L)	20.1 (7.1)	19.9 (6.5)	20.8 (5.2)	20.8 (7.7)	0.105	22.8 (8.7)	24.0 (9.0)	24.1 (11.9)	22.9 (7.8)	0.221
Mean (SD) GGT (units/L)	27.7 (26.8)	25.0 (17.3)	26.9 (19.7)	26.3 (18.9)	0.109	59.0 (64.4)	59.0 (64.9)	56.0 (56.0)	60.7 (75.4)	0.963
Hypertension†	9.9	9.8	10.4	14.6	0.068	18.8	20.1	24.8	29.1	0.058
Diabetes‡	3.2	2.5	2.5	7.5	< 0.001	5.5	6.5	5.9	5.8	0.966
Dyslipidemia¶	21.1	20.3	21.1	20.8	0.982	21.8	24.7	15.8	18.6	0.341
Meat intake					0.732					0.686
Never or seldom	41.0	38.9	37.1	41.9		41.4	38.3	43.6	48.8	
Once per 2 days	31.9	34.3	33.0	30.8		31.6	35.7	27.7	26.7	
Once a day or more	27.0	26.8	29.9	27.3		27.0	26.0	28.7	24.4	
Vegetable intake					< 0.001					0.231
Never or seldom	20.4	14.4	15.4	14.6		28.0	20.1	25.7	19.8	
Once per 2 days	20.5	22.0	14.8	20.1		23.8	24.0	24.8	23.3	
Once a day or more	59.1	63.6	69.8	65.3		48.2	55.8	49.5	57.0	
Low-intensity PA					< 0.001					0.088
<1x/wk	61.5	68.0	68.9	76.0		65.3	67.5	73.3	80.2	
1x/wk	9.6	9.2	7.9	4.2		10.1	10.4	7.9	3.5	
2x/wk	6.8	5.9	6.3	4.2		6.1	7.1	6.9	1.2	
≥3x/wk	22.0	16.9	17.0	15.6		18.4	14.9	11.9	15.1	
Vigorous-intensity PA					< 0.001					< 0.001
<1x/wk	89.7	83.7	84.0	83.8		88.2	81.8	90.1	84.9	
1x/wk	3.8	9.6	4.1	4.2		4.4	12.3	4.0	3.5	
2x/wk	3.1	4.2	5.3	3.6		3.2	4.5	4.0	1.2	
≥3x/wk	3.4	2.5	6.6	8.4		4.1	1.3	2.0	10.5	

Values are percentages unless stated otherwise.

ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, GGT: gamma glutamyltransferase, PA: physical activity.

†Systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, diagnosis history or drug usage for hypertension.

‡Fasting plasma glucose ≥7.0 mmol/L, HbA1c ≥6.5%, diagnosis history or drug usage for diabetes.

¶Low-density lipoprotein-cholesterol ≥4.1 mmol/L, high-density lipoprotein-cholesterol ≤1.0 mmol/L, serum triglycerides ≥2.3 mmol/L, diagnosis history or drug usage for dyslipidemia.

Table 1-c. Baseline characteristics of participants by frequency of *vigorous-intensity* physical activity

	Never-moderate alcohol drinkers (n=7803)					Heavy alcohol drinkers (n=2343)				
	Vigorous-intensity physical activity (times/week)					Vigorous-intensity physical activity (times/week)				
Baseline variables	<1x	1x	2x	≥3x	*P* value	<1x	1x	2x	≥3x	*P* value
Number	6935	328	254	286		2055	115	77	96	
Mean (SD) age (years)	47.7 (10.9)	46.4 (10.3)	48.8 (11.3)	49.4 (11.0)	0.004	49.2 (9.8)	47.4 (9.8)	48.0 (10.1)	50.0 (10.6)	0.159
Male Gender	39.3	40.9	38.6	43.4	0.520	79.4	79.1	79.2	83.3	0.829
Mean (SD) BMI (kg/m^2)	21.6 (2.6)	21.8 (2.4)	21.6 (2.2)	21.8 (2.6)	0.215	22.5 (2.5)	22.9 (2.4)	22.6 (2.3)	22.9 (2.0)	0.142
Daily alcohol consumption										
Never	18.4	11.9	18.1	18.5	0.029	–	–	–	–	
Low-moderate (<23.0 g)	81.6	88.1	81.9	81.5		–	–	–	–	
Heavy (23.0–45.9 g)	–	–	–	–		76.6	70.4	64.9	71.9	0.039
Very heavy (≥46.0 g)	–	–	–	–		23.4	29.6	35.1	28.1	
Smoking status					< 0.001					< 0.001
Never	60.4	63.4	62.6	60.1		23.9	26.1	22.1	34.4	
Former	19.5	25.6	20.9	26.2		33.6	41.7	50.6	47.9	
Current	20.0	11.0	16.5	13.6		42.4	32.2	27.3	17.7	
Family history of hepatic disease	6.0	2.4	7.9	5.6	0.029	5.9	7.8	10.4	7.3	0.335
Mean (SD) ALT (units/L)	19.3 (9.0)	19.0 (8.0)	19.6 (8.1)	20.4 (7.7)	0.175	22.5 (11.7)	22.0 (9.1)	22.5 (8.8)	22.3 (17.9)	0.981
Mean (SD) AST (units/L)	20.0 (7.0)	20.3 (7.1)	21.0 (6.8)	22.6 (7.1)	< 0.001	22.9 (8.9)	23.4 (7.9)	23.4 (6.8)	23.9 (9.8)	0.589
Mean (SD) GGT (units/L)	27.5 (26.0)	26.9 (20.2)	28.3 (24.3)	28.0 (27.2)	0.912	59.8 (66.3)	53.9 (55.4)	55.9 (48.1)	49.2 (44.8)	0.330
Hypertension†	10.2	6.7	13.8	8.4	0.030	20.6	10.4	10.4	14.6	0.004
Diabetes‡	3.4	2.1	2.8	4.2	0.492	5.6	4.3	5.2	8.3	0.635
Dyslipidemia¶	21.3	18.0	19.7	19.6	0.444	22.2	18.3	26.0	10.4	0.028
Meat intake					0.070					< 0.001
Never or seldom	40.8	36.3	38.6	47.9		42.5	25.2	42.9	38.5	
Once per 2 days	32.0	32.9	34.3	31.1		31.8	28.7	29.9	31.3	
Once a day or more	27.2	30.8	27.2	21.0		25.7	46.1	27.3	30.2	
Vegetable intake					< 0.001					< 0.001
Never or seldom	20.2	18.0	13.0	14.0		28.6	14.8	22.1	13.5	
Once per 2 days	20.5	20.7	22.0	15.4		24.2	23.5	18.2	20.8	
Once a day or more	59.4	61.3	65.0	70.6		47.2	61.7	59.7	65.6	
Low-intensity PA					< 0.001					< 0.001
<1x/wk	62.0	61.6	71.3	76.2		65.0	68.7	77.9	82.3	
1x/wk	9.4	10.7	7.9	6.3		9.8	14.8	7.8	6.3	
2x/wk	6.6	7.3	6.3	5.6		6.3	1.7	7.8	4.2	
≥3x/wk	21.9	20.4	14.6	11.9		18.9	14.8	6.5	7.3	
Moderate-intensity PA					< 0.001					< 0.001
<1x/wk	86.7	78.0	81.1	79.4		85.9	77.4	84.4	86.5	
1x/wk	5.8	14.0	7.9	4.2		6.1	16.5	9.1	2.1	
2x/wk	3.9	4.0	6.7	7.3		4.4	3.5	5.2	2.1	
≥3x/wk	3.7	4.0	4.3	9.1		3.6	2.6	1.3	9.4	

Values are percentages unless stated otherwise.

ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, GGT: gamma glutamyltransferase, PA: physical activity.

†Systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, diagnosis history or drug usage for hypertension.

‡Fasting plasma glucose ≥7.0 mmol/L, HbA1c ≥6.5%, diagnosis history or drug usage for diabetes.

¶Low-density lipoprotein-cholesterol ≥4.1 mmol/L, high-density lipoprotein-cholesterol ≤1.0 mmol/L, serum triglycerides ≥2.3 mmol/L, diagnosis history or drug usage for dyslipidemia.

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

	Frequency of engaging in physical activity (times/week)			
		Hazard ratio (95% CI)		
	<1x	1x	2x	≥3x
Low-intensity physical activity				
No. of person-years	21679	3278	2269	7422
No. 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 – 1.09)	1.05 (0.84 – 1.31)	0.93 (0.81 – 1.07)
Adjusted for age and gender	1.00	0.87 (0.71 – 1.07)	0.98 (0.78 – 1.22)	**0.86 (0.74 – 0.99)**
Model 1†	1.00	0.95 (0.78 – 1.16)	1.00 (0.80 – 1.25)	0.87 (0.75 – 1.00)
Model 2‡	1.00	0.91 (0.74 – 1.12)	0.96 (0.77 – 1.20)	**0.82 (0.71 – 0.95)**
Moderate-intensity physical activity				
No. of person-years	29579	2200	1441	1428
No. 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 – 1.04)	0.76 (0.55 – 1.03)	**0.56 (0.39 – 0.81)**
Adjusted for age and gender	1.00	0.81 (0.63 – 1.03)	**0.71 (0.52 – 0.97)**	**0.52 (0.36 – 0.75)**
Model 1†	1.00	0.88 (0.69 – 1.13)	**0.73 (0.53 – 1.00)**	**0.56 (0.39 – 0.81)**
Model 2‡	1.00	0.87 (0.68 – 1.12)	0.73 (0.54 – 1.00)	**0.56 (0.39 – 0.81)**
Vigorous-intensity physical activity				
No. of person-years	30641	1484	1181	1342
No. 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 – 1.15)	**0.54 (0.36 – 0.82)**	**0.60 (0.42 – 0.86)**
Adjusted for age and gender	1.00	0.84 (0.63 – 1.12)	**0.54 (0.36 – 0.82)**	**0.55 (0.38 – 0.79)**
Model 1†	1.00	0.86 (0.64 – 1.15)	**0.58 (0.39 – 0.87)**	**0.55 (0.38 – 0.79)**
Model 2‡	1.00	0.85 (0.64 – 1.14)	**0.57 (0.38 – 0.85)**	**0.55 (0.38 – 0.79)**

Bold 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, gamma glutamyltransferase, hypertension, diabetes, dyslipidemia, and meat and vegetable intakes.

‡ Additional adjustment of model 1 for other intensity types of physical activity.

The hazard ratios of all covariates in model 2 are presented in Supplementary Table 1.

Table 3. Hazard ratios of incident fatty liver by frequency of physical activity in heavy alcohol drinkers

	Frequency of engaging in physical activity (times/week)							
		Hazard ratio (95% CI)						
	<1x	1x		2x		≥3x		
Low-intensity physical activity								
No. of person-years	6412	901		597		1686		
No. 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 – 1.33)	1.07	(0.75 – 1.53)	1.14	(0.91 – 1.42)	
Adjusted for age and gender	1.00	0.93	(0.69 – 1.27)	1.03	(0.72 – 1.47)	1.09	(0.87 – 1.37)	
Model 1†	1.00	0.97	(0.71 – 1.32)	0.97	(0.68 – 1.39)	1.18	(0.93 – 1.49)	
Model 2‡	1.00	0.98	(0.72 – 1.34)	0.96	(0.67 – 1.38)	1.18	(0.93 – 1.50)	
Moderate-intensity physical activity								
No. of person-years	8149	666		457		324		
No. 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 – 1.21)	1.09	(0.74 – 1.61)	1.17	(0.75 – 1.81)	
Adjusted for age and gender	1.00	0.81	(0.56 – 1.17)	1.02	(0.69 – 1.50)	1.05	(0.68 – 1.64)	
Model 1†	1.00	0.82	(0.56 – 1.18)	1.15	(0.78 – 1.71)	1.06	(0.68 – 1.66)	
Model 2‡	1.00	0.81	(0.56 – 1.18)	1.16	(0.78 – 1.72)	1.13	(0.72 – 1.77)	
Vigorous-intensity physical activity								
No. of person-years	8377	488		312		419		
No. 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 – 1.38)	1.20	(0.78 – 1.86)	0.82	(0.52 – 1.31)	
Adjusted for age and gender	1.00	0.92	(0.61 – 1.39)	1.25	(0.81 – 1.94)	0.79	(0.50 – 1.25)	
Model 1†	1.00	0.85	(0.55 – 1.29)	1.26	(0.81 – 1.97)	0.75	(0.47 – 1.21)	
Model 2‡	1.00	0.87	(0.56 – 1.33)	1.32	(0.85 – 2.07)	0.77	(0.47 – 1.24)	

Bold 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, aspartate aminotransferase, gamma glutamyltransferase, hypertension, diabetes, dyslipidemia, and meat and vegetable intakes.

‡ Additional adjustment of model 1 for other intensity types of physical activity.

The hazard ratios of all covariates in model 2 are presented in Supplementary Table 1.

