Effect of exercise on the development of new fatty liver and the resolution of existing fatty liver

Development of new fatty liver, or resolution of existing fatty liver, over 5 years of follow up: effect of exercise

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Type of Manuscript: Clinical research study

Running title: Change in fatty liver status and exercise

Keywords: non alcoholic fatty liver disease, exercise, type 2 diabetes, obesity, insulin resistance, metabolic syndrome

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All authors declare that:

1) the paper is not under consideration elsewhere;

2) none of the paper's contents have been previously published;

3) all authors have read and approved the manuscript;

4) the full disclosure of any relationship with industry;

5) All authors have no relevant conflicts of interest.

Financial support: No

Author's contribution:

K.S contributed to the hypothesis, wrote methods and contributed to discussion. S.R analysed data, C.D.B. wrote introduction, results and discussion, J.K, S.H.W and J.L reviewed/edited the manuscript and contributed to discussion. K.S. is the guarantor for the article.

Abbreviations: International Physical Activity Questionnaire Short Form, IPAQ-SF; NAFLD, nonalcoholic fatty liver disease; NAFL, non alcoholic fatty liver; HDL-C, high density lipoprotein cholesterol, LDL-C, low density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; BMI, body mass index

Manuscript word count =5779/6000 (including Abstract, Tables and references)

The lay summary:

The amount of exercise/physical activity to benefit fatty liver disease in non alcoholic fatty liver disease (NAFLD) is not known. In a large study of free-living people, our aim was to determine the amount of exercise that was linked with a decrease in new fatty liver and also improvement of existing fatty liver over 5 years of follow up. Compared to no exercise, exercise ≥5 times per week (lasting at least 10 minutes on each occasion) was linked to a highly significantly benefit for both a decrease in new fatty liver and also improvement of existing fatty liver.

Abstract=246 words

Background & Aims Guidelines about recommendations for amounts of exercise/physical activity are variable in non alcoholic fatty liver disease (NAFLD). Our aim was to determine the amount of exercise that was associated with two outcomes: a) development of incident liver fat and b) resolution of baseline liver fat, at five year follow-up.

Methods In an occupational health screening program, weekly frequency of exercise was assessed using the validated Korean version of the International Physical Activity Questionnaire Short Form (IPAQ-SF). Liver fat was identified by ultrasonography (3.5MHz probe) at baseline and at five year follow up. Fully adjusted Cox proportional hazards models were used to estimate hazard ratios (HRs and 95% confidence intervals) for incident fatty liver and resolution of fatty liver at follow up.

Results 233,676 men and women were studied between 2002 and 2014. 126,811 individuals were identified without fatty liver, and of these subjects, 29014 subjects developed incident fatty liver during follow up. At baseline, there were 42,536 individuals with liver fat and of these individuals, fatty liver resolved in 14,514, during follow up. After full adjustment, compared to no exercise, exercise was associated with benefit for both outcomes; for exercise ≥5 times per week for incident fatty liver: HR 0.86 (95%CIs 0.80,0.92), $p<0.001$, and for resolution of fatty liver HR 1.40 (95%CIs 1.25,1.55), $p<0.001$.

Conclusions Moderate to vigorous exercise is beneficial in decreasing risk of development of new fatty liver or improving resolution of existing fatty liver during 5 years of follow up.

Introduction

It is now accepted that the clinical burden of non-alcoholic fatty liver disease (NAFLD) extends beyond liver-related morbidity and mortality, with the concept that NAFLD is a multisystem disease that also affects several extra-hepatic organs and regulatory pathways[1] [2]. Incidence rates for NAFLD are uncertain (because of difficulties with establishing a precise diagnosis during sequential follow-up) but current incidence rates are approximately 20/10,000 person-years, peaking in the sixth decade of life with NAFLD being more common in men [3]. NAFLD comprises a complex spectrum of disease that begins with liver fat accumulation (non alcoholic fatty liver or NAFL) and progress with inflammation and fibrosis (non alcoholic steatohepatitis or NASH). There is now a wealth of evidence that NAFLD increases risk of type 2 diabetes (summarised in [1, 4]) but there is limited evidence to date that treatment of NAFLD decreases risk of T2DM. We have shown previously that resolution of fatty liver (detected by ultrasound) over 5 years, was independently associated with marked attenuation of the risk of incident T2DM [5] and also incident hypertension [6], over five years of follow up. Recently our findings for attenuation of the risk of T2DM has been verified in a Japanese population (that also confirmed the resolution of liver fat by ultrasonography) [7]. In contrast to previous notions that NAFL did not cause serious chronic liver disease, increasing evidence is now showing that NAFL is not harmless. Recently it has been shown that NAFL is an important risk factor for the development of clinically relevant liver fibrosis[8-11] and consequently it is now being realized that it is important to understand what interventions and treatments are effective for decreasing liver fat[12] within the spectrum of liver disease in NAFLD.

