Received: 14 November 2016 | Accepted: 13 August 2017

DOI: 10.1111/liv.13553

GENETIC AND METABOLIC LIVER DISEASE

WILEY Liver INTERNATIONAL

Exercise might prevent cirrhosis in overweight and obese adults

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Funding information
This study was supported in part by grants from the National Science Council (NSC 102-2119-M-040 -001) and the Ministry of Science and Technology (MOST 103-2119-M-040 -001, MOST 104-2119-M-040-002).

Handling Editor: Helena Cortez-Pinto

Abstract

Background & Aims: Exercise in overweight patients with liver disease has improved liver enzymes, insulin levels and quality of life. Scientific evidence is incomplete regarding the role of exercise in the prevention of cirrhosis. We investigated the effect of exercise on the occurrence of cirrhosis in obese and overweight adults.

Methods: Exercise was assessed using the 2012 Adult Preventive Medical Service dataset while cirrhosis was identified using the National Health Insurance Research Database. All participants were aged 40 years and older. Unconditional logistic regression was used to estimate the odds ratios for cirrhosis.

Results: Overall, 1586 overweight and 1525 obese adults were identified with cirrhosis. Weekly exercise >150 min was significantly protective for cirrhosis in obese men and women. However, exercise <150 min/wk was significantly protective only in men compared to women. For weekly exercise >150 mins, the odds ratio for cirrhosis in obese men and women was 0.701 (95% CI: 0.584-0.841) and 0.736 (95% CI: 0.562-0.964) respectively. The adjusted odds ratios in overweight men and women were 0.734 (95% CI: 0.622-0.866) and 0.503 (CI: 0.37-0.684). For weekly exercise <150 min/wk, overweight and obese men had odds ratios of 0.879 (CI: 0.0.788-0.98) and 0.874 (CI: 0.782-0.977) compared to 0.918 (95% CI: 0.778-1.083) and 0.916 (95% CI: 0.780-1.075) in overweight and obese women respectively.

Conclusions: Moderate exercise might significantly prevent obese and overweight adults from developing cirrhosis. The benefits appear to be greater for persons who exceed the minimum recommendations of 150 min/wk.

KEYWORDS

cirrhosis, exercise, metabolic syndrome, Steatohepatitis

Abbreviations: ACS, acute coronary syndrome; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accidents; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate, epidermal growth factor receptor; FLD, fatty liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; HDL, high-density lipoprotein; HPA, Health Promotion Administration; HR, hazard ratio; HTN, hypertension; ICD-9-CM, International Classification of Diseases, Ninth Revision; LDL, low-density lipoprotein, Clinical Modification; NAFLD, nonalcoholic fatty liver diseases; NHIRD, National Health Insurance Research Database; ORs, odds ratio; TB, tuberculosis.

Trial registration number: Not applicable.

1 | INTRODUCTION

Cirrhosis is increasingly becoming a serious threat to global health.[1,2] It results from different mechanisms of liver injury that lead to necroinflammation and fibrogenesis.[2] Common risk factors in developed countries include alcoholic liver disease and hepatitis C, whereas hepatitis B is the major risk factor particularly in Africa and Asia.[3] The proportion of individuals with cirrhosis is projected to reach 37.2% in 2020, and 44.9% in 2030.[4] In addition, the economic burden associated with the disease is overwhelming.[5] Liver transplant remains the only cure for the disease. Preventing the need for liver transplantation in patients with cirrhosis is the greatest challenge in the 21st century.[2]

Physical activity has been suggested to have survival benefits among individuals with liver disease. Exercise has improved liver enzymes, serum insulin levels and quality of life in overweight patients with liver disease.[6] In addition, moderate-to-vigorous physical ≥250 min/wk as part of lifestyle management is believed to improve non-alcoholic fatty liver disease (NAFLD) pathophysiology in men through reducing inflammation and oxidative stress levels and altering fatty acid metabolism.[7] Improvement in exercise capacity and muscle strength have been reported after physical training in patients with cirrhosis.[8] The relationship between physical activity and chronic liver diseases is poorly understood. Furthermore, studies to investigate the impact of physical activity on cirrhosis and other liver diseases are relatively recent.[9,10]

Increasing sedentary behaviour is becoming a growing problem in populations.[11] Sedentary behaviour is reported to be higher in people predisposed to metabolic syndrome, excessive adiposity, and Type 2 DM. Increases in sedentary time could play a potential role in the development of NAFLD independent of exercise.[11] According to the 2015 Hepatitis C Support Project, NAFLD is expected to be the leading cause of cirrhosis in the coming decades.