Supplementary Table 1. Hazard ratios of incident fatty liver according physical activity and other variables in never-moderate and heavy alcohol drinkers

	Never-moderate alcohol drinkers (n=7803)		Heavy alcohol drinkers (n=2343)	
	HR	95% CI	HR	95% CI
Age (years)	**1.015**	**(1.009 – 1.021)**	1.009	(0.997 – 1.020)
Gender				
Male	1.000		1.000	
Female	**0.580**	**(0.507 – 0.662)**	**0.598**	**(0.436 – 0.821)**
Body mass index (kg/m^2)	**1.360**	**(1.334 – 1.386)**	**1.306**	**(1.260 – 1.354)**
Daily alcohol consumption				
Never	1.000		–	
Low-moderate (<23.0 g)	**0.852**	**(0.736 – 0.987)**	–	
Heavy (23.0–45.9 g)	–		1.000	
Very heavy (≥46.0 g)	–		0.890	(0.722 – 1.099)
Smoking status				
Never	1.000		1.000	
Former	0.931	(0.802 – 1.081)	1.116	(0.866 – 1.439)
Current	**1.173**	**(1.012 – 1.361)**	**1.382**	**(1.081 – 1.768)**
Family history of liver disease				
No	1.000		1.000	
Yes	1.151	(0.915 – 1.447)	1.176	(0.828 – 1.671)
ALT (units/L)	**1.011**	**(1.003 – 1.018)**	1.008	(1.000 – 1.016)
AST (units/L)	1.000	(0.990 – 1.009)	1.004	(0.991 – 1.017)
GGT (units/L)	1.001	(1.000 – 1.003)	**1.001**	**(1.000 – 1.002)**
Hypertension				
No	1.000		1.000	
Yes	1.087	(0.927 – 1.274)	0.992	(0.794 – 1.238)
Diabetes				
No	1.000		1.000	
Yes	1.243	(0.975 – 1.585)	1.098	(0.793 – 1.520)
Dyslipidemia				
No	1.000		1.000	
Yes	**1.251**	**(1.108 – 1.413)**	**1.299**	**(1.072 – 1.575)**
Meat intake				
Never or seldom	1.000		1.000	
Once per 2 days	**0.852**	**(0.743 – 0.977)**	0.958	(0.773 – 1.187)
Once a day or more	0.959	(0.828 – 1.110)	0.842	(0.663 – 1.070)
Vegetable intake				
Never or seldom	1.000		1.000	
Once per 2 days	0.929	(0.786 – 1.097)	0.955	(0.745 – 1.225)
Once a day or more	**0.829**	**(0.717 – 0.959)**	1.042	(0.832 – 1.304)
Low-intensity physical activity				
<1x/wk	1.000		1.000	
1x/wk	0.911	(0.743 – 1.117)	0.979	(0.717 – 1.337)
2x/wk	0.963	(0.770 – 1.205)	0.960	(0.669 – 1.379)
≥3x/wk	**0.821**	**(0.707 – 0.954)**	1.181	(0.929 – 1.502)
Moderate-intensity physical activity				
<1x/wk	1.000		1.000	
1x/wk	0.872	(0.680 – 1.119)	0.815	(0.561 – 1.184)
2x/wk	0.733	(0.536 – 1.002)	1.159	(0.780 – 1.723)
≥3x/wk	**0.559**	**(0.388 – 0.806)**	1.126	(0.715 – 1.774)
Vigorous-intensity physical activity				
<1x/wk	1.000		1.000	
1x/wk	0.852	(0.636 – 1.140)	0.866	(0.565 – 1.329)
2x/wk	**0.569**	**(0.379 – 0.854)**	1.322	(0.846 – 2.066)
≥3x/wk	**0.547**	**(0.380 – 0.789)**	0.766	(0.474 – 1.238)

Bold numbers indicate $P<0.05$.

ALT: alanine aminotransferase, AST: aspartate aminotransferase, GGT: gamma glutamyltransferase.

All variables were entered simultaneously for both never-moderate and heavy alcohol drinkers.

Supplementary Table 2. Propensity-adjusted hazard ratios of incident fatty liver according to physical activity in never-moderate and heavy alcohol drinkers

	Never-moderate alcohol drinkers		Heavy alcohol drinkers	
	Hazard ratio (95% CI)		Hazard ratio (95% CI)	
	<1x/wk vs. ≥3x/wk		<1x/wk vs. ≥3x/wk	
Low-intensity physical activity				
Adjusted for propensity	0.89	(0.77 – 1.03)	1.11	(0.88 – 1.41)
Adjusted for propensity and selected covariates†	**0.82**	**(0.71 – 0.96)**	1.14	(0.89 – 1.46)
Adjusted for propensity and all covariates	**0.82**	**(0.70 – 0.95)**	1.15	(0.90 – 1.47)
Moderate-intensity physical activity				
Adjusted for propensity	**0.55**	**(0.38 – 0.80)**	1.16	(0.74 – 1.82)
Adjusted for propensity and selected covariates†	**0.56**	**(0.39 – 0.81)**	1.09	(0.69 – 1.72)
Adjusted for propensity and all covariates	**0.57**	**(0.39 – 0.82)**	1.07	(0.67 – 1.69)
Vigorous-intensity physical activity				
Adjusted for propensity	**0.58**	**(0.40 – 0.83)**	0.83	(0.51 – 1.33)
Adjusted for propensity and selected covariates†	**0.56**	**(0.39 – 0.80)**	0.80	(0.49 – 1.29)
Adjusted for propensity and all covariates	**0.55**	**(0.38 – 0.79)**	0.74	(0.45 – 1.22)

Bold numbers indicate $P<0.05$.

†Adjusted for significant predictors on incident fatty liver (see Supplementary Table 1).

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Reported on manuscript page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1–2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N.A.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5–8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5–8
Bias	9	Describe any efforts to address potential sources of bias	N.A.
Study size	10	Explain how the study size was arrived at	N.A.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6–8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8–9
		(*b*) Describe any methods used to examine subgroups and interactions	N.A.
		(*c*) Explain how missing data were addressed	5, Figure 1
		(*d*) If applicable, explain how loss to follow-up was addressed	5, Figure 1
		(*e*) Describe any sensitivity analyses	8–9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5, Figure 1
		(b) Give reasons for non-participation at each stage	5, Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9, Table 1a–c
		(b) Indicate number of participants with missing data for each variable of interest	N.A.
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9, Table 2–3
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9–10, Table 2–3

		(*b*) Report category boundaries when continuous variables were categorized	6–8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N.A.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8–10, Supplementary Table 2
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12–13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10–13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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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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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 if physical activity affects future incident fatty liver in people with never-moderate and heavy alcohol consumption.

Design: Prospective cohort study.

Setting: Health check-up program of 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 >3x/wk of low-intensity (HR=0.82, 95% CI=0.71 to 0.95) 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 <1x/wk. For vigorous-intensity physical activity, frequencies of both 2x/wk (HR=0.57, 95% CI=0.38 to 0.85) and >3x/wk (HR=0.55, 95% CI=0.38 to 0.79) were significantly associated with lower incident risk of fatty liver. In propensity-adjusted models, these significant associations still remained. By contrast, in heavy alcohol drinkers, there were no significant associations between type or frequency of physical activity and incident fatty liver.

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

Key words: exercise; NAFLD; AFLD; hepatic steatosis; obesity

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 hazard ratios 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-alcoholic fatty liver disease (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] 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 more 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 dyslipidemia.[12] Since both 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 both 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 future incident fatty liver diagnosed by ultrasound in two populations: those who are never-moderate alcohol drinkers and those who are 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 to 2007 survey data (n=25,056, aged 18 years or older) as our baseline data. Of these people, 2541 individuals were excluded due to 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 hemangioma, 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 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. This study was approved by the Ethical Committee of Meiji Yasuda Life Foundation of Health and Welfare.

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 to 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±1.0% (range, 22.2 to 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 whiskey, or 0.5 cup of *shochu*. We used a scoring method for frequency of alcohol consumption as follows: 0.5 for an occasional drink, 1.5 for 1–2 days per week, 3.5 for 3–4 days per week, 5.5 for daily with day off drinking, and 7.0 for daily without day off drinking. We set four alcohol categories by calculating average daily alcohol consumption: never, moderate (less than 23.0 g of alcohol per day), heavy (23.0 g to 45.9 g per day), and very heavy (46.0 g per 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 alcohol intake status at baseline, participants were divided into never to moderate alcohol drinkers (n=7803) and heavy alcohol drinkers (n=2343).[27]

Physical activity

A questionnaire assessed leisure-time PA in a typical week by frequency (never, <1x/wk, 1x/wk, 2x/wk, and >3x/wk), 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 to 5 metabolic equivalents (METs), moderate-intensity corresponded to 5 to 7 METs, and vigorous-intensity corresponded to 7 or more METs.[29 30]

Since 10 minutes is considered the minimum for a single event activity,[31] we determined a single session of PA to be >10 minutes. Each frequency (<1x/wk, 1x/wk, 2x/wk, and >3x/wk) of low-, moderate-, 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 two 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 dyslipidemia. A blood sample was drawn from each subject after an overnight fast. The serum triglycerides (TG), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma 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 subject rested at least 15 minutes in a sitting

position.

Exposure and outcome

The study's exposure is PA level at baseline and outcome is future incident fatty liver. In both 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 dyslipidemia. 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 ≥7.0 mmol/L, HbA1c ≥6.5%, there was a diagnosis history or drug usage for diabetes. Dyslipidemia was coded "yes" if LDL-C ≥4.1 mmol/L, HDL ≤1.0 mmol/L, TG ≥2.3 mmol/L, there was a diagnosis history or drug usage for dyslipidemia.

We performed all analyses on both the never-moderate and heavy alcohol drinking groups. To compare baseline characteristics by PA frequencies, we used chi-squared tests for categorical variables and analysis of variance for continuous variables. We used the Cox proportional-hazards analysis to determine prospective associations between 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), AST (continuous), GGT (continuous), hypertension (yes or no), diabetes (yes or no), dyslipidemia (yes or no), and meat and green/yellow vegetable intakes (never or seldom, once every two days, or one or more times per day). 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 >3x/wk.[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 <1x/wk and >3x/wk, but did not conduct the matching analysis.[32] The areas under the receiver operating curves of propensity scores were 0.70 to 0.77, 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 version 21.0 (IBM, Inc., Armonk, NY).

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 males representing 39.5% of this group. The heavy drinkers' mean age was 49.1±9.8 years with 79.6% male. In both groups, almost half the people did not engage in any PA. Baseline characteristics for all three intensities of PA are presented in Supplementary Tables 1a–c.

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 summarizes 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 0.95) or moderate-intensity PA (HR=0.56, 95% CI=0.39 to 0.81) >3x/wk significantly reduced their risks of incident fatty liver, compared to those who engaged in PA <1x/wk. When participants engaged in vigorous-intensity PA >2/wk, they decreased their risk of fatty liver by about half (2x/wk: HR=0.57, 95% CI=0.38 to 0.85; >3x: HR=0.55, 95% CI=0.38 to 0.79). All hazard ratios in model 2, including covariates, are shown in Supplementary Table 2. The final propensity-adjusted Cox models (Supplementary Table 3), also confirmed the significant preventive effects of >3x/wk of lower-intensity (HR=0.82, 95% CI=0.70 to 0.95), moderate-intensity (HR=0.57, 95% CI=0.39 to 0.82), 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 type or frequency of PA and incident risk of 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 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]

Previous Chinese [33] and Korean [22] cohort studies using an 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 to 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 intensity and frequency increased. When participants engaged in PA >3x/wk, their incident risks of fatty liver decreased significantly regardless of PA intensity. In particular, those who engaged in moderate-intensity PA >3x/wk, or vigorous-intensity PA >2x/wk had decreased hazard ratios. In a retrospective study,[22] engaging in PA >3x/wk 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 occurs with 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 utilization 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 at reducing liver fat and enzymes compared with diet alone. However, that meta-analysis could not incorporate exercise intensity because of the lack of data,[40] which may hide the independent benefit of exercise on NAFLD. Future intervention studies should consider exercise intensity in addition to 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 both 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 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 dyslipidemia were independent predictors for incident fatty liver (Supplementary Table 2), 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 dyslipidemia 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 both 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 hazard ratios according to PA frequencies and intensities which revealed the advantages of higher frequencies and intensities of PA. PA is a cost-effective and noninvasive 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 diagnose

requires liver biopsy. In addition, using several ultrasonography machines during the study may limit the accuracy of diagnoses. However, we believe 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 (e.g. serum iron and ferritin) and fibrosis markers (e.g. 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 incident 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 PA frequency in our questionnaire only went as high as ">3x/wk", 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 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 generalize 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 >3x/wk 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 future risk of incident fatty liver in people with never-moderate or heavy alcohol consumption. In never-moderate alcohol drinkers, PA independently reduced future risk of fatty liver, and hazard ratios decreased as 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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Contributions: KT and YK conceived and designed the study, analyzed and interpreted the data, and drafted the manuscript. KU and TK acquired and interpreted the data and critically revised the manuscript. TN interpreted the data, critically revised the manuscript, and supervised and coordinated the study. All authors read and approved the final manuscript.