In short duration studies, lifestyle changes that have focussed on diet and exercise modification have shown promise in decreasing liver fat as a manifestation of early disease in NAFLD [13-16]. However, guidelines from Specialist societies regarding recommendations for amounts and intensity of exercise/physical activity in NAFLD are variable. For example, the American Association for the Study of Liver Diseases (AASLD) Guideline does not make a specific recommendation about the amount or the desired intensity of exercise in NAFLD and states that 'exercise alone in adults (with NAFLD) may reduce hepatic steatosis, but its ability to improve other aspects of liver histology are unknown[17]. The European Association for the Study of the Liver (EASL) recommends that in NAFLD guidelines for patients with type 2 diabetes are followed and recommends 150 minutes per week of moderate intensity exercise[18] and this recommendation is largely in keeping with guidelines for the general population[19]. Thus, at present it is unclear how much exercise is needed or how intense that exercise should be to prevent development of new fatty liver or to resolve existing fatty liver. We have utilized a retrospective study design of an occupational cohort in which there were measurements of exercise/physical activity at baseline and at follow up (as key exposures) with measurements of fatty liver assessed by ultrasonography at baseline and at follow up (as the key outcomes) to assess relationships between exercise and change in fatty liver status over time. Although ultrasonography has limited sensitivity to detect liver fat in NAFLD, liver ultrasonography is a good technique to assess whether liver fat is present, providing liver fat accumulation is approximately 30% [20, 21]. Since it remains uncertain how much exercise is needed, or for how long that exercise is needed, (to treat liver fat and to decrease risk of developing new liver fat), we have studied relationships between numbers of weekly exercise sessions at baseline and change in numbers of

weekly exercise sessions between baseline and follow up, with both incident fatty liver at follow up and resolution of baseline fatty liver at follow up. Specifically, our aim was to determine the amount of baseline exercise that was associated with: a) decreased development of incident liver fat and b) resolution of baseline liver fat (as the outcomes of interest), at five year follow up. Additionally, we aimed to assess whether any increase in the number of exercise sessions between baseline and follow up was associated with these fatty liver-related outcomes at five year follow up after adjusting for key confounders that also included change in body mass index (BMI) between baseline and follow up.

Methods

Study population

The Kangbuk Samsung Health Study is a cohort study of South Korean men and women 18 years of age or older who underwent a comprehensive annual or biennial health examination at the clinics of the Kangbuk Samsung Hospital Total Healthcare Center in Seoul and Suwon, South Korea. More than 80% of participants were employees of various companies and local governmental organizations and their spouses. In South Korea, the Industrial Safety and Health Law requires annual or biennial health screening examinations of all employees, offered free of charge. The remaining participants were subjects voluntarily taking part in the screening examinations. The study population consisted of individuals who participated in a comprehensive health screening program, at least twice, at Kangbuk Samsung Hospital, Seoul, Korea from 2002 to 2014 (n = 233,676). Among these subjects, to test relationships between exercise and incident fatty liver, and exercise and resolution of existing fatty liver, we excluded subjects in which there was missing data for smoking, exercise, fatty liver and cancer (n=19,613). Subjects were also excluded if they were HbsAg positive (n=9,297), HCV Ab positive (n=307), and daily alcohol consumption was more than 20g (men) and 10g (women) (n=38,296). Also for testing relationships with incident fatty liver at follow up subjects with baseline fatty liver (n=60,522) were excluded. Thus 126,811 subjects were included in this analysis and their mean±SD follow up period was 4.95±3.29) years. Relationships between exercise and resolution of fatty liver were examined in 42,536 individuals and subjects were included who had fatty liver at baseline. Mean±SD follow up was 4.29 (3.26) years. The study was approved by the Institutional Review Board of Kangbuk Samsung Hospital and any requirement for informed consent was waived

by the Board, because de-identified information was retrieved retrospectively.

Measurements

As part of the health screening program, individuals completed self-administered questionnaires, related to their medical and social history and medication use. Individuals were asked about duration of education (years), smoking history (never, former, or current) and alcohol consumption (grams, g/week). We assessed the weekly frequency of moderate- or vigorous-intensity physical activity which was assessed using the validated Korean version of the International Physical Activity Questionnaire Short Form (IPAQ-SF)[22]. The IPAQ-SF measures the frequency and duration of moderate to vigorous physical activity undertaken for more than 10 continuous minutes across all usual activities at work, home or during leisure for middle aged individuals during a seven-day period. To assess the number of exercise sessions undertaken per week by each participant, the following specific questions were asked to gauge the number of times per week a participant engaged in exercise. "How many days did you undertake physical activity (enough to perspire)?" or “during the last seven days, on how many days did you do moderate intensity physical activity e.g. carrying light loads, bicycling at a steady pace, or playing tennis? Do not include walking in your response” If the answer was greater than zero, additional questions were asked such as “How much time did you usually spend doing moderate or vigorous physical activities on one of those days?” In our study, subjects were classified into four categories for analysis of exercise as the exposure with the outcomes of interest. No regular physical activity, exercise 1-2 times per week, exercise 3-4 times per week and exercise ≥5 times per week. Additionally we defined change in exercise between baseline and follow up, according to a decrease, no change, or an increase in the number of weekly

exercise sessions per week.

Trained staff also collected anthropometric measurements and vital statistics. Body weight was measured in light clothing with no shoes to the nearest 0.1 kilogram using a digital scale. Height was measured to the nearest 0.1 centimeter. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Blood samples were collected after at least 10-hours of fasting and analyzed in the same core clinical laboratory. The core clinical laboratory has been accredited and participates annually in inspections and surveys by the Korean Association of Quality Assurance for Clinical Laboratories.