Liver transplantation remains the only curative option for a selected group of patients with cirrhosis.[3] However, it is beneficial only to a small number of individuals because of its high expense. Alternative measures for both the prevention and treatment of cirrhosis and other liver diseases are vitally essential. As mentioned earlier, regular physical activity has prevented the onset and progression of numerous chronic diseases. Nonetheless, the role of exercise in the prevention of cirrhosis has not been widely discussed in previous publications. The aim of this study was to investigate the links between exercise and cirrhosis in obese and overweight adults.

Key points

- Cirrhosis is increasingly becoming a serious threat to global health.
- Studies to investigate the impact of physical activity on cirrhosis and other liver diseases are relatively recent.
- Exercise has improved liver enzymes, serum insulin levels and quality of life among overweight patients with liver disease.
- Moderate exercise, even at levels below the recommended minimum might significantly prevent obese and overweight adults from developing cirrhosis.

2 | MATERIALS AND METHODS

2.1 | Data source

Data sources used in this study included the 2012 Preventive Medical Service dataset provided by the Health Promotion Administration (HPA) and the National Health Insurance Research Database (NHIRD) provided by the statistics department of the Ministry of Health and Welfare. Informed consent was not applicable because the study made use of a de-identified secondary data. The study protocol conformed to the ethical standards established by the Declaration of Helsinki. This study was approved by the central regional research ethics committee of Taiwan (CRREC-104-015). Free preventive medical services have been provided to adults in Taiwan since 1996. The HPA has maintained the electronic records (physical examinations, health-related behaviours/education, blood lipid profiles and urine tests) of individuals who have used the services. Frequency limitations of these services varied according to different age groups, i.e., once per 3 years for the persons aged 40-64 years and once per year for those over 65.

2.2 | Inclusion criteria

We selected individuals ≥40 years old who were engaged in free adult preventive medical services in 2012 (Figure 1). The index date was the date each participant received the preventive care service which included physical examination, health consultations and blood and urine tests. Male and female participants were categorized as obese (BMI ≥ 27 kg/m^2) and overweight (BMI ≥24 and <27 kg/m^2), as defined by the "Department of Health in Taiwan." Patients were defined as having cirrhosis if they had one-time hospitalization or two outpatient visits with reported International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM) codes: 571.2, 571.5 and 571.6. The diagnostic period was from the 4th to the 12th month following the index date.

2.3 | Exclusion criteria

Excluded were patients with missing data and those diagnosed with liver cancer (*International Classification of Diseases, 9th Revision, Clinical Modification* [ICD-9-CM] codes 155.0, 155.2), cirrhosis (ICD 9: 571.2, 571.5, 571.6), ascites (ICD 9: 789.5), hepatic encephalopathy (ICD-9: 572.2) and spontaneous bacterial peritonitis (ICD-9: 567.2, 567.8, 567.9) before and within 3 months of index assessment (biometric and laboratory data). The final samples included 721 551 overweight and obese adults. Physical exercise was defined based on the current recommendations (i.e., 150 min/wk) and was categorized as follows: moderate exercise <150 min/wk and moderate exercise >150 min/wk. The reference group included adults with no weekly physical activity.