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Table 1. Baseline characteristics of participants by frequency of physical activity

Baseline variables	Never–moderate alcohol drinkers (n=7803, mean age=47.8±10.9 years, male=39.5%) Physical activity (times/week) <1x		1x		2x		≥3x		*P* value	Heavy alcohol drinkers (n=2343, mean age=49.1±9.8 years, male=79.6%) Physical activity (times/week) <1x		1x		2x		≥3x		*P* value
No. 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)	19.4	(9.3)	19.4	(9.3)	19.4	(8.0)	19.3	(8.1)	0.948	22.6	(12.3)	22.7	(10.9)	22.4	(9.3)	22.1	(12.4)	0.816
Mean (SD) AST (Units/l)	19.7	(7.5)	20.0	(6.9)	20.6	(6.0)	20.7	(6.5)	< 0.001	22.6	(9.3)	23.6	(8.1)	23.3	(9.0)	23.1	(8.3)	0.306
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
Dyslipidemia¶	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.
ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, GGT: gamma glutamyltransferase, PA: physical activity.
†Systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, diagnosis history or drug usage for hypertension.
‡Fasting plasma glucose ≥7.0 mmol/L, HbA1c ≥6.5%, diagnosis history or drug usage for diabetes.

¶Low-density lipoprotein-cholesterol ≥4.1 mmol/L, high-density lipoprotein-cholesterol ≤1.0 mmol/L, serum triglycerides ≥2.3 mmol/L, diagnosis history or drug usage for dyslipidemia.

Baseline characteristics for all three intensities of physical activity are presented in Supplementary Tables 1a-c.

Table 2. Hazard ratios of incident fatty liver by frequency of physical activity in never–moderate alcohol drinkers

	Frequency of engaging in physical activity (times/week)			
		Hazard ratio (95% CI)		
	<1x	1x	2x	≥3x
Low-intensity physical activity				
No. of participants	4900	728	516	1659
No. of person-years	21679	3278	2269	7422
No. 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 – 1.09)	1.05 (0.84 – 1.31)	0.93 (0.81 – 1.07)
Adjusted for age and gender	1.00	0.87 (0.71 – 1.07)	0.98 (0.78 – 1.22)	**0.86 (0.74 – 0.99)**
Model 1†	1.00	0.95 (0.78 – 1.16)	1.00 (0.80 – 1.25)	0.87 (0.75 – 1.00)
Model 2‡	1.00	0.91 (0.74 – 1.12)	0.96 (0.77 – 1.20)	**0.82 (0.71 – 0.95)**
Moderate-intensity physical activity				
No. of participants	6699	478	318	308
No. of person-years	29579	2200	1441	1428
No. 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 – 1.04)	0.76 (0.55 – 1.03)	**0.56 (0.39 – 0.81)**
Adjusted for age and gender	1.00	0.81 (0.63 – 1.03)	**0.71 (0.52 – 0.97)**	**0.52 (0.36 – 0.75)**
Model 1†	1.00	0.88 (0.69 – 1.13)	**0.73 (0.53 – 1.00)**	**0.56 (0.39 – 0.81)**
Model 2‡	1.00	0.87 (0.68 – 1.12)	0.73 (0.54 – 1.00)	**0.56 (0.39 – 0.81)**
Vigorous-intensity physical activity				
No. of participants	6935	328	254	286
No. of person-years	30641	1484	1181	1342
No. 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 – 1.15)	**0.54 (0.36 – 0.82)**	**0.60 (0.42 – 0.86)**
Adjusted for age and gender	1.00	0.84 (0.63 – 1.12)	**0.54 (0.36 – 0.82)**	**0.55 (0.38 – 0.79)**
Model 1†	1.00	0.86 (0.64 – 1.15)	**0.58 (0.39 – 0.87)**	**0.55 (0.38 – 0.79)**
Model 2‡	1.00	0.85 (0.64 – 1.14)	**0.57 (0.38 – 0.85)**	**0.55 (0.38 – 0.79)**

Bold 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, gamma glutamyltransferase, hypertension, diabetes, dyslipidemia, and meat and vegetable intakes.

‡Additional adjustment of model 1 for other intensity types of physical activity.

The hazard ratios of all covariates in model 2 are presented in Supplementary Table 2.

Table 3. Hazard ratios of incident fatty liver by frequency of physical activity in heavy alcohol drinkers

	Frequency of engaging in physical activity (times/week)			
		Hazard ratio (95% CI)		
	<1x	1x	2x	≥3x
Low-intensity physical activity				
No. of participants	1554	230	142	417
No. of person-years	6412	901	597	1686
No. 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 – 1.33)	1.07 (0.75 – 1.53)	1.14 (0.91 – 1.42)
Adjusted for age and gender	1.00	0.93 (0.69 – 1.27)	1.03 (0.72 – 1.47)	1.09 (0.87 – 1.37)
Model 1†	1.00	0.97 (0.71 – 1.32)	0.97 (0.68 – 1.39)	1.18 (0.93 – 1.49)
Model 2‡	1.00	0.98 (0.72 – 1.34)	0.96 (0.67 – 1.38)	1.18 (0.93 – 1.50)
Moderate-intensity physical activity				
No. of participants	2002	154	101	86
No. of person-years	8149	666	457	324
No. 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 – 1.21)	1.09 (0.74 – 1.61)	1.17 (0.75 – 1.81)
Adjusted for age and gender	1.00	0.81 (0.56 – 1.17)	1.02 (0.69 – 1.50)	1.05 (0.68 – 1.64)
Model 1†	1.00	0.82 (0.56 – 1.18)	1.15 (0.78 – 1.71)	1.06 (0.68 – 1.66)
Model 2‡	1.00	0.81 (0.56 – 1.18)	1.16 (0.78 – 1.72)	1.13 (0.72 – 1.77)
Vigorous-intensity physical activity				
No. of participants	2055	115	77	96
No. of person-years	8377	488	312	419
No. 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 – 1.38)	1.20 (0.78 – 1.86)	0.82 (0.52 – 1.31)
Adjusted for age and gender	1.00	0.92 (0.61 – 1.39)	1.25 (0.81 – 1.94)	0.79 (0.50 – 1.25)
Model 1†	1.00	0.85 (0.55 – 1.29)	1.26 (0.81 – 1.97)	0.75 (0.47 – 1.21)
Model 2‡	1.00	0.87 (0.56 – 1.33)	1.32 (0.85 – 2.07)	0.77 (0.47 – 1.24)

Bold 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, aspartate aminotransferase, gamma glutamyltransferase, hypertension, diabetes, dyslipidemia, and meat and vegetable intakes.

‡Additional adjustment of model 1 for other intensity types of physical activity.

The hazard ratios of all covariates in model 2 are presented in Supplementary Table 2.

Article title

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

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Objective: To investigate if physical activity affects future incident fatty liver in people with never-moderate and heavy alcohol consumption.

Design: Prospective cohort study.

Setting: Health check-up program of 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 ≥3x/wk of low-intensity (HR=0.82, 95% CI=0.71 to 0.95) 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 <1x/wk. For vigorous-intensity physical activity, frequencies of both 2x/wk (HR=0.57, 95% CI=0.38 to 0.85) and ≥3x/wk (HR=0.55, 95% CI=0.38 to 0.79) were significantly associated with lower incident risk of fatty liver. In propensity-adjusted models, these significant associations still remained. By contrast, in heavy alcohol drinkers, there were no significant associations between type or frequency of physical activity and incident fatty liver.

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

Key words: exercise; NAFLD; AFLD; hepatic steatosis; obesity

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 hazard ratios 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-alcoholic fatty liver disease (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] 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 more 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 dyslipidemia.[12] Since both 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 both 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 future incident fatty liver diagnosed by ultrasound in two populations: those who are never-moderate alcohol drinkers and those who are 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 to 2007 survey data (n=25,056, aged 18 years or older) as our baseline data. Of these people, 2541 individuals were excluded due to 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 hemangioma, 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 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. This study was approved by the Ethical Committee of Meiji Yasuda Life Foundation of Health and Welfare.

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 to 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±1.0% (range, 22.2 to 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 whiskey, or 0.5 cup of *shochu*. We used a scoring method for frequency of alcohol consumption as follows: 0.5 for an occasional drink, 1.5 for 1–2 days per week, 3.5 for 3–4 days per week, 5.5 for daily with day off drinking, and 7.0 for daily without day off drinking. We set four alcohol categories by calculating average daily alcohol consumption: never, moderate (less than 23.0 g of alcohol per day), heavy (23.0 g to 45.9 g per day), and very heavy (46.0 g per 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 alcohol intake status at baseline, participants were divided into never to moderate alcohol drinkers (n=7803) and heavy alcohol drinkers (n=2343).[27]

Physical activity

A questionnaire assessed leisure-time PA in a typical week by frequency (never, <1x/wk, 1x/wk, 2x/wk, and ≥3x/wk), 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 to 5 metabolic equivalents (METs), moderate-intensity corresponded to 5 to 7 METs, and vigorous-intensity corresponded to 7 or more METs.[29 30]

Since 10 minutes is considered the minimum for a single event activity,[31] we determined a single session of PA to be ≥10 minutes. Each frequency (<1x/wk, 1x/wk, 2x/wk, and ≥3x/wk) of low-, moderate-, 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 two 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 dyslipidemia. A blood sample was drawn from each subject after an overnight fast. The serum triglycerides (TG), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma 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 subject rested at least 15 minutes in a sitting

position.

Exposure and outcome

The study's exposure is PA level at baseline and outcome is future incident fatty liver. In both 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 dyslipidemia. 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 ≥7.0 mmol/L, HbA1c ≥6.5%, there was a diagnosis history or drug usage for diabetes. Dyslipidemia was coded "yes" if LDL-C ≥4.1 mmol/L, HDL ≤1.0 mmol/L, TG ≥2.3 mmol/L, there was a diagnosis history or drug usage for dyslipidemia.

We performed all analyses on both the never-moderate and heavy alcohol drinking groups. To compare baseline characteristics by PA frequencies, we used chi-squared tests for categorical variables and analysis of variance for continuous variables. We used the Cox proportional-hazards analysis to determine prospective associations between 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), AST (continuous), GGT (continuous), hypertension (yes or no), diabetes (yes or no), dyslipidemia (yes or no), and meat and green/yellow vegetable intakes (never or seldom, once every two days, or one or more times per day). 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 ≥3x/wk.[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 <1x/wk and ≥3x/wk, but did not conduct the matching analysis.[32] The areas under the receiver operating curves of propensity scores were 0.70 to 0.77, 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 version 21.0 (IBM, Inc., Armonk, NY).

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 males representing 39.5% of this group. The heavy drinkers' mean age was 49.1±9.8 years with 79.6% male. In both groups, almost half the people did not engage in any PA. Baseline characteristics for all three intensities of PA are presented in Supplementary Tables 1a–c.

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 summarizes 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 0.95) or moderate-intensity PA (HR=0.56, 95% CI=0.39 to 0.81) ≥3x/wk significantly reduced their risks of incident fatty liver, compared to those who engaged in PA <1x/wk. When participants engaged in vigorous-intensity PA ≥2/wk, they decreased their risk of fatty liver by about half (2x/wk: HR=0.57, 95% CI=0.38 to 0.85; ≥3x: HR=0.55, 95% CI=0.38 to 0.79). All hazard ratios in model 2, including covariates, are shown in Supplementary Table 2. The final propensity-adjusted Cox models (Supplementary Table 3), also confirmed the significant preventive effects of ≥3x/wk of lower-intensity (HR=0.82, 95% CI=0.70 to 0.95), moderate-intensity (HR=0.57, 95% CI=0.39 to 0.82), 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 type or frequency of PA and incident risk of 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 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]

Previous Chinese [33] and Korean [22] cohort studies using an 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 to 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 intensity and frequency increased. When participants engaged in PA ≥3x/wk, their incident risks of fatty liver decreased significantly regardless of PA intensity. In particular, those who engaged in moderate-intensity PA ≥3x/wk, or vigorous-intensity PA ≥2x/wk had decreased hazard ratios. In a retrospective study,[22] engaging in PA ≥3x/wk 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 occurs with 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 utilization 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 at reducing liver fat and enzymes compared with diet alone. However, that meta-analysis could not incorporate exercise intensity because of the lack of data,[40] which may hide the independent benefit of exercise on NAFLD. Future intervention studies should consider exercise intensity in addition to 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 both 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 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 dyslipidemia were independent predictors for incident fatty liver (Supplementary Table 2), 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 dyslipidemia 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 both 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 hazard ratios according to PA frequencies and intensities which revealed the advantages of higher frequencies and intensities of PA. PA is a cost-effective and noninvasive 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 diagnose

requires liver biopsy. In addition, using several ultrasonography machines during the study may limit the accuracy of diagnoses. However, we believe 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 (e.g. serum iron and ferritin) and fibrosis markers (e.g. 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 incident 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 PA frequency in our questionnaire only went as high as ">3x/wk", 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 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 generalize 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 ≥3x/wk 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 future risk of incident fatty liver in people with never-moderate or heavy alcohol consumption. In never-moderate alcohol drinkers, PA independently reduced future risk of fatty liver, and hazard ratios decreased as 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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Contributions: KT and YK conceived and designed the study, analyzed and interpreted the data, and drafted the manuscript. KU and TK acquired and interpreted the data and critically revised the manuscript. TN interpreted the data, critically revised the manuscript, and supervised and coordinated the study. All authors read and approved the final manuscript.