Abdominal ultrasonography (Logic Q700 MR; GE, Milwaukee, WI, USA) was undertaken by clinical radiologists using a 3.5MHz probe for all subjects at baseline and after five years. The following images were undertaken; i) sagittal view of the right lobe of the liver and right kidney, ii) transverse view of the left lateral segment of the liver and spleen and iii) transverse view of the liver for altered echo texture. Fatty infiltration of the liver (fatty liver) was identified if there was an increase in echogenicity of the liver compared with the echogenicity of the renal cortex where the diaphragm and intrahepatic vessels appeared normal[21]

Statistical analyses

The statistical analysis was performed using STATA version 11.2 (StataCorp LP, College Station, TX, USA). Reported P values were two-tailed, and <0.05 were considered statistically significant. The distribution of continuous variables was evaluated and transformations were conducted for nonparametric variables. Cox proportional hazards models were used to estimate hazard ratios (HRs and 95% confidence intervals) for incident fatty liver and resolution of fatty liver. For testing

linear risk trends across exercise groups in the regression models, we used the categories rank as a continuous variable. For each outcome, three regression models were generated. Model 1: adjustment for age, sex, center, year of screening exam, smoking status, alcohol intake, education level; model 2: model 1 adjustments plus adjustment for BMI, diabetes, hypertension (HTN), history of CVD ; model 3 model 2+ BMI change. To test the effect of exercise change to the outcome we included adjustment for baseline exercise in model 3.

Results

233,676 men and women were studied between 2002 and 2014. 128,811 individuals were identified without fatty liver, and of these subjects, 97,797 remained free from fatty liver at follow up, whereas 29,014 subjects (22.5%) developed incident fatty liver during follow up. The baseline characteristics of the cohort according to the development of incident fatty liver at follow up are shown in **Table 1.** All traditional cardiovascular and metabolic risk factors were adversely affected in individuals who developed incident fatty liver at follow up examination, compared with subjects remaining free from fatty liver at follow up.

Table 2 shows the baseline characteristics of the subjects according to four exercise groups (0, 1-2, 3-4 and ≥5 times per week). BMI was 0.9 kg/m^2 higher in subjects exercising ≥5 times per week, compared with BMI in subjects who did not exercise. Also, in subjects exercising ≥5 times per week, mean ±SD systolic blood pressure was higher 113.4(14.0) mmHg compared with systolic blood pressure 109.6(12.6) mmHg in the subjects who did not exercise. Importantly there was no significant differences in change in BMI between baseline and follow up examination for the four different exercise groups. Surprisingly there was a slightly higher proportion of people with diabetes, hypertension and existing CVD in the highest exercise group.

Table 3 shows the risk of incident fatty liver at follow up. After adjustment for all covariates and potential confounders (i.e. age, sex, center, year of screening exam, smoking status, alcohol intake, education level, BMI, diabetes, hypertension, CVD, and BMI change (between baseline and follow up)); compared with no exercise, any exercise was associated with benefit and reduced risk of development of incident fatty liver at follow up (E.g. for exercise ≥5 times per week for incident fatty liver: HR 0.86 (95%CIs 0.8,0.92), p<0.001).

In clinically relevant sub groups the associations between exercise and incident fatty liver at follow up were investigated. **Supplementary Table 1** shows the HRs for risk of incident fatty liver, in the four exercise groups (0, 1-2, 3-4 and ≥5 times per week) with no exercise as the reference group. Very similar results were noted regardless of subgroup and there were no significant sub-group by exercise group interactions. Since we showed there was a clear association between baseline exercise and development of incident fatty liver at follow up, even after adjusting for change in BMI between baseline and follow up, we investigated whether change in exercise (between baseline and follow up) was associated with development of incident fatty liver at follow up. Three exposure groups were generated according to whether there had been: a) a decrease in number of exercise sessions per week which was the reference group; b) no change in numbers of exercise sessions per week between baseline and end of study; and c) an increase in the number of exercise sessions per week between baseline and follow up. **Table 4** shows associations between change in exercise and incident fatty liver at follow up. In the fully adjusted regression model that also included adjustment for change in BMI between baseline and end of study, in subjects in whom there was an increase in number of exercise sessions between baseline and follow up, there was a decreased risk of incident fatty liver at follow up [(HR 0.87, (95%CIs 0.82.0.93), p<0.001].

At baseline, there were 42,536 individuals with baseline liver fat and of these individuals, fatty liver resolved in 14,514 (34.1%), during follow up. The baseline characteristics of the cohort according to the resolution of fatty liver at follow up is shown in **Table 5.** Between baseline and follow up there was a 0.5 kg/m^2 decrease in BMI in subjects whom fat liver resolved between baseline and follow up examination,

compared with a 0.1 kg/m^2 increase in subjects in whom fatty liver was present at both baseline and follow up examination.

Table 6 shows the association between different amounts of exercise and resolution of fatty liver at follow up. (N.B. all individuals included in these analyses had fatty liver at baseline examination). After adjustment for all covariates and potential confounders age, sex, center, year of screening exam, smoking status, alcohol intake, education level, BMI, diabetes, hypertension, CVD, hs CRP and BMI change (between baseline and follow up); compared with no exercise, any exercise was associated with benefit and resolution of fatty liver at follow up . E.g. for exercise ≥5 times per week was associated with an increased HR for resolution of fatty liver at follow up HR 1.40 (95%CIs 1.25, 1.55), p<0.001.

In clinically relevant sub groups the associations between exercise and resolution of fatty liver at follow up was investigated. **Supplementary Table 2** shows the HRs for the associations between exercise and resolution of fatty liver, in the four exercise groups (0, 1-2, 3-4 and ≥5 times per week) with no exercise as the reference group. There were strong significant trends for the strength of the associations across exercise groups with resolution of fatty liver, with a stronger association between greater amounts of exercise and resolution of fatty liver. For both incident fatty liver (Supplementary Table 1) and resolution of existing fatty liver (Supplementary Table 2), there was an interaction between male sex and both incident fatty liver and resolution of existing fatty liver, (although it should be noted that for men and women in each of the three exercise groups, the 95%Cis around the point estimates of the HRs overlapped between the sexes).