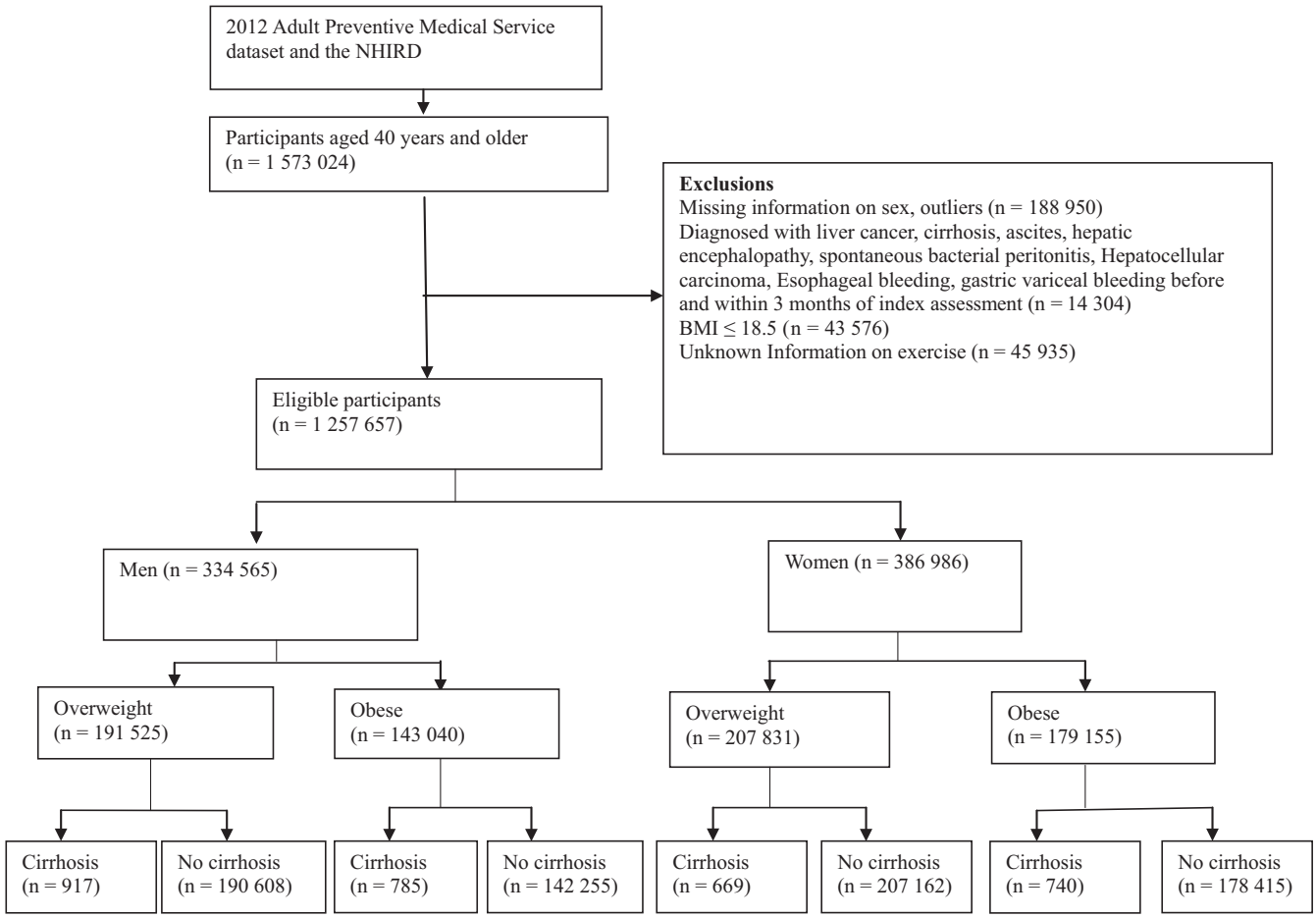

FIGURE 1 Flow chart of the study participants

2.4 | Statistical analysis

The Chi-square test was used to compare the difference between nominal variables among groups. Unconditional logistic regression was used to estimate the odds ratios for cirrhosis. Exercise was treated as the exposure variable in the model. Potential confounders included low-income, age, smoking, alcohol drinking, glutamic-pyruvic transaminase (GPT), estimated glomerular filtration rate (eGFR), hepatitis B and C virus (HBV and HCV), alcoholism, hospitalization, medication (statin and fibrate), betel nut chewing, Cho/HDL, LDL/HDL, diabetes mellitus (DM), and comorbidities (metabolic syndrome, asthma, chronic obstructive pulmonary disease [COPD], tuberculosis [TB], acute coronary syndrome [ACS], cerebrovascular accidents [CVA] and hypertension [HTN]). Data analyses were made using the SAS 9.3 statistical software.