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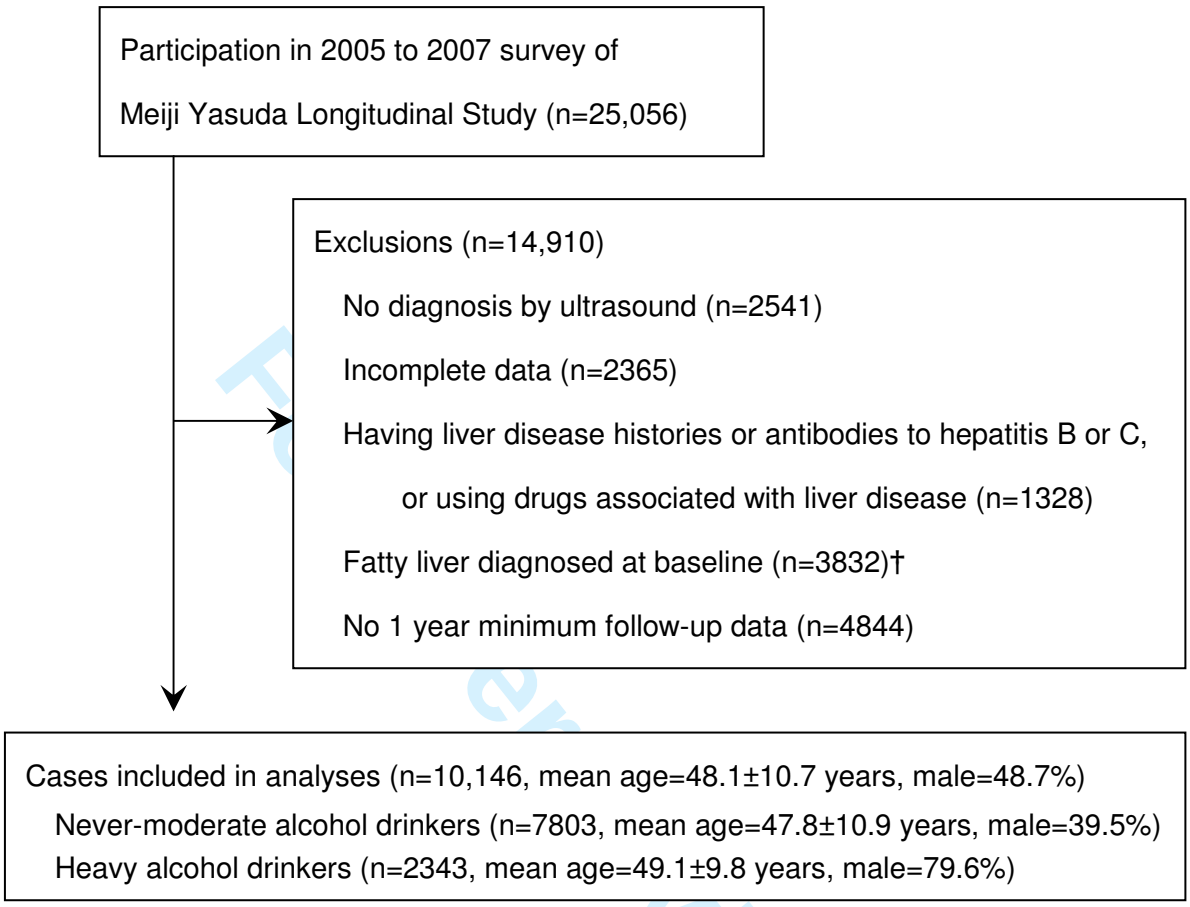

Figure 1. Flow of eligible participants in this study

†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 baseline.

Table 1. Baseline characteristics of participants by frequency of physical activity

	Never-moderate alcohol drinkers (n=7803, mean age=47.8±10.9 yr, male=39.5%)					Heavy alcohol drinkers (n=2343, mean age=49.1±9.8 yr, male=79.6%)				
	Physical activity (times/week)					Physical activity (times/week)				
Baseline variables	<1x	1x	2x	≥3x	*P* value	<1x	1x	2x	≥3x	*P* value
No. 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)	19.4 (9.3)	19.4 (9.3)	19.4 (8.0)	19.3 (8.1)	0.948	22.6 (12.3)	22.7 (10.9)	22.4 (9.3)	22.1 (12.4)	0.816
Mean (SD) AST (Units/l)	19.7 (7.5)	20.0 (6.9)	20.6 (6.0)	20.7 (6.5)	< 0.001	22.6 (9.3)	23.6 (8.1)	23.3 (9.0)	23.1 (8.3)	0.306
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
Dyslipidemia¶	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.

ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, GGT: gamma glutamyltransferase, PA: physical activity.

†Systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, diagnosis history or drug usage for hypertension.

‡Fasting plasma glucose ≥7.0 mmol/L, HbA1c ≥6.5%, diagnosis history or drug usage for diabetes.

¶Low-density lipoprotein-cholesterol ≥4.1 mmol/L, high-density lipoprotein-cholesterol ≤1.0 mmol/L, serum triglycerides ≥2.3 mmol/L, diagnosis history or drug usage for dyslipidemia.

Baseline characteristics for all three intensities of physical activity are presented in Supplementary Tables 1a–c.

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

	Frequency of engaging in physical activity (times/week)			
		Hazard ratio (95% CI)		
	<1x	1x	2x	≥3x
Low-intensity physical activity				
No. of participants	4900	728	516	1659
No. of person-years	21679	3278	2269	7422
No. 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 – 1.09)	1.05 (0.84 – 1.31)	0.93 (0.81 – 1.07)
Adjusted for age and gender	1.00	0.87 (0.71 – 1.07)	0.98 (0.78 – 1.22)	**0.86 (0.74 – 0.99)**
Model 1†	1.00	0.95 (0.78 – 1.16)	1.00 (0.80 – 1.25)	0.87 (0.75 – 1.00)
Model 2‡	1.00	0.91 (0.74 – 1.12)	0.96 (0.77 – 1.20)	**0.82 (0.71 – 0.95)**
Moderate-intensity physical activity				
No. of participants	6699	478	318	308
No. of person-years	29579	2200	1441	1428
No. 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 – 1.04)	0.76 (0.55 – 1.03)	**0.56 (0.39 – 0.81)**
Adjusted for age and gender	1.00	0.81 (0.63 – 1.03)	**0.71 (0.52 – 0.97)**	**0.52 (0.36 – 0.75)**
Model 1†	1.00	0.88 (0.69 – 1.13)	**0.73 (0.53 – 1.00)**	**0.56 (0.39 – 0.81)**
Model 2‡	1.00	0.87 (0.68 – 1.12)	0.73 (0.54 – 1.00)	**0.56 (0.39 – 0.81)**
Vigorous-intensity physical activity				
No. of participants	6935	328	254	286
No. of person-years	30641	1484	1181	1342
No. 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 – 1.15)	**0.54 (0.36 – 0.82)**	**0.60 (0.42 – 0.86)**
Adjusted for age and gender	1.00	0.84 (0.63 – 1.12)	**0.54 (0.36 – 0.82)**	**0.55 (0.38 – 0.79)**
Model 1†	1.00	0.86 (0.64 – 1.15)	**0.58 (0.39 – 0.87)**	**0.55 (0.38 – 0.79)**
Model 2‡	1.00	0.85 (0.64 – 1.14)	**0.57 (0.38 – 0.85)**	**0.55 (0.38 – 0.79)**

Bold 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, gamma glutamyltransferase, hypertension, diabetes, dyslipidemia, and meat and vegetable intakes.

‡ Additional adjustment of model 1 for other intensity types of physical activity.

The hazard ratios of all covariates in model 2 are presented in Supplementary Table 2.

Table 3. Hazard ratios of incident fatty liver by frequency of physical activity in heavy alcohol drinkers

	Frequency of engaging in physical activity (times/week)							
		Hazard ratio (95% CI)						
	<1x	1x		2x		≥3x		
Low-intensity physical activity								
No. of participants	1554	230		142		417		
No. of person-years	6412	901		597		1686		
No. 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 – 1.33)	1.07	(0.75 – 1.53)	1.14	(0.91 – 1.42)	
Adjusted for age and gender	1.00	0.93	(0.69 – 1.27)	1.03	(0.72 – 1.47)	1.09	(0.87 – 1.37)	
Model 1†	1.00	0.97	(0.71 – 1.32)	0.97	(0.68 – 1.39)	1.18	(0.93 – 1.49)	
Model 2‡	1.00	0.98	(0.72 – 1.34)	0.96	(0.67 – 1.38)	1.18	(0.93 – 1.50)	
Moderate-intensity physical activity								
No. of participants	2002	154		101		86		
No. of person-years	8149	666		457		324		
No. 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 – 1.21)	1.09	(0.74 – 1.61)	1.17	(0.75 – 1.81)	
Adjusted for age and gender	1.00	0.81	(0.56 – 1.17)	1.02	(0.69 – 1.50)	1.05	(0.68 – 1.64)	
Model 1†	1.00	0.82	(0.56 – 1.18)	1.15	(0.78 – 1.71)	1.06	(0.68 – 1.66)	
Model 2‡	1.00	0.81	(0.56 – 1.18)	1.16	(0.78 – 1.72)	1.13	(0.72 – 1.77)	
Vigorous-intensity physical activity								
No. of participants	2055	115		77		96		
No. of person-years	8377	488		312		419		
No. 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 – 1.38)	1.20	(0.78 – 1.86)	0.82	(0.52 – 1.31)	
Adjusted for age and gender	1.00	0.92	(0.61 – 1.39)	1.25	(0.81 – 1.94)	0.79	(0.50 – 1.25)	
Model 1†	1.00	0.85	(0.55 – 1.29)	1.26	(0.81 – 1.97)	0.75	(0.47 – 1.21)	
Model 2‡	1.00	0.87	(0.56 – 1.33)	1.32	(0.85 – 2.07)	0.77	(0.47 – 1.24)	

Bold 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, aspartate aminotransferase, gamma glutamyltransferase, hypertension, diabetes, dyslipidemia, and meat and vegetable intakes.

‡ Additional adjustment of model 1 for other intensity types of physical activity.

The hazard ratios of all covariates in model 2 are presented in Supplementary Table 2.

Supplementary Table 1-a.

Baseline characteristics of participants by frequency of *low-intensity* physical activity

	Never-moderate alcohol drinkers (n=7803)					Heavy alcohol drinkers (n=2343)				
	Low-intensity physical activity (times/week)					Low-intensity physical activity (times/week)				
Baseline variables	<1x	1x	2x	≥3x	*P* value	<1x	1x	2x	≥3x	*P* value
No. of participants	4900	728	516	1659		1554	230	142	417	
Mean (SD) age (years)	46.1 (10.3)	47.8 (10.8)	50.9 (10.8)	51.7 (11.5)	< 0.001	47.6 (9.3)	50.2 (9.4)	51.0 (9.4)	53.3 (10.5)	< 0.001
Male Gender	2009 (41.0)	275 (37.8)	203 (39.3)	593 (35.7)	0.002	1232 (79.3)	192 (83.5)	118 (83.1)	322 (77.2)	0.191
Mean (SD) BMI (kg/m^2)	21.6 (2.6)	21.5 (2.5)	21.6 (2.5)	21.6 (2.6)	0.761	22.5 (2.5)	22.7 (2.5)	22.8 (2.4)	22.5 (2.4)	0.482
Daily alcohol consumption										
Never	851 (17.4)	134 (18.4)	93 (18.0)	338 (20.4)	0.056	–	–	–	–	
Low-moderate (<23.0 g)	4049 (82.6)	594 (81.6)	423 (82.0)	1321 (79.6)		–	–	–	–	
Heavy (23.0–45.9 g)	–	–	–	–		1158 (74.5)	189 (82.2)	104 (73.2)	324 (77.7)	0.050
Very heavy (≥46.0 g)	–	–	–	–		396 (25.5)	41 (17.8)	38 (26.8)	93 (22.3)	
Smoking status					< 0.001					< 0.001
Never	2875 (58.7)	452 (62.1)	316 (61.2)	1088 (65.6)		379 (24.4)	49 (21.3)	36 (25.4)	108 (25.9)	
Former	897 (18.3)	170 (23.4)	120 (23.3)	380 (22.9)		489 (31.5)	96 (41.7)	62 (43.7)	177 (42.4)	
Current	1128 (23.0)	106 (14.6)	80 (15.5)	191 (11.5)		686 (44.1)	85 (37.0)	44 (31.0)	132 (31.7)	
Family history of hepatic disease	283 (5.8)	40 (5.5)	32 (6.2)	103 (6.2)	0.870	95 (6.1)	10 (4.3)	14 (9.9)	26 (6.2)	0.199
Mean (SD) ALT (Units/l)	19.4 (9.0)	19.2 (9.3)	19.7 (8.4)	19.2 (8.4)	0.737	22.7 (12.5)	21.6 (9.2)	23.5 (10.0)	21.8 (11.0)	0.264
Mean (SD) AST (Units/l)	20.0 (7.3)	20.0 (6.7)	21.3 (6.7)	20.4 (6.0)	< 0.001	23.0 (9.3)	22.8 (7.0)	23.6 (8.2)	22.9 (8.1)	0.819
Mean (SD) GGT (Units/l)	27.5 (24.2)	28.0 (37.2)	29.5 (29.9)	26.7 (22.9)	0.172	60.8 (71.2)	54.9 (40.3)	63.1 (59.3)	52.8 (48.6)	0.084
Hypertension†	412 (8.4)	52 (7.1)	79 (15.3)	248 (14.9)	< 0.001	257 (16.5)	45 (19.6)	39 (27.5)	116 (27.8)	< 0.001
Diabetes‡	115 (2.3)	24 (3.3)	28 (5.4)	92 (5.5)	< 0.001	65 (4.2)	15 (6.5)	13 (9.2)	39 (9.4)	< 0.001
Dyslipidemia¶	936 (19.1)	158 (21.7)	134 (26.0)	411 (24.8)	< 0.001	309 (19.9)	55 (23.9)	34 (23.9)	109 (26.1)	0.030
Meat intake					< 0.001					0.105
Never or seldom	1895 (38.7)	289 (39.7)	241 (46.7)	756 (45.6)		626 (40.3)	86 (37.4)	65 (45.8)	196 (47.0)	
Once per 2 days	1613 (32.9)	238 (32.7)	169 (32.8)	484 (29.2)		492 (31.7)	77 (33.5)	46 (32.4)	124 (29.7)	
Once a day or more	1392 (28.4)	201 (27.6)	106 (20.5)	419 (25.3)		436 (28.1)	67 (29.1)	31 (21.8)	97 (23.3)	
Vegetable intake					< 0.001					< 0.001
Never or seldom	1156 (23.6)	103 (14.1)	82 (15.9)	190 (11.5)		477 (30.7)	53 (23.0)	34 (23.9)	71 (17.0)	
Once per 2 days	1124 (22.9)	147 (20.2)	89 (17.2)	228 (13.7)		395 (25.4)	56 (24.3)	32 (22.5)	76 (18.2)	
Once a day or more	2620 (53.5)	478 (65.7)	345 (66.9)	1241 (74.8)		682 (43.9)	121 (52.6)	76 (53.5)	270 (64.7)	
Moderate-intensity PA					< 0.001					0.088
<1x/wk	4122 (84.1)	646 (88.7)	455 (88.2)	1476 (89.0)		1307 (84.1)	203 (88.3)	123 (86.6)	369 (88.5)	
1x/wk	325 (6.6)	44 (6.0)	28 (5.4)	81 (4.9)		104 (6.7)	16 (7.0)	11 (7.7)	23 (5.5)	
2x/wk	219 (4.5)	25 (3.4)	20 (3.9)	54 (3.3)		74 (4.8)	8 (3.5)	7 (4.9)	12 (2.9)	
≥3x/wk	234 (4.8)	13 (1.8)	13 (2.5)	48 (2.9)		69 (4.4)	3 (1.3)	1 (0.7)	13 (3.1)	
Vigorous-intensity PA					< 0.001					< 0.001
<1x/wk	4299 (87.7)	655 (90.0)	460 (89.1)	1521 (91.7)		1336 (86.0)	201 (87.4)	130 (91.5)	388 (93.0)	
1x/wk	202 (4.1)	35 (4.8)	24 (4.7)	67 (4.0)		79 (5.1)	17 (7.4)	2 (1.4)	17 (4.1)	
2x/wk	181 (3.7)	20 (2.7)	16 (3.1)	37 (2.2)		60 (3.9)	6 (2.6)	6 (4.2)	5 (1.2)	
≥3x/wk	218 (4.4)	18 (2.5)	16 (3.1)	34 (2.0)		79 (5.1)	6 (2.6)	4 (2.8)	7 (1.7)	