Since we showed there was a clear association between baseline exercise and resolution of fatty liver at follow up, even after adjusting for change in BMI between baseline and follow up, we also investigated whether change in exercise (between baseline and follow up) was associated with resolution of fatty liver at follow up. As for the analyses examining associations between exercise and incident fatty liver, three exposure groups were generated according to whether there had been: a) a decrease in number of exercise sessions per week which was the reference group; b) no change in numbers of exercise sessions per week between baseline and end of study; and c) an increase in the number of exercise sessions per week between baseline and follow up. A decrease in exercise between baseline and end of study was the reference category. **Table 7** shows associations between change in exercise and resolution of fatty liver at follow up. In the fully adjusted model, and after adjusting for change in BMI between baseline and follow up, in subjects in whom there was an increase in number of exercise sessions between baseline and follow up, there was a significant association with resolution of fatty liver at follow up [HR 1.13, (95%CIs 1.03, 1.24), p=0.01].

Discussion

The novel results of our study are that any amount exercise is beneficial in either decreasing risk of development of new fatty liver, or in improving resolution of existing fatty liver, over 5 years of follow up. Additionally, and importantly, our data shows that over this period of follow up, any increase in the number of weekly exercise sessions was associated with both a decrease in risk of incident fatty liver and also in resolution of existing fatty liver. Given the accepted importance of losing weight to ameliorate liver fat in the treatment of overweight patients with NAFLD, we also adjusted for change in BMI between baseline and follow up. Our findings clearly showed that for both incident fatty liver and for resolution of existing fatty liver, relationships between exercise and fatty liver status were independent of any change in BMI during the follow up period. Furthermore, as can be seen from the regression models in Tables 3 and 6 (for incident fatty liver and resolution of fatty liver respectively), there were linear trends between increasing numbers of weekly exercise sessions and the outcomes of interest, with an increasing strength of association between exercise and fatty liver status, with increasing numbers of weekly exercise sessions.

Interestingly, for both incident fatty liver (Supplementary Table 1) and resolution of existing fatty liver (Supplementary Table 2), there was an interaction between male sex and both incident fatty liver and resolution of existing fatty liver. It is important to be cautious in interpreting this result. Furthermore, it should be noted that for men and for women in each of the three exercise groups, the 95%CIs around the point estimates of the HRs overlapped between the sexes. Additionally, for resolution of fatty liver, the n number for women (n=7,572) was much smaller than it was for men

(n=34,964). However, that said, we suggest more research is needed to test whether sex-exercise interactions exist to influence changes in fatty liver status over time.

The available evidence to date suggests a benefit of exercise to decrease fatty liver in NAFLD [13-16, 23], and the question of the optimum prescribed 'dose' of exercise for all liver diseases [14] and the effect of aerobic exercise on liver fat [24] have recently been examined. These analyses show that it remains uncertain as to what exercise should be advised and how intense (and for how long), that exercise needs to be, in order to influence liver fat. We have therefore investigated the potential benefit of exercise on development of incident liver fat and resolution of existing liver fat in NAFLD in free-living individuals, because most evidence to date is limited to short term clinical trials with a supervised intervention.

We acknowledge that a limitation of our study is that we do not have an objective assessment of exercise/physical activity in our cohort, our data show that any amount of exercise for >10 minutes per week is beneficial, compared with no exercise. Moreover, the validated Korean version of the International Physical Activity Questionnaire Short Form (IPAQ-SF)[22] measures not only the frequency, but also provides information about the relative intensity of the exercise. The questionnaire asks about the number of weekly exercise sessions where participants participate in moderate to vigorous physical activity undertaken for more than 10 continuous minutes either at work, home or during leisure. Thus, although we conclude from our data that any exercise is beneficial (to affect the specified NAFL outcomes), it is also possible to qualify this conclusion by stating that any moderate to vigorous physical activity lasting at least 10 mins per week is beneficial to affect

these liver fat outcomes. Self-reported measures of recalled physical activity levels are prone to overestimation of the recalled amount of exercise. However, it reassuring to note that we have observed linear trends between the amount of exercise and most cardiovascular and metabolic risk factors, with a suggested ‘dose-response’ effect indicating a more favorable cardio-metabolic profile in subjects reporting higher levels of exercise. We are not able to take account of an individual altering the number of their weekly exercise sessions and at the same time altering the intensity of this weekly exercise, during the follow up period.

Additionally, although there are better techniques than ultrasound such as magnetic resonance imaging for quantifying subtle changes in liver fat with exercise[25], it was not possible to use magnetic resonance techniques in this many subjects, and ultrasound can be used to assess whether liver fat is present or not if levels of liver fat are approximately 30%. Furthermore, imprecision in the measurement of both the exposure and the outcome, would possibly result in some misclassification of the exercise-related exposures and the liver-related outcomes . However, that said, it is important to recognize that resulting misclassification bias would attenuate the strengths of our findings and would bias the results towards the null. That we observe independent, consistent and graded associations between amounts of exercise and our liver fat outcomes of interest, provides confidence that these associations have not arisen by chance. We have also adjusted for key confounders and in particular change in BMI between baseline and follow up, and in this very large cohort there are no other obvious causes of bias that might have produced these results.

Studies that have shown a benefit of exercise to decrease liver fat have tended to be very short term interventions and have used very variable exercise regimes such as 2-3 sessions of exercise a week for 30-60 minutes of exercise[17]. Other interventional studies have tested and shown a benefit of short term resistance training in NAFLD[26] but it remains uncertain what amount and how intense the exercise or physical activity needs to be to both decrease existing liver fat and to decrease risk of development of new cases of non alcoholic fatty liver (NAFL). Based on the presented results, how might moderate to vigorous physical activity reduce the level of existing liver fat or alteratively decrease risk of liver fat developing in NAFLD, independently of weight loss? It is known from animal studies that chronic exercise decreases liver fat by reducing the activity of key enzymes in hepatic lipid synthesis such as acetyl CoA carboxylase (ACC) and fatty acid synthesis [27]. A reduction in activity of these enzymes would result in decreased triglyceride accumulation and a decrease in liver fat. It is also plausible that the more physically active subjects in our study had better cardiorespiratory fitness with better skeletal muscle and cardiac muscle fatty acid oxidation resulting in diminished substrate flux (of fatty acids) to the liver for hepatic triglyceride synthesis [28]. In support of a relationship between higher levels of physical activity and greater cardiorespiratory fitness in NAFLD, a 16 week supervised exercise program to intervene with modest exercise in middle aged patients with NAFLD, showed that not only did liver fat percentage decrease, but also V02 max was improved, by the modest limited duration exercise intervention of 16 weeks duration [23].

In conclusion, these data show that any amount moderate weekly exercise lasting at least 10 minutes was beneficial in either decreasing risk of development of new fatty

liver, or in improving resolution of existing fatty liver, over 5 years of follow up. During follow up, any increase in the number of weekly exercise sessions was associated with both a decrease in risk of incident fatty liver and resolution of existing fatty liver, and these associations were independent of any change in BMI during the period of follow up.

Acknowledgments.

We acknowledge the efforts of the health screening group at Kangbuk Samsung Hospital, Korea. CDB is supported in part by the Southampton National Institute for Health Research Biomedical Research Centre.

All authors have no relationships with industry.

Conflict of Interest. All authors have no conflicts of interest.

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Table 1. Baseline characteristics of the cohort according to incident fatty liver at follow up

	NO	FATTY LIVER	*P*
Baseline characteristics			
Number	97,797	29,014	
N (%) Men	40.1	70.2	
Age (years)	36.9(7.7)	37.5(7.5)	<0.001
BMI (kg/m^2)	21.8(2.5)	23.9(2.5)	<0.001
Systolic BP (mmHg)	109.9(12.8)	114.4(12.9)	<0.001
Diastolic BP (mmHg)	70.5(9.2)	74.1(9.5)	<0.001
Higher education (%)[a]	75.9	77.9	<0.001
Current smoker	17.0	31.3	<0.001
Alcohol intake (g/day)	3(0-6)	4(0-10)	<0.001
Obesity (%)[b]	10.0	30.2	<0.001
Insulin (IU/mL)	4.09(2.85-5.7)	5.12(3.61-7.07)	<0.001
Glucose (mg/dl)	91.0(10.2)	93.3(12.1)	<0.001
Total cholesterol (mg/dl)	185.7(32.0)	196.2(33.4)	<0.001
LDL-C (mg/dl)	105.8(27.3)	117.0(28.3)	<0.001
HDL-C (mg/dl	59.2(12.9)	53.0(11.2)	<0.001
Triglycerides (mg/dl)	80(61-109)	113(82-156)	<0.001
HOMA IR	1.50(1.08-1.98)	1.76(1.32-2.27)	<0.001
Hs-CRP (mg/L)	0.3(0.1-0.6)	0.5(0.2-1.0)	<0.001
Diabetes (%)	1.0	1.9	<0.001
Hypertension (%)	7.3	13.4	<0.001
Cardiovascular disease (%)	3.2	2.9	0.001
BMI change between baseline and follow up	0.1(1.0)	0.5(1.1)	<0.001

[a] ≥college graduate

[b] BMI≥ 25

Table 2. Baseline characteristics of study subjects according to the numbers of exercise sessions per week

Characteristics	Overall	Exercise sessions (per week)				*P* for trend
		0	1-2	3-4	≥5	
N=	126,811	73,313	33,877	13,816	5,805	
Age (years)	40.5(9.7)	36.1(7.1)	37.6(7.7)	39.3(8.4)	40.5(9.7)	<0.001
Men (%)	47.0	38.8	63.0	51.7	45.7	<0.001
BMI (kg/m^2)	22.2(2.6)	21.9(2.6)	22.7(2.5)	22.9(2.5)	22.8(2.5)	<0.001
Systolic BP (mmHg)	110.9(13.0)	109.6(12.6)	112.7(13.0)	112.9(13.5)	113.4(14.0)	<0.001
Diastolic BP (mmHg)	71.3(9.4)	70.3(9.2)	72.7(9.4)	72.8(9.6)	72.9(9.6)	<0.001
Higher education (%)	76.4	76.1	79.3	74.2	67.5	<0.001
Current smoker	20.3	17.7	25.5	19.5	22.9	<0.001
Alcohol intake g/day	3(0-6)	2(0-6)	3(0-9)	3(0-8)	3(0-6)	<0.001
Obesity (%)	14.7	11.9	18.0	19.4	18.7	<0.001
Insulin (IU/ml)	4.23(2.95-5.91)	4.3(2.99-6.01)	4.19(2.93-5.88)	4.08(2.83-5.61)	3.91(2.71-5.53)	<0.001
Glucose (mg/dl)	91.5(10.7)	90.9(9.7)	92.1(12.0)	92.2(11.5)	92.8(13.0)	<0.001
Total cholesterol (mg/dl)	188.1(32.7)	186.1(32.5)	190.(32.6)	191.3(32.7)	191.7(33.0)	<0.001
LDL-C (mg/dl)	108.4(28.0)	106.9(27.9)	110.8(27.9)	110.2(27.9)	109.0(28.0)	<0.001
HDL-C (mg/dl	57.8(12.8)	58.0(12.8)	56.6(12.4)	58.5(13.0)	60.4(13.8)	<0.001
Triglycerides (mg/dl)	86(64-120)	84(63-117)	92(68-128)	86(64-119)	80(60-112)	<0.001
HOMA IR	1.56(1.13-2.05)	1.56(1.13-2.06)	1.56(1.14-2.04)	1.55(1.15-2.03)	1.50(1.09-1.98)	0.038
Hs-CRP(mg/L)	0.3(0.1-0.7)	0.3(0.1-0.7)	0.4(0.1-0.8)	0.3(0.1-0.7)	0.3(0.1-0.7)	<0.001
Diabetes (%)	1.2	0.8	1.4	2.2	3.3	<0.001
Hypertension (%)	8.7	6.7	10.5	12.2	13.7	<0.001
Cardiovascular disease (%)	3.1	2.9	2.9	4.1	5.0	<0.001
BMI change between baseline and follow up	0.2(1.0)	0.2(1.1)	0.2(1.0)	0.2(1.0)	0.2(1.1)	0.272