Values are numbers (percentages) unless stated otherwise.

ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, GGT: gamma glutamyltransferase, PA: physical activity.

†Systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, diagnosis history or drug usage for hypertension.

‡Fasting plasma glucose ≥7.0 mmol/L, HbA1c ≥6.5%, diagnosis history or drug usage for diabetes.

¶Low-density lipoprotein-cholesterol ≥4.1 mmol/L, high-density lipoprotein-cholesterol ≤1.0 mmol/L, serum triglycerides ≥2.3 mmol/L, diagnosis history or drug usage for dyslipidemia.

Supplementary Table 1-b.

Baseline characteristics of participants by frequency of *moderate-intensity* physical activity

	Never-moderate alcohol drinkers (n=7803)					Heavy alcohol drinkers (n=2343)				
	Moderate-intensity physical activity (times/week)					Moderate-intensity physical activity (times/week)				
Baseline variables	<1x	1x	2x	≥3x	*P* value	<1x	1x	2x	≥3x	*P* value
No. of participants	6699	478	318	308		2002	154	101	86	
Mean (SD) age (years)	47.4 (10.8)	48.3 (11.0)	50.1 (10.9)	52.5 (11.7)	< 0.001	48.7 (9.8)	49.1 (8.8)	52.1 (9.1)	53.9 (10.6)	< 0.001
Male Gender	2658 (39.7)	172 (36.0)	129 (40.6)	121 (39.3)	0.437	1580 (78.9)	129 (83.8)	83 (82.2)	72 (83.7)	0.318
Mean (SD) BMI (kg/m^2)	21.6 (2.6)	21.5 (2.4)	21.8 (2.5)	21.7 (2.4)	0.436	22.5 (2.5)	22.8 (2.3)	22.7 (2.1)	22.6 (2.3)	0.425
Daily alcohol consumption										
Never	1231 (18.4)	62 (13.0)	57 (17.9)	66 (21.4)	0.011	–	–	–	–	
Low-moderate (<23.0 g)	5468 (81.6)	416 (87.0)	261 (82.1)	242 (78.6)		–	–	–	–	
Heavy (23.0–45.9 g)	–	–	–	–		1525 (76.2)	111 (72.1)	72 (71.3)	67 (77.9)	0.451
Very heavy (≥46.0 g)	–	–	–	–		477 (23.8)	43 (27.9)	29 (28.7)	19 (22.1)	
Smoking status					< 0.001					< 0.001
Never	3997 (59.7)	329 (68.8)	207 (65.1)	198 (64.3)		483 (24.1)	35 (22.7)	27 (26.7)	27 (31.4)	
Former	1319 (19.7)	105 (22.0)	72 (22.6)	71 (23.1)		669 (33.4)	62 (40.3)	48 (47.5)	45 (52.3)	
Current	1383 (20.6)	44 (9.2)	39 (12.3)	39 (12.7)		850 (42.5)	57 (37.0)	26 (25.7)	14 (16.3)	
Family history of hepatic disease	381 (5.7)	40 (8.4)	18 (5.7)	19 (6.2)	0.118	123 (6.1)	8 (5.2)	7 (6.9)	7 (8.1)	0.819
Mean (SD) ALT (Units/l)	19.4 (9.1)	18.8 (8.0)	19.3 (7.0)	18.4 (7.3)	0.117	22.3 (11.7)	23.9 (12.6)	22.8 (13.0)	22.7 (12.0)	0.419
Mean (SD) AST (Units/l)	20.1 (7.1)	19.9 (6.5)	20.8 (5.2)	20.8 (7.7)	0.105	22.8 (8.7)	24.0 (9.0)	24.1 (11.9)	22.9 (7.8)	0.221
Mean (SD) GGT (Units/l)	27.7 (26.8)	25.0 (17.3)	26.9 (19.7)	26.3 (18.9)	0.109	59.0 (64.4)	59.0 (64.9)	56.0 (56.0)	60.7 (75.4)	0.963
Hypertension†	666 (9.9)	47 (9.8)	33 (10.4)	45 14.6	0.068	376 (18.8)	31 (20.1)	25 (24.8)	25 (29.1)	0.058
Diabetes‡	216 (3.2)	12 (2.5)	8 (2.5)	23 7.5	< 0.001	111 (5.5)	10 (6.5)	6 (5.9)	5 (5.8)	0.966
Dyslipidemia¶	1411 (21.1)	97 (20.3)	67 (21.1)	64 20.8	0.982	437 (21.8)	38 (24.7)	16 (15.8)	16 (18.6)	0.341
Meat intake					0.732					0.686
Never or seldom	2748 (41.0)	186 (38.9)	118 (37.1)	129 41.9		828 (41.4)	59 (38.3)	44 (43.6)	42 (48.8)	
Once per 2 days	2140 (31.9)	164 (34.3)	105 (33.0)	95 30.8		633 (31.6)	55 (35.7)	28 (27.7)	23 (26.7)	
Once a day or more	1811 (27.0)	128 (26.8)	95 (29.9)	84 27.3		541 (27.0)	40 (26.0)	29 (28.7)	21 (24.4)	
Vegetable intake					< 0.001					0.231
Never or seldom	1368 (20.4)	69 (14.4)	49 (15.4)	45 14.6		561 (28.0)	31 (20.1)	26 (25.7)	17 (19.8)	
Once per 2 days	1374 (20.5)	105 (22.0)	47 (14.8)	62 20.1		477 (23.8)	37 (24.0)	25 (24.8)	20 (23.3)	
Once a day or more	3957 (59.1)	304 (63.6)	222 (69.8)	201 65.3		964 (48.2)	86 (55.8)	50 (49.5)	49 (57.0)	
Low-intensity PA					< 0.001					0.088
<1x/wk	4122 (61.5)	325 (68.0)	219 (68.9)	234 (76.0)		1307 (65.3)	104 (67.5)	74 (73.3)	69 (80.2)	
1x/wk	646 (9.6)	44 (9.2)	25 (7.9)	13 (4.2)		203 (10.1)	16 (10.4)	8 (7.9)	3 (3.5)	
2x/wk	455 (6.8)	28 (5.9)	20 (6.3)	13 (4.2)		123 (6.1)	11 (7.1)	7 (6.9)	1 (1.2)	
≥3x/wk	1476 (22.0)	81 (16.9)	54 (17.0)	48 (15.6)		369 (18.4)	23 (14.9)	12 (11.9)	13 (15.1)	
Vigorous-intensity PA					< 0.001					< 0.001
<1x/wk	6010 (89.7)	400 (83.7)	267 (84.0)	258 (83.8)		1765 (88.2)	126 (81.8)	91 (90.1)	73 (84.9)	
1x/wk	256 (3.8)	46 (9.6)	13 (4.1)	13 (4.2)		89 (4.4)	19 (12.3)	4 (4.0)	3 (3.5)	
2x/wk	206 (3.1)	20 (4.2)	17 (5.3)	11 (3.6)		65 (3.2)	7 (4.5)	4 (4.0)	1 (1.2)	
≥3x/wk	227 (3.4)	12 (2.5)	21 (6.6)	26 (8.4)		83 (4.1)	2 (1.3)	2 (2.0)	9 (10.5)	

Values are numbers (percentages) unless stated otherwise.

ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, GGT: gamma glutamyltransferase, PA: physical activity.

†Systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, diagnosis history or drug usage for hypertension.

‡Fasting plasma glucose ≥7.0 mmol/L, HbA1c ≥6.5%, diagnosis history or drug usage for diabetes.

¶Low-density lipoprotein-cholesterol ≥4.1 mmol/L, high-density lipoprotein-cholesterol ≤1.0 mmol/L, serum triglycerides ≥2.3 mmol/L, diagnosis history or drug usage for dyslipidemia.

Supplementary Table 1-c.

Baseline characteristics of participants by frequency of *vigorous-intensity* physical activity