Table 3. Risk of incident fatty liver according to baseline number of exercise sessions (per week)

Exercise sessions (per week)	Person-years	Number of events	incident (100,000 person-year)	Age-sex adjusted HR (95% CI)	Multivariate HR*(95% CI)		
					Model 1	Model 2	Model 3
	Incident fatty liver	Incident fatty liver	Incident fatty liver				
0	371,025.9	15,083	4,065.2	1.00(reference)	1.00(reference)	1.00(reference)	1.00(reference)
1-2	163,943.7	9,220	5,623.9	1.04(1.01-1.07)	1.04(1.00-1.07)	0.94(0.91-0.97)	0.93(0.90-0.96)
3-4	66,092.2	3,488	5,217.0	1.06(1.02-1.10)	1.07(1.02-1.12)	0.90(0.86-0.94)	0.87(0.83-0.91)
≥5	27,148.6	1,263	4,652.2	0.98(0.93-1.04)	1.03(0.96-1.11)	0.90(0.84-0.97)	0.86(0.80-0.92)
***P* for trend**				0.026	0.004	<0.001	<0.001

*Model 1: adjustment for age, sex, center, year of screening exam, smoking status, alcohol intake, education level;
*Model 2: model 1 adjustments plus adjustment for BMI, diabetes, HTN, CVD
*Model 3: model 2 adjustments plus adjustment for change in BMI between baseline and follow up

Table 4. Risk of incident fatty liver according to change in number of exercise sessions per week between baseline and follow up

Change in Exercise sessions (per week)	Person-years	Number of events	incident rate (100,000 person-year)	Age-sex adjusted HR (95% CI)	Multivariate HR*(95% CI)		
					Model 1	Model 2	Model 3
	Incident fatty liver	Incident fatty liver	Incident fatty liver				
Decrease	98,995.2	3,458	349.3	1.00(reference)	1.00(reference)	1.00(reference)	1.00(reference)
No change	284,527.8	8,291	2,914.0	0.89(0.85-0.92)	0.91(0.87-0.96)	0.93(0.89-0.98)	0.95(0.90-1.00)
Increase	120,597.5	3,582	2,970.2	0.89(0.85-0.93)	0.90(0.84-0.95)	0.84(0.79-0.89)	0.87(0.82-0.93)
***P* for trend**				<0.001	0.001	<0.001	<0.001

*Model 1: adjustment for age, sex, center, year of screening exam, smoking status, alcohol intake, education level and number of baseline exercise sessions.
*Model 2: model 1 adjustments plus adjustment for BMI, diabetes, hypertension, history of CVD
*Model 3: model 2 adjustments plus adjustment for change in BMI between baseline and follow up.

Table 5. Baseline characteristics of the cohort according to resolution of fatty liver follow up

Baseline characteristics	Fatty liver at baseline and at follow up	Fatty liver at baseline but not at follow up	*P*
Number	28,022	14,514	
N (%) Men	84.5	77.8	
Age (years)	39.1(8.6)	39.0(8.4)	0.628
BMI (kg/m^2)	26.2(2.8)	25.5(2.7)	<0.001
Systolic BP (mmHg)	118.9(13.4)	117.8(13.7)	<0.001
Diastolic BP (mmHg)	77.4(9.7)	76.6(9.8)	<0.001
Higher education (%)[a]	81.4	78.7	<0.001
Current smoker	35.5	31.3	<0.001
Alcohol intake g/day	6(0-11)	5(0-11)	0.089
Obesity (%)	64.8	54.8	<0.001
Insulin (IU/mL)	7.22(5.19-9.98)	6.09(4.4-8.53)	<0.001
Glucose (mg/dl)	99.2(19.5)	98.3(19.2)	<0.001
Total cholesterol (mg/dl)	208.8(35.2)	206.5(35.0)	<0.001
LDL-C (mg/dl)	128.4(30.6)	124.9(30.0)	<0.001
HDL-C (mg/dl	48.3(9.4)	50.2(10.2)	<0.001
Triglycerides (mg/dl)	156(113-216)	142(104-197)	<0.001
HOMA IR	2.27(1.68-3.00)	2.11(1.57-2.74)	<0.001
Hs-CRP (mg/L)	0.8(0.4-1.5)	0.7(0.4-1.3)	<0.001
Diabetes (%)	6.4	5.4	<0.001
Hypertension (%)	23.4	21.3	<0.001
Cardiovascular disease (%)	4.6	3.9	0.001
Change in BMI between baseline and follow up	0.1(1.0)	-0.5(1.2)	<0.001

Table 6. Associations between number of sessions of exercise per weeks and resolution of fatty liver at follow up

Exercise sessions (per week)	Person-years	Number of events	incident (100,000 person-year)	Age-sex adjusted HR (95% CI)	Multivariate HR*(95% CI)		
					Model 1	Model 2	Model 3
	Resolution of fatty liver	Resolution of fatty liver	Resolution of fatty liver				
0	98,400.7	7,677	7,801.8	1.00(reference)	1.00(reference)	1.00(reference)	1.00(reference)
1-2	60,514.3	4,699	7,765.1	1.04(1.00-1.08)	1.03(0.98-1.07)	1.05(1.01-1.10)	1.05(1.01- 1.10)
3-4	17,872.4	1,571	8,790.1	1.10(1.04-1.16)	1.07(1.00-1.15)	1.10(1.03-1.18)	1.18(1.10- 1.26)
≥5	5,556.2	567	10,204.8	1.19(1.09-1.30)	1.21(1.08-1.34)	1.26(1.14-1.41)	1.40(1.25- 1.55)
***P* for trend**				<0.001	0.001	<0.001	<0.001

*Model 1: adjustment for age, sex, center, year of screening exam, smoking status, alcohol intake, education level;
*Model 2: model 1 adjustments plus adjustment for BMI, diabetes, hypertension, CVD
*Model 3: model 2 adjustments plus adjustment for change in BMI between baseline and end of study

Table 7. Associations between change in numbers of weekly exercise sessions and resolution of fatty liver at follow up

Change in Exercise sessions (per week)	Person-years	Number of events	Disappear rate (100,000 person-year)	Age-sex adjusted HR (95% CI)	Multivariate HR*(95% CI)		
					Model 1	Model 2	Model 3
	Resolution of fatty liver	Resolution of fatty liver	Resolution of fatty liver				
Decrease	32,215.8	1,359	4,218.4	1.00(reference)	1.00(reference)	1.00(reference)	1.00(reference)
No change	75,345.3	3,354	445.2	1.04(0.98-1.11)	1.07(0.98-1.16)	1.06(0.98-1.16)	1.05(0.96-1.14)
Increase	35,096.6	1,675	4,772.6	1.12(1.04-1.20)	1.17(1.07-1.29)	1.18(1.07-1.30)	1.13(1.03-1.24)
***P* for trend**				0.002	0.001	<0.001	0.010

*Model 1: adjustment for age, sex, center, year of screening exam, smoking status, alcohol intake, education level and number of weekly baseline exercise sessions
*Model 2: model 1 adjustments plus adjustment for BMI, diabetes, hypertension, history of CVD
*Model 3: model 2 adjustments plus adjustment for change in BMI between baseline and follow up

SUPPLEMENTARY TABLES

Supplementary Table 1. Risk of incident fatty liver according to exercise group in clinically relevant subgroups.

	Exercise (per week)				*p* for trend	*p* for interaction
	0	**1-2**	**3-4**	**≥5**		
Men (*n*=59,618)	1.00(reference)	0.90(0.87-0.94)	0.85(0.81-0.90)	0.86(0.78-0.93)	<0.001	0.000
aHR (95% CI)						
Women (*n*=67,193)	1.00(reference)	1.03(0.96-1.09)	0.96(0.88-1.05)	0.89(0.79-1.00)	0.826	
aHR (95% CI)						
Age <50 years (*n*=117,937)	1.00(reference)	0.94(0.91-0.97)	0.89(0.85-0.93)	0.90(0.84-0.97)	0.001	0.244
aHR (95% CI)						
Age ≥50 years (*n*=8,874)	1.00(reference)	0.89(0.77-1.02)	0.87(0.74-1.02)	0.83(0.69-1.01)	0.096	
aHR (95% CI)						
Non or ever smoker(*n*=101,133)	1.00(reference)	0.95(0.92-0.99)	0.88(0.83-0.93)	0.85(0.78-0.92)	0.014	0.127
aHR (95% CI)						
Current smoker(*n*=25,678)	1.00(reference)	0.90(0.85-0.95)	0.88(0.81-0.96)	0.90(0.79-1.03)	<0.001	
aHR (95% CI)						
<college graduate(*n*=20,147)	1.00(reference)	0.94(0.88-1.01)	0.87(0.79-0.95)	0.86(0.76-0.98)	0.136	0.964
aHR (95% CI)						
≥college graduate(*n*=65,227)	1.00(reference)	0.92(0.89-0.96)	0.87(0.83-0.92)	0.85(0.78-0.93)	<0.001	
aHR (95% CI)						
HTN NO	1.00(reference)	0.93(0.90-0.96)	0.85(0.81-0.90)	0.86(0.80-0.93)	<0.001	0.430
aHR (95% CI)						
HTN YES	1.00(reference)	0.94(0.86-1.03)	0.97(0.86-1.08)	0.86(0.73-1.01)	0.070	
aHR (95% CI)						