	Never-moderate alcohol drinkers (n=7803)					Heavy alcohol drinkers (n=2343)				
	Vigorous-intensity physical activity (times/week)					Vigorous-intensity physical activity (times/week)				
Baseline variables	<1x	1x	2x	≥3x	*P* value	<1x	1x	2x	≥3x	*P* value
No. of participants	6935	328	254	286		2055	115	77	96	
Mean (SD) age (years)	47.7 (10.9)	46.4 (10.3)	48.8 (11.3)	49.4 (11.0)	0.004	49.2 (9.8)	47.4 (9.8)	48.0 (10.1)	50.0 (10.6)	0.159
Male Gender	2724 (39.3)	134 (40.9)	98 (38.6)	124 (43.4)	0.520	1632 (79.4)	91 (79.1)	61 (79.2)	80 (83.3)	0.829
Mean (SD) BMI (kg/m^2)	21.6 (2.6)	21.8 (2.4)	21.6 (2.2)	21.8 (2.6)	0.215	22.5 (2.5)	22.9 (2.4)	22.6 (2.3)	22.9 (2.0)	0.142
Daily alcohol consumption										
Never	1278 (18.4)	39 (11.9)	46 (18.1)	53 (18.5)	0.029	–	–	–	–	
Low-moderate (<23.0 g)	5657 (81.6)	289 (88.1)	208 (81.9)	233 (81.5)		–	–	–	–	
Heavy (23.0–45.9 g)	–	–	–	–		1575 (76.6)	81 (70.4)	50 (64.9)	69 (71.9)	0.039
Very heavy (≥46.0 g)	–	–	–	–		480 (23.4)	34 (29.6)	27 (35.1)	27 (28.1)	
Smoking status					< 0.001					< 0.001
Never	4192 (60.4)	208 (63.4)	159 (62.6)	172 (60.1)		492 (23.9)	30 (26.1)	17 (22.1)	33 (34.4)	
Former	1355 (19.5)	84 (25.6)	53 (20.9)	75 (26.2)		691 (33.6)	48 (41.7)	39 (50.6)	46 (47.9)	
Current	1388 (20.0)	36 (11.0)	42 (16.5)	39 (13.6)		872 (42.4)	37 (32.2)	21 (27.3)	17 (17.7)	
Family history of hepatic disease	414 (6.0)	8 (2.4)	20 (7.9)	16 (5.6)	0.029	121 (5.9)	9 (7.8)	8 (10.4)	7 (7.3)	0.335
Mean (SD) ALT (Units/l)	19.3 (9.0)	19.0 (8.0)	19.6 (8.1)	20.4 (7.7)	0.175	22.5 (11.7)	22.0 (9.1)	22.5 (8.8)	22.3 (17.9)	0.981
Mean (SD) AST (Units/l)	20.0 (7.0)	20.3 (7.1)	21.0 (6.8)	22.6 (7.1)	< 0.001	22.9 (8.9)	23.4 (7.9)	23.4 (6.8)	23.9 (9.8)	0.589
Mean (SD) GGT (Units/l)	27.5 (26.0)	26.9 (20.2)	28.3 (24.3)	28.0 (27.2)	0.912	59.8 (66.3)	53.9 (55.4)	55.9 (48.1)	49.2 (44.8)	0.330
Hypertension†	710 (10.2)	22 (6.7)	35 (13.8)	24 8.4	0.030	423 (20.6)	12 (10.4)	8 (10.4)	14 (14.6)	0.004
Diabetes‡	233 (3.4)	7 (2.1)	7 (2.8)	12 4.2	0.492	115 (5.6)	5 (4.3)	4 (5.2)	8 (8.3)	0.635
Dyslipidemia¶	1474 (21.3)	59 (18.0)	50 (19.7)	56 19.6	0.444	456 (22.2)	21 (18.3)	20 (26.0)	10 (10.4)	0.028
Meat intake					0.070					< 0.001
Never or seldom	2827 (40.8)	119 (36.3)	98 (38.6)	137 47.9		874 (42.5)	29 (25.2)	33 (42.9)	37 (38.5)	
Once per 2 days	2220 (32.0)	108 (32.9)	87 (34.3)	89 31.1		653 (31.8)	33 (28.7)	23 (29.9)	30 (31.3)	
Once a day or more	1888 (27.2)	101 (30.8)	69 (27.2)	60 21.0		528 (25.7)	53 (46.1)	21 (27.3)	29 (30.2)	
Vegetable intake					< 0.001					< 0.001
Never or seldom	1399 (20.2)	59 (18.0)	33 (13.0)	40 14.0		588 (28.6)	17 (14.8)	17 (22.1)	13 (13.5)	
Once per 2 days	1420 (20.5)	68 (20.7)	56 (22.0)	44 15.4		498 (24.2)	27 (23.5)	14 (18.2)	20 (20.8)	
Once a day or more	4116 (59.4)	201 (61.3)	165 (65.0)	202 70.6		969 (47.2)	71 (61.7)	46 (59.7)	63 (65.6)	
Low-intensity PA					< 0.001					< 0.001
<1x/wk	4299 (62.0)	202 (61.6)	181 (71.3)	218 (76.2)		1336 (65.0)	79 (68.7)	60 (77.9)	79 (82.3)	
1x/wk	655 (9.4)	35 (10.7)	20 (7.9)	18 (6.3)		201 (9.8)	17 (14.8)	6 (7.8)	6 (6.3)	
2x/wk	460 (6.6)	24 (7.3)	16 (6.3)	16 (5.6)		130 (6.3)	2 (1.7)	6 (7.8)	4 (4.2)	
≥3x/wk	1521 (21.9)	67 (20.4)	37 (14.6)	34 (11.9)		388 (18.9)	17 (14.8)	5 (6.5)	7 (7.3)	
Moderate-intensity PA					< 0.001					< 0.001
<1x/wk	6010 (86.7)	256 (78.0)	206 (81.1)	227 (79.4)		1765 (85.9)	89 (77.4)	65 (84.4)	83 (86.5)	
1x/wk	400 (5.8)	46 (14.0)	20 (7.9)	12 (4.2)		126 (6.1)	19 (16.5)	7 (9.1)	2 (2.1)	
2x/wk	267 (3.9)	13 (4.0)	17 (6.7)	21 (7.3)		91 (4.4)	4 (3.5)	4 (5.2)	2 (2.1)	
≥3x/wk	258 (3.7)	13 (4.0)	11 (4.3)	26 (9.1)		73 (3.6)	3 (2.6)	1 (1.3)	9 (9.4)	

Values are numbers (percentages) unless stated otherwise.

ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, GGT: gamma glutamyltransferase, PA: physical activity.

†Systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, diagnosis history or drug usage for hypertension.

‡Fasting plasma glucose ≥7.0 mmol/L, HbA1c ≥6.5%, diagnosis history or drug usage for diabetes.

¶Low-density lipoprotein-cholesterol ≥4.1 mmol/L, high-density lipoprotein-cholesterol ≤1.0 mmol/L, serum triglycerides ≥2.3 mmol/L, diagnosis history or drug usage for dyslipidemia.

Supplementary Table 2. Hazard ratios of incident fatty liver according physical activity and other variables in never-moderate and heavy alcohol drinkers

	Never-moderate alcohol drinkers (n=7803)		Heavy alcohol drinkers (n=2343)	
	HR	95% CI	HR	95% CI
Age (years)	**1.015**	**(1.009 – 1.021)**	1.009	(0.997 – 1.020)
Gender				
Male	1.000		1.000	
Female	**0.580**	**(0.507 – 0.662)**	**0.598**	**(0.436 – 0.821)**
Body mass index (kg/m^2)	**1.360**	**(1.334 – 1.386)**	**1.306**	**(1.260 – 1.354)**
Daily alcohol consumption				
Never	1.000		–	
Low-moderate (<23.0 g)	**0.852**	**(0.736 – 0.987)**	–	
Heavy (23.0–45.9 g)	–		1.000	
Very heavy (≥46.0 g)	–		0.890	(0.722 – 1.099)
Smoking status				
Never	1.000		1.000	
Former	0.931	(0.802 – 1.081)	1.116	(0.866 – 1.439)
Current	**1.173**	**(1.012 – 1.361)**	**1.382**	**(1.081 – 1.768)**
Family history of liver disease				
No	1.000		1.000	
Yes	1.151	(0.915 – 1.447)	1.176	(0.828 – 1.671)
ALT (units/L)	**1.011**	**(1.003 – 1.018)**	1.008	(1.000 – 1.016)
AST (units/L)	1.000	(0.990 – 1.009)	1.004	(0.991 – 1.017)
GGT (units/L)	1.001	(1.000 – 1.003)	**1.001**	**(1.000 – 1.002)**
Hypertension				
No	1.000		1.000	
Yes	1.087	(0.927 – 1.274)	0.992	(0.794 – 1.238)
Diabetes				
No	1.000		1.000	
Yes	1.243	(0.975 – 1.585)	1.098	(0.793 – 1.520)
Dyslipidemia				
No	1.000		1.000	
Yes	**1.251**	**(1.108 – 1.413)**	**1.299**	**(1.072 – 1.575)**
Meat intake				
Never or seldom	1.000		1.000	
Once per 2 days	**0.852**	**(0.743 – 0.977)**	0.958	(0.773 – 1.187)
Once a day or more	0.959	(0.828 – 1.110)	0.842	(0.663 – 1.070)
Vegetable intake				
Never or seldom	1.000		1.000	
Once per 2 days	0.929	(0.786 – 1.097)	0.955	(0.745 – 1.225)
Once a day or more	**0.829**	**(0.717 – 0.959)**	1.042	(0.832 – 1.304)
Low-intensity physical activity				
<1x/wk	1.000		1.000	
1x/wk	0.911	(0.743 – 1.117)	0.979	(0.717 – 1.337)
2x/wk	0.963	(0.770 – 1.205)	0.960	(0.669 – 1.379)
≥3x/wk	**0.821**	**(0.707 – 0.954)**	1.181	(0.929 – 1.502)
Moderate-intensity physical activity				
<1x/wk	1.000		1.000	
1x/wk	0.872	(0.680 – 1.119)	0.815	(0.561 – 1.184)
2x/wk	0.733	(0.536 – 1.002)	1.159	(0.780 – 1.723)
≥3x/wk	**0.559**	**(0.388 – 0.806)**	1.126	(0.715 – 1.774)
Vigorous-intensity physical activity				
<1x/wk	1.000		1.000	
1x/wk	0.852	(0.636 – 1.140)	0.866	(0.565 – 1.329)
2x/wk	**0.569**	**(0.379 – 0.854)**	1.322	(0.846 – 2.066)
≥3x/wk	**0.547**	**(0.380 – 0.789)**	0.766	(0.474 – 1.238)

Bold numbers indicate $P<0.05$.

ALT: alanine aminotransferase, AST: aspartate aminotransferase, GGT: gamma glutamyltransferase.

All variables were entered simultaneously for both never-moderate and heavy alcohol drinkers.

Supplementary Table 3. Propensity-adjusted hazard ratios of incident fatty liver according to physical activity in never-moderate and heavy alcohol drinkers

	Never-moderate alcohol drinkers		Heavy alcohol drinkers	
	Hazard ratio (95% CI)		Hazard ratio (95% CI)	
	<1x/wk vs. ≥3x/wk		<1x/wk vs. ≥3x/wk	
Low-intensity physical activity				
Adjusted for propensity	0.89	(0.77 – 1.03)	1.11	(0.88 – 1.41)
Adjusted for propensity and selected covariates†	**0.82**	**(0.71 – 0.96)**	1.14	(0.89 – 1.46)
Adjusted for propensity and all covariates	**0.82**	**(0.70 – 0.95)**	1.15	(0.90 – 1.47)
Moderate-intensity physical activity				
Adjusted for propensity	**0.55**	**(0.38 – 0.80)**	1.16	(0.74 – 1.82)
Adjusted for propensity and selected covariates†	**0.56**	**(0.39 – 0.81)**	1.09	(0.69 – 1.72)
Adjusted for propensity and all covariates	**0.57**	**(0.39 – 0.82)**	1.07	(0.67 – 1.69)
Vigorous-intensity physical activity				
Adjusted for propensity	**0.58**	**(0.40 – 0.83)**	0.83	(0.51 – 1.33)
Adjusted for propensity and selected covariates†	**0.56**	**(0.39 – 0.80)**	0.80	(0.49 – 1.29)
Adjusted for propensity and all covariates	**0.55**	**(0.38 – 0.79)**	0.74	(0.45 – 1.22)

Bold numbers indicate $P<0.05$.

†Adjusted for significant predictors on incident fatty liver (see Supplementary Table 2).

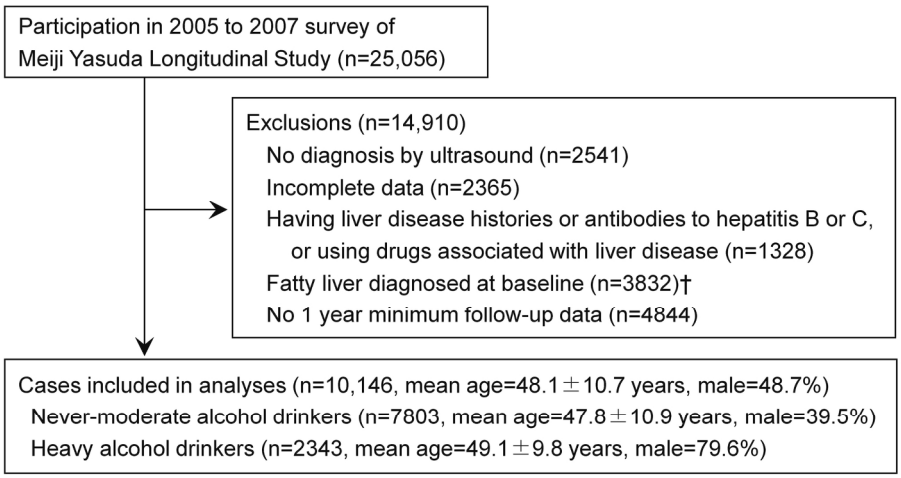

Figure 1. Flow of eligible participants in this study

†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 baseline.

190x142mm (300 x 300 DPI)

Supplementary Table 1-a.