DM NO	1.00(reference)	0.93(0.90-0.96)	0.87(0.83-0.91)	0.86(0.80-0.92)	<0.001	0.902
aHR (95% CI)						
DM YES	1.00(reference)	0.96(0.74-1.25)	1.01(0.75-1.35)	0.95(0.66-1.38)	0.688	
aHR (95% CI)						
CVD NO	1.00(reference)	0.93(0.90-0.96)	0.87(0.83-0.91)	0.86(0.80-0.92)	<0.001	0.148
aHR (95% CI)						
CVD YES	1.00(reference)	1.51(0.97-2.37)	1.39(0.83-2.33)	1.15(0.59-2.21)	0.226	
aHR (95% CI)						
Homa75=0 (*n*=107,849)	1.00(reference)	0.93(0.90-0.96)	0.87(0.82-0.91)	0.87(0.80-0.94)	<0.001	0.124
aHR (95% CI)						
Homa75=1 (*n*=15,638)	1.00(reference)	0.97(0.90-1.05)	1.03(0.92-1.16)	0.85(0.71-1.02)	0.183	
aHR (95% CI)						
BMI <25 kg/m^2 (*n*=108,230)	1.00(reference)	1.01(0.97-1.05)	0.99(0.93-1.04)	0.89(0.82-0.98)	0.840	0.010
aHR (95% CI)						
BMI ≥25 kg/m^2 (*n*=18,570)	1.00(reference)	0.96(0.91-1.02)	0.96(0.89-1.03)	0.99(0.88-1.11)	0.338	
aHR (95% CI)						
CRP>1.0 (*n*=102,380)	1.00(reference)	0.92(0.89-0.96)	0.87(0.82-0.91)	0.85(0.78-0.92)	<0.001	0.705
aHR (95% CI)						
CRP<1.0 (*n*=23,458)	1.00(reference)	0.95(0.89-1.01)	0.82(0.84-1.01)	0.91(0.78-1.05)	0.106	
aHR (95% CI)						

Supplementary Table 2. Associations between exercise group and resolution of fatty liver at follow up in clinically relevant subgroups.

	Exercise (per week)				p for trend	p for interaction
	0	1-2	3-4	≥5		
Men (n=34,964)	1.00(reference)	1.07(1.02-1.12)	1.22(1.13-1.31)	1.36(1.20-1.54)	0.002	0.007
aHR (95% CI)						
Women (n=7,572)	1.00(reference)	0.99(0.89-1.10)	1.04(0.89-1.20)	1.43(1.16-1.75)	0.416	
aHR (95% CI)						
Age <50 years (n=37,634)	1.00(reference)	1.05(1.00-1.10)	1.17(1.09-1.26)	1.31(1.16-1.49)	0.011	0.007
aHR (95% CI)						
Age ≥50 years (n=4,902)	1.00(reference)	1.13(0.96-1.32)	1.34(1.12-1.60)	1.75(1.40-2.18)	0.016	
aHR (95% CI)						
Non or ever smoker(n=28,053)	1.00(reference)	1.03(0.98-1.09)	1.15(1.06-1.24)	1.48(1.30-1.68)	0.021	0.067
aHR (95% CI)						
Current smoker(n=14,483)	1.00(reference)	1.10(1.02-1.19)	1.29(1.14-1.47)	1.25(1.02-1.52)	0.024	
aHR (95% CI)						
<college graduate(n=5,450)	1.00(reference)	1.04(0.94-1.15)	1.17(1.01-1.35)	1.62(1.34-1.97)	0.063	0.449
aHR (95% CI)						
≥college graduate(n=22,342)	1.00(reference)	1.05(1.00-1.10)	1.17(1.08-1.26)	1.29(1.13-1.47)	0.035	
aHR (95% CI)						
HTN NO	1.00(reference)	1.07(1.01-1.12)	1.16(1.07-1.26)	1.34(1.18-1.52)	0.003	0.764
aHR (95% CI)						
HTN YES	1.00(reference)	1.03(0.94-1.14)	1.21(1.06-1.38)	1.53(1.25-1.87)	0.155	
aHR (95% CI)						
DM NO	1.00(reference)	1.05(1.01-1.10)	1.18(1.10-1.27)	1.42(1.27-1.59)	0.002	0.702
aHR (95% CI)						
DM YES	1.00(reference)	1.07(0.88-1.31)	1.04(0.81-1.35)	1.11(0.76-1.62)	0.438	
aHR (95% CI)						

CVD NO	1.00(reference)	1.06(1.01-1.10)	1.18(1.10-1.26)	1.39(1.24-1.55)	0.002	0.801
aHR (95% CI)						
CVD YES	1.00(reference)	0.90(0.54-1.52)	1.04(0.53-2.04)	1.72(0.79-3.74)	0.879	
aHR (95% CI)						
Homa75=0 (n=24,534)	1.00(reference)	1.06(1.00-1.12)	1.12(1.03-1.22)	1.33(1.17-1.52)	0.008	0.297
aHR (95% CI)						
Homa75=1 (n=16,981)	1.00(reference)	1.03(0.96-1.12)	1.28(1.13-1.44)	1.47(1.21-1.79)	0.212	
aHR (95% CI)						
BMI <25 kg/m2 (n=16,438)	1.00(reference)	1.03(0.96-1.10)	1.15(1.03-1.27)	1.36(1.14-1.61)	0.214	0.886
aHR (95% CI)						
BMI ≥25 kg/m2 (n=26,095)	1.00(reference)	1.04(0.98-1.11)	1.16(1.06-1.27)	1.33(1.16-1.53)	0.057	
aHR (95% CI)						