Baseline characteristics of participants by frequency of *low-intensity* physical activity

	Never-moderate alcohol drinkers (n=7803)					Heavy alcohol drinkers (n=2343)				
	Low-intensity physical activity (times/week)					Low-intensity physical activity (times/week)				
Baseline variables	<1x	1x	2x	≥3x	*P* value	<1x	1x	2x	≥3x	*P* value
No. of participants	4900	728	516	1659		1554	230	142	417	
Mean (SD) age (years)	46.1 (10.3)	47.8 (10.8)	50.9 (10.8)	51.7 (11.5)	< 0.001	47.6 (9.3)	50.2 (9.4)	51.0 (9.4)	53.3 (10.5)	< 0.001
Male Gender	2009 (41.0)	275 (37.8)	203 (39.3)	593 (35.7)	0.002	1232 (79.3)	192 (83.5)	118 (83.1)	322 (77.2)	0.191
Mean (SD) BMI (kg/m^2)	21.6 (2.6)	21.5 (2.5)	21.6 (2.5)	21.6 (2.6)	0.761	22.5 (2.5)	22.7 (2.5)	22.8 (2.4)	22.5 (2.4)	0.482
Daily alcohol consumption										
Never	851 (17.4)	134 (18.4)	93 (18.0)	338 (20.4)	0.056	–	–	–	–	
Low-moderate (<23.0 g)	4049 (82.6)	594 (81.6)	423 (82.0)	1321 (79.6)		–	–	–	–	
Heavy (23.0–45.9 g)	–	–	–	–		1158 (74.5)	189 (82.2)	104 (73.2)	324 (77.7)	0.050
Very heavy (≥46.0 g)	–	–	–	–		396 (25.5)	41 (17.8)	38 (26.8)	93 (22.3)	
Smoking status					< 0.001					< 0.001
Never	2875 (58.7)	452 (62.1)	316 (61.2)	1088 (65.6)		379 (24.4)	49 (21.3)	36 (25.4)	108 (25.9)	
Former	897 (18.3)	170 (23.4)	120 (23.3)	380 (22.9)		489 (31.5)	96 (41.7)	62 (43.7)	177 (42.4)	
Current	1128 (23.0)	106 (14.6)	80 (15.5)	191 (11.5)		686 (44.1)	85 (37.0)	44 (31.0)	132 (31.7)	
Family history of hepatic disease	283 (5.8)	40 (5.5)	32 (6.2)	103 (6.2)	0.870	95 (6.1)	10 (4.3)	14 (9.9)	26 (6.2)	0.199
Mean (SD) ALT (Units/l)	19.4 (9.0)	19.2 (9.3)	19.7 (8.4)	19.2 (8.4)	0.737	22.7 (12.5)	21.6 (9.2)	23.5 (10.0)	21.8 (11.0)	0.264
Mean (SD) AST (Units/l)	20.0 (7.3)	20.0 (6.7)	21.3 (6.7)	20.4 (6.0)	< 0.001	23.0 (9.3)	22.8 (7.0)	23.6 (8.2)	22.9 (8.1)	0.819
Mean (SD) GGT (Units/l)	27.5 (24.2)	28.0 (37.2)	29.5 (29.9)	26.7 (22.9)	0.172	60.8 (71.2)	54.9 (40.3)	63.1 (59.3)	52.8 (48.6)	0.084
Hypertension†	412 (8.4)	52 (7.1)	79 (15.3)	248 (14.9)	< 0.001	257 (16.5)	45 (19.6)	39 (27.5)	116 (27.8)	< 0.001
Diabetes‡	115 (2.3)	24 (3.3)	28 (5.4)	92 (5.5)	< 0.001	65 (4.2)	15 (6.5)	13 (9.2)	39 (9.4)	< 0.001
Dyslipidemia¶	936 (19.1)	158 (21.7)	134 (26.0)	411 (24.8)	< 0.001	309 (19.9)	55 (23.9)	34 (23.9)	109 (26.1)	0.030
Meat intake					< 0.001					0.105
Never or seldom	1895 (38.7)	289 (39.7)	241 (46.7)	756 (45.6)		626 (40.3)	86 (37.4)	65 (45.8)	196 (47.0)	
Once per 2 days	1613 (32.9)	238 (32.7)	169 (32.8)	484 (29.2)		492 (31.7)	77 (33.5)	46 (32.4)	124 (29.7)	
Once a day or more	1392 (28.4)	201 (27.6)	106 (20.5)	419 (25.3)		436 (28.1)	67 (29.1)	31 (21.8)	97 (23.3)	
Vegetable intake					< 0.001					< 0.001
Never or seldom	1156 (23.6)	103 (14.1)	82 (15.9)	190 (11.5)		477 (30.7)	53 (23.0)	34 (23.9)	71 (17.0)	
Once per 2 days	1124 (22.9)	147 (20.2)	89 (17.2)	228 (13.7)		395 (25.4)	56 (24.3)	32 (22.5)	76 (18.2)	
Once a day or more	2620 (53.5)	478 (65.7)	345 (66.9)	1241 (74.8)		682 (43.9)	121 (52.6)	76 (53.5)	270 (64.7)	
Moderate-intensity PA					< 0.001					0.088
<1x/wk	4122 (84.1)	646 (88.7)	455 (88.2)	1476 (89.0)		1307 (84.1)	203 (88.3)	123 (86.6)	369 (88.5)	
1x/wk	325 (6.6)	44 (6.0)	28 (5.4)	81 (4.9)		104 (6.7)	16 (7.0)	11 (7.7)	23 (5.5)	
2x/wk	219 (4.5)	25 (3.4)	20 (3.9)	54 (3.3)		74 (4.8)	8 (3.5)	7 (4.9)	12 (2.9)	
≥3x/wk	234 (4.8)	13 (1.8)	13 (2.5)	48 (2.9)		69 (4.4)	3 (1.3)	1 (0.7)	13 (3.1)	
Vigorous-intensity PA					< 0.001					< 0.001
<1x/wk	4299 (87.7)	655 (90.0)	460 (89.1)	1521 (91.7)		1336 (86.0)	201 (87.4)	130 (91.5)	388 (93.0)	
1x/wk	202 (4.1)	35 (4.8)	24 (4.7)	67 (4.0)		79 (5.1)	17 (7.4)	2 (1.4)	17 (4.1)	
2x/wk	181 (3.7)	20 (2.7)	16 (3.1)	37 (2.2)		60 (3.9)	6 (2.6)	6 (4.2)	5 (1.2)	
≥3x/wk	218 (4.4)	18 (2.5)	16 (3.1)	34 (2.0)		79 (5.1)	6 (2.6)	4 (2.8)	7 (1.7)	

Values are numbers (percentages) unless stated otherwise.

ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, GGT: gamma glutamyltransferase, PA: physical activity.

†Systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, diagnosis history or drug usage for hypertension.

‡Fasting plasma glucose ≥7.0 mmol/L, HbA1c ≥6.5%, diagnosis history or drug usage for diabetes.

¶Low-density lipoprotein-cholesterol ≥4.1 mmol/L, high-density lipoprotein-cholesterol ≤1.0 mmol/L, serum triglycerides ≥2.3 mmol/L, diagnosis history or drug usage for dyslipidemia.

Supplementary Table 1-b.

Baseline characteristics of participants by frequency of *moderate-intensity* physical activity

	Never-moderate alcohol drinkers (n=7803)					Heavy alcohol drinkers (n=2343)				
	Moderate-intensity physical activity (times/week)					Moderate-intensity physical activity (times/week)				
Baseline variables	<1x	1x	2x	≥3x	*P* value	<1x	1x	2x	≥3x	*P* value
No. of participants	6699	478	318	308		2002	154	101	86	
Mean (SD) age (years)	47.4 (10.8)	48.3 (11.0)	50.1 (10.9)	52.5 (11.7)	< 0.001	48.7 (9.8)	49.1 (8.8)	52.1 (9.1)	53.9 (10.6)	< 0.001
Male Gender	2658 (39.7)	172 (36.0)	129 (40.6)	121 (39.3)	0.437	1580 (78.9)	129 (83.8)	83 (82.2)	72 (83.7)	0.318
Mean (SD) BMI (kg/m^2)	21.6 (2.6)	21.5 (2.4)	21.8 (2.5)	21.7 (2.4)	0.436	22.5 (2.5)	22.8 (2.3)	22.7 (2.1)	22.6 (2.3)	0.425
Daily alcohol consumption										
Never	1231 (18.4)	62 (13.0)	57 (17.9)	66 (21.4)	0.011	–	–	–	–	
Low-moderate (<23.0 g)	5468 (81.6)	416 (87.0)	261 (82.1)	242 (78.6)		–	–	–	–	
Heavy (23.0–45.9 g)	–	–	–	–		1525 (76.2)	111 (72.1)	72 (71.3)	67 (77.9)	0.451
Very heavy (≥46.0 g)	–	–	–	–		477 (23.8)	43 (27.9)	29 (28.7)	19 (22.1)	
Smoking status					< 0.001					< 0.001
Never	3997 (59.7)	329 (68.8)	207 (65.1)	198 (64.3)		483 (24.1)	35 (22.7)	27 (26.7)	27 (31.4)	
Former	1319 (19.7)	105 (22.0)	72 (22.6)	71 (23.1)		669 (33.4)	62 (40.3)	48 (47.5)	45 (52.3)	
Current	1383 (20.6)	44 (9.2)	39 (12.3)	39 (12.7)		850 (42.5)	57 (37.0)	26 (25.7)	14 (16.3)	
Family history of hepatic disease	381 (5.7)	40 (8.4)	18 (5.7)	19 (6.2)	0.118	123 (6.1)	8 (5.2)	7 (6.9)	7 (8.1)	0.819
Mean (SD) ALT (Units/l)	19.4 (9.1)	18.8 (8.0)	19.3 (7.0)	18.4 (7.3)	0.117	22.3 (11.7)	23.9 (12.6)	22.8 (13.0)	22.7 (12.0)	0.419
Mean (SD) AST (Units/l)	20.1 (7.1)	19.9 (6.5)	20.8 (5.2)	20.8 (7.7)	0.105	22.8 (8.7)	24.0 (9.0)	24.1 (11.9)	22.9 (7.8)	0.221
Mean (SD) GGT (Units/l)	27.7 (26.8)	25.0 (17.3)	26.9 (19.7)	26.3 (18.9)	0.109	59.0 (64.4)	59.0 (64.9)	56.0 (56.0)	60.7 (75.4)	0.963
Hypertension†	666 (9.9)	47 (9.8)	33 (10.4)	45 14.6	0.068	376 (18.8)	31 (20.1)	25 (24.8)	25 (29.1)	0.058
Diabetes‡	216 (3.2)	12 (2.5)	8 (2.5)	23 7.5	< 0.001	111 (5.5)	10 (6.5)	6 (5.9)	5 (5.8)	0.966
Dyslipidemia¶	1411 (21.1)	97 (20.3)	67 (21.1)	64 20.8	0.982	437 (21.8)	38 (24.7)	16 (15.8)	16 (18.6)	0.341
Meat intake					0.732					0.686
Never or seldom	2748 (41.0)	186 (38.9)	118 (37.1)	129 41.9		828 (41.4)	59 (38.3)	44 (43.6)	42 (48.8)	
Once per 2 days	2140 (31.9)	164 (34.3)	105 (33.0)	95 30.8		633 (31.6)	55 (35.7)	28 (27.7)	23 (26.7)	
Once a day or more	1811 (27.0)	128 (26.8)	95 (29.9)	84 27.3		541 (27.0)	40 (26.0)	29 (28.7)	21 (24.4)	
Vegetable intake					< 0.001					0.231
Never or seldom	1368 (20.4)	69 (14.4)	49 (15.4)	45 14.6		561 (28.0)	31 (20.1)	26 (25.7)	17 (19.8)	
Once per 2 days	1374 (20.5)	105 (22.0)	47 (14.8)	62 20.1		477 (23.8)	37 (24.0)	25 (24.8)	20 (23.3)	
Once a day or more	3957 (59.1)	304 (63.6)	222 (69.8)	201 65.3		964 (48.2)	86 (55.8)	50 (49.5)	49 (57.0)	
Low-intensity PA					< 0.001					0.088
<1x/wk	4122 (61.5)	325 (68.0)	219 (68.9)	234 (76.0)		1307 (65.3)	104 (67.5)	74 (73.3)	69 (80.2)	
1x/wk	646 (9.6)	44 (9.2)	25 (7.9)	13 (4.2)		203 (10.1)	16 (10.4)	8 (7.9)	3 (3.5)	
2x/wk	455 (6.8)	28 (5.9)	20 (6.3)	13 (4.2)		123 (6.1)	11 (7.1)	7 (6.9)	1 (1.2)	
≥3x/wk	1476 (22.0)	81 (16.9)	54 (17.0)	48 (15.6)		369 (18.4)	23 (14.9)	12 (11.9)	13 (15.1)	
Vigorous-intensity PA					< 0.001					< 0.001
<1x/wk	6010 (89.7)	400 (83.7)	267 (84.0)	258 (83.8)		1765 (88.2)	126 (81.8)	91 (90.1)	73 (84.9)	
1x/wk	256 (3.8)	46 (9.6)	13 (4.1)	13 (4.2)		89 (4.4)	19 (12.3)	4 (4.0)	3 (3.5)	
2x/wk	206 (3.1)	20 (4.2)	17 (5.3)	11 (3.6)		65 (3.2)	7 (4.5)	4 (4.0)	1 (1.2)	
≥3x/wk	227 (3.4)	12 (2.5)	21 (6.6)	26 (8.4)		83 (4.1)	2 (1.3)	2 (2.0)	9 (10.5)	

Values are numbers (percentages) unless stated otherwise.

ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, GGT: gamma glutamyltransferase, PA: physical activity.

†Systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, diagnosis history or drug usage for hypertension.

‡Fasting plasma glucose ≥7.0 mmol/L, HbA1c ≥6.5%, diagnosis history or drug usage for diabetes.

¶Low-density lipoprotein-cholesterol ≥4.1 mmol/L, high-density lipoprotein-cholesterol ≤1.0 mmol/L, serum triglycerides ≥2.3 mmol/L, diagnosis history or drug usage for dyslipidemia.

Supplementary Table 1-c.

Baseline characteristics of participants by frequency of *vigorous-intensity* physical activity

	Never-moderate alcohol drinkers (n=7803)					Heavy alcohol drinkers (n=2343)				
	Vigorous-intensity physical activity (times/week)					Vigorous-intensity physical activity (times/week)				
Baseline variables	<1x	1x	2x	≥3x	*P* value	<1x	1x	2x	≥3x	*P* value
No. of participants	6935	328	254	286		2055	115	77	96	
Mean (SD) age (years)	47.7 (10.9)	46.4 (10.3)	48.8 (11.3)	49.4 (11.0)	0.004	49.2 (9.8)	47.4 (9.8)	48.0 (10.1)	50.0 (10.6)	0.159
Male Gender	2724 (39.3)	134 (40.9)	98 (38.6)	124 (43.4)	0.520	1632 (79.4)	91 (79.1)	61 (79.2)	80 (83.3)	0.829
Mean (SD) BMI (kg/m^2)	21.6 (2.6)	21.8 (2.4)	21.6 (2.2)	21.8 (2.6)	0.215	22.5 (2.5)	22.9 (2.4)	22.6 (2.3)	22.9 (2.0)	0.142
Daily alcohol consumption										
Never	1278 (18.4)	39 (11.9)	46 (18.1)	53 (18.5)	0.029	–	–	–	–	
Low-moderate (<23.0 g)	5657 (81.6)	289 (88.1)	208 (81.9)	233 (81.5)		–	–	–	–	
Heavy (23.0–45.9 g)	–	–	–	–		1575 (76.6)	81 (70.4)	50 (64.9)	69 (71.9)	0.039
Very heavy (≥46.0 g)	–	–	–	–		480 (23.4)	34 (29.6)	27 (35.1)	27 (28.1)	
Smoking status					< 0.001					< 0.001
Never	4192 (60.4)	208 (63.4)	159 (62.6)	172 (60.1)		492 (23.9)	30 (26.1)	17 (22.1)	33 (34.4)	
Former	1355 (19.5)	84 (25.6)	53 (20.9)	75 (26.2)		691 (33.6)	48 (41.7)	39 (50.6)	46 (47.9)	
Current	1388 (20.0)	36 (11.0)	42 (16.5)	39 (13.6)		872 (42.4)	37 (32.2)	21 (27.3)	17 (17.7)	
Family history of hepatic disease	414 (6.0)	8 (2.4)	20 (7.9)	16 (5.6)	0.029	121 (5.9)	9 (7.8)	8 (10.4)	7 (7.3)	0.335
Mean (SD) ALT (Units/l)	19.3 (9.0)	19.0 (8.0)	19.6 (8.1)	20.4 (7.7)	0.175	22.5 (11.7)	22.0 (9.1)	22.5 (8.8)	22.3 (17.9)	0.981
Mean (SD) AST (Units/l)	20.0 (7.0)	20.3 (7.1)	21.0 (6.8)	22.6 (7.1)	< 0.001	22.9 (8.9)	23.4 (7.9)	23.4 (6.8)	23.9 (9.8)	0.589
Mean (SD) GGT (Units/l)	27.5 (26.0)	26.9 (20.2)	28.3 (24.3)	28.0 (27.2)	0.912	59.8 (66.3)	53.9 (55.4)	55.9 (48.1)	49.2 (44.8)	0.330
Hypertension†	710 (10.2)	22 (6.7)	35 (13.8)	24 8.4	0.030	423 (20.6)	12 (10.4)	8 (10.4)	14 (14.6)	0.004
Diabetes‡	233 (3.4)	7 (2.1)	7 (2.8)	12 4.2	0.492	115 (5.6)	5 (4.3)	4 (5.2)	8 (8.3)	0.635
Dyslipidemia¶	1474 (21.3)	59 (18.0)	50 (19.7)	56 19.6	0.444	456 (22.2)	21 (18.3)	20 (26.0)	10 (10.4)	0.028
Meat intake					0.070					< 0.001
Never or seldom	2827 (40.8)	119 (36.3)	98 (38.6)	137 47.9		874 (42.5)	29 (25.2)	33 (42.9)	37 (38.5)	
Once per 2 days	2220 (32.0)	108 (32.9)	87 (34.3)	89 31.1		653 (31.8)	33 (28.7)	23 (29.9)	30 (31.3)	
Once a day or more	1888 (27.2)	101 (30.8)	69 (27.2)	60 21.0		528 (25.7)	53 (46.1)	21 (27.3)	29 (30.2)	
Vegetable intake					< 0.001					< 0.001
Never or seldom	1399 (20.2)	59 (18.0)	33 (13.0)	40 14.0		588 (28.6)	17 (14.8)	17 (22.1)	13 (13.5)	
Once per 2 days	1420 (20.5)	68 (20.7)	56 (22.0)	44 15.4		498 (24.2)	27 (23.5)	14 (18.2)	20 (20.8)	
Once a day or more	4116 (59.4)	201 (61.3)	165 (65.0)	202 70.6		969 (47.2)	71 (61.7)	46 (59.7)	63 (65.6)	
Low-intensity PA					< 0.001					< 0.001
<1x/wk	4299 (62.0)	202 (61.6)	181 (71.3)	218 (76.2)		1336 (65.0)	79 (68.7)	60 (77.9)	79 (82.3)	
1x/wk	655 (9.4)	35 (10.7)	20 (7.9)	18 (6.3)		201 (9.8)	17 (14.8)	6 (7.8)	6 (6.3)	
2x/wk	460 (6.6)	24 (7.3)	16 (6.3)	16 (5.6)		130 (6.3)	2 (1.7)	6 (7.8)	4 (4.2)	
≥3x/wk	1521 (21.9)	67 (20.4)	37 (14.6)	34 (11.9)		388 (18.9)	17 (14.8)	5 (6.5)	7 (7.3)	
Moderate-intensity PA					< 0.001					< 0.001
<1x/wk	6010 (86.7)	256 (78.0)	206 (81.1)	227 (79.4)		1765 (85.9)	89 (77.4)	65 (84.4)	83 (86.5)	
1x/wk	400 (5.8)	46 (14.0)	20 (7.9)	12 (4.2)		126 (6.1)	19 (16.5)	7 (9.1)	2 (2.1)	
2x/wk	267 (3.9)	13 (4.0)	17 (6.7)	21 (7.3)		91 (4.4)	4 (3.5)	4 (5.2)	2 (2.1)	
≥3x/wk	258 (3.7)	13 (4.0)	11 (4.3)	26 (9.1)		73 (3.6)	3 (2.6)	1 (1.3)	9 (9.4)	

Values are numbers (percentages) unless stated otherwise.

ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, GGT: gamma glutamyltransferase, PA: physical activity.

†Systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, diagnosis history or drug usage for hypertension.

‡Fasting plasma glucose ≥7.0 mmol/L, HbA1c ≥6.5%, diagnosis history or drug usage for diabetes.

¶Low-density lipoprotein-cholesterol ≥4.1 mmol/L, high-density lipoprotein-cholesterol ≤1.0 mmol/L, serum triglycerides ≥2.3 mmol/L, diagnosis history or drug usage for dyslipidemia.

Supplementary Table 2. Hazard ratios of incident fatty liver according physical activity and other variables in never-moderate and heavy alcohol drinkers

	Never-moderate alcohol drinkers (n=7803)		Heavy alcohol drinkers (n=2343)	
	HR	95% CI	HR	95% CI
Age (years)	**1.015**	**(1.009 – 1.021)**	1.009	(0.997 – 1.020)
Gender				
Male	1.000		1.000	
Female	**0.580**	**(0.507 – 0.662)**	**0.598**	**(0.436 – 0.821)**
Body mass index (kg/m^2)	**1.360**	**(1.334 – 1.386)**	**1.306**	**(1.260 – 1.354)**
Daily alcohol consumption				
Never	1.000		–	
Low-moderate (<23.0 g)	**0.852**	**(0.736 – 0.987)**	–	
Heavy (23.0–45.9 g)	–		1.000	
Very heavy (≥46.0 g)	–		0.890	(0.722 – 1.099)
Smoking status				
Never	1.000		1.000	
Former	0.931	(0.802 – 1.081)	1.116	(0.866 – 1.439)
Current	**1.173**	**(1.012 – 1.361)**	**1.382**	**(1.081 – 1.768)**
Family history of liver disease				
No	1.000		1.000	
Yes	1.151	(0.915 – 1.447)	1.176	(0.828 – 1.671)
ALT (units/L)	**1.011**	**(1.003 – 1.018)**	1.008	(1.000 – 1.016)
AST (units/L)	1.000	(0.990 – 1.009)	1.004	(0.991 – 1.017)
GGT (units/L)	1.001	(1.000 – 1.003)	**1.001**	**(1.000 – 1.002)**
Hypertension				
No	1.000		1.000	
Yes	1.087	(0.927 – 1.274)	0.992	(0.794 – 1.238)
Diabetes				
No	1.000		1.000	
Yes	1.243	(0.975 – 1.585)	1.098	(0.793 – 1.520)
Dyslipidemia				
No	1.000		1.000	
Yes	**1.251**	**(1.108 – 1.413)**	**1.299**	**(1.072 – 1.575)**
Meat intake				
Never or seldom	1.000		1.000	
Once per 2 days	**0.852**	**(0.743 – 0.977)**	0.958	(0.773 – 1.187)
Once a day or more	0.959	(0.828 – 1.110)	0.842	(0.663 – 1.070)
Vegetable intake				
Never or seldom	1.000		1.000	
Once per 2 days	0.929	(0.786 – 1.097)	0.955	(0.745 – 1.225)
Once a day or more	**0.829**	**(0.717 – 0.959)**	1.042	(0.832 – 1.304)
Low-intensity physical activity				
<1x/wk	1.000		1.000	
1x/wk	0.911	(0.743 – 1.117)	0.979	(0.717 – 1.337)
2x/wk	0.963	(0.770 – 1.205)	0.960	(0.669 – 1.379)
≥3x/wk	**0.821**	**(0.707 – 0.954)**	1.181	(0.929 – 1.502)
Moderate-intensity physical activity				
<1x/wk	1.000		1.000	
1x/wk	0.872	(0.680 – 1.119)	0.815	(0.561 – 1.184)
2x/wk	0.733	(0.536 – 1.002)	1.159	(0.780 – 1.723)
≥3x/wk	**0.559**	**(0.388 – 0.806)**	1.126	(0.715 – 1.774)
Vigorous-intensity physical activity				
<1x/wk	1.000		1.000	
1x/wk	0.852	(0.636 – 1.140)	0.866	(0.565 – 1.329)
2x/wk	**0.569**	**(0.379 – 0.854)**	1.322	(0.846 – 2.066)
≥3x/wk	**0.547**	**(0.380 – 0.789)**	0.766	(0.474 – 1.238)

Bold numbers indicate $P<0.05$.

ALT: alanine aminotransferase, AST: aspartate aminotransferase, GGT: gamma glutamyltransferase.

All variables were entered simultaneously for both never-moderate and heavy alcohol drinkers.

Supplementary Table 3. Propensity-adjusted hazard ratios of incident fatty liver according to physical activity in never-moderate and heavy alcohol drinkers

	Never-moderate alcohol drinkers		Heavy alcohol drinkers	
	Hazard ratio (95% CI)		Hazard ratio (95% CI)	
	<1x/wk vs. ≥3x/wk		<1x/wk vs. ≥3x/wk	
Low-intensity physical activity				
Adjusted for propensity	0.89	(0.77 – 1.03)	1.11	(0.88 – 1.41)
Adjusted for propensity and selected covariates†	**0.82**	**(0.71 – 0.96)**	1.14	(0.89 – 1.46)
Adjusted for propensity and all covariates	**0.82**	**(0.70 – 0.95)**	1.15	(0.90 – 1.47)
Moderate-intensity physical activity				
Adjusted for propensity	**0.55**	**(0.38 – 0.80)**	1.16	(0.74 – 1.82)
Adjusted for propensity and selected covariates†	**0.56**	**(0.39 – 0.81)**	1.09	(0.69 – 1.72)
Adjusted for propensity and all covariates	**0.57**	**(0.39 – 0.82)**	1.07	(0.67 – 1.69)
Vigorous-intensity physical activity				
Adjusted for propensity	**0.58**	**(0.40 – 0.83)**	0.83	(0.51 – 1.33)
Adjusted for propensity and selected covariates†	**0.56**	**(0.39 – 0.80)**	0.80	(0.49 – 1.29)
Adjusted for propensity and all covariates	**0.55**	**(0.38 – 0.79)**	0.74	(0.45 – 1.22)

Bold numbers indicate $P<0.05$.

†Adjusted for significant predictors on incident fatty liver (see Supplementary Table 2).

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Reported on manuscript page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1–2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5–8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5–8
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6–8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8–9
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	5, Figure 1
		(*d*) If applicable, explain how loss to follow-up was addressed	5, Figure 1
		(*e*) Describe any sensitivity analyses	9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5, Figure 1
		(b) Give reasons for non-participation at each stage	5, Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9, Table 1, Supplementary Table 1a–c
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9, Table 2–3
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders	9–10, Table 2–3

		were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	6–8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8–10, Supplementary Table 3
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12–13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10–13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Correction

Tsunoda K, Kai Y, Uchida K, *et al*. Physical activity and risk of fatty liver in people with different levels of alcohol consumption: a prospective cohort study. *BMJ Open* 2014;4: e005824. There are three corrections in this paper. These corrections do not change any results or conclusions of the paper.

1. Throughout the paper, the frequencies of physical activity, '>2x/week' and '>3x/week', should be corrected to '≥2x/week' and '≥3x/week', respectively.
2. In Table 2, the entry on the line for Model 1 of Moderate-intensity physical activity in the 2x column (0.74 (0.54 to 1.01)) should not be italicised.
3. Table 2 lists aspartate aminotransferase as an adjustment variable. However, as mentioned in the statistical methods, the correct hazard models do not include aspartate aminotransferase, so it should be removed from the table's adjustment variables.

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