3 | RESULTS

Tables 1 and 2 show the demographic characteristics of the study population. Cirrhotic individuals with a BMI ≥24 and <27 kg/m^2 (overweight) included 917 men and 669 women while those with a BMI ≥27 kg/m^2 (Obese) included 785 men and 740 women.

Tables 3 and 4 show the odds ratio for cirrhosis in overweight and obese individuals. Exercise <150 min/wk was significantly protective for cirrhosis particularly in obese individuals and overweight men. In addition, exercise >150 min/wk was found to be more beneficial in preventing cirrhosis in overweigh and obese individuals of both sexes. For weekly exercise <150 minutes, the adjusted odds ratios for cirrhosis in overweight men and women were 0.879 (CI: 0.788-0.980) and 0.98 (95% CI: 0.778-1.083), respectively, and were 0.734 (95% CI: 0.622-0.866) and 0.503 (95% CI: 0.370-0.684) for exercise >150 minutes a week. Similarly, the odds ratios for cirrhosis in obese men and women who had less than 150 minutes of exercise/week were 0.874 (95% CI: 0.782-0.977) and 0.916 (95% CI: 0.780-1.075). Obese men and women who had more than 150 min/wk had odds ratios of 0.701 (95% CI: 0.584-0.841) and 0.736 (95% CI: 0.562-0.964) respectively. Results also showed that physical exercise was associated with a reduced risk of cirrhosis in obese men and women in a dose–response manner (tests for trend, P = .0005 and <0.0001 respectively). The P-value for trend was also significant in overweight women (P < .0001) and was only slightly non-significant in their male counterparts (P = .0757). Further analysis showed that cirrhotic individuals with normal BMI (18.5 ≤ BMI < 24) had ORs of 0.868 CI: 0.787-0.957 (men) and 0.796 CI: 0.679-0.933 (women) for exercise <150 min/wk and 0.752 CI: 0.649-0.871 (men) and 0.621 CI: 0.481-0.802 (women) for exercise >150 minutes.

TABLE 1 Demographic, anthropometric and clinical and laboratory characteristics of male participants

	Overweight 24 ≤ BMI < 27			Obesity BMI ≥ 27		
	Cirrhosis N = 917	No cirrhosis N = 190 608	*P*-value	Cirrhosis N = 785	No cirrhosis N = 142 255	*P*-value
Follow-up time(mo)	10.60			10.74		
Exercise			.005			.0011
No	482 (52.56)	89 979 (47.21)		447 (56.94)	72 846 (51.21)	
<150 min/w	306 (33.37)	70 050 (36.75)		262 (33.38)	50 516 (35.51)	
>150 min/w	129 (14.07)	30 579 (16.04)		76 (9.68)	18 893 (13.28)	
Low income	17 (1.85)	1876 (0.98)	.0079	14 (1.78)	1678 (1.18)	.1186
Age (y)			<.0001			<.0001
40 ≤ Age < 60	282 (30.75)	78 104 (40.98)		270 (34.39)	67 316 (47.32)	
60 ≤ Age < 80	517 (56.38)	91 996 (48.26)		424 (54.01)	63 820 (44.86)	
80 < Age	118 (12.87)	20 508 (10.76)		91 (11.59)	11 119 (7.82)	
Smoking			<.0001			.1224
Never	656 (71.54)	148 688 (78.01)		577 (73.5)	10 8647 (76.37)	
≤1 pack/d	197 (21.48)	31 684 (16.62)		148 (18.85)	24 690 (17.36)	
>1 pack/d	64 (6.98)	10 236 (5.37)		60 (7.64)	8918 (6.27)	
Drinking			<.0001			<.0001
Never	650 (70.88)	136 928 (71.84)		531 (67.64)	98 847 (69.49)	
Sometime	185 (20.17)	44 316 (23.25)		174 (22.17)	35 819 (25.18)	
Frequent	82 (8.94)	9364 (4.91)		80 (10.19)	7589 (5.33)	
GPT (U/L)			<.0001			<.0001
GPT < 40	452 (49.29)	156 692 (82.21)		364 (46.37)	102 501 (72.05)	
GPT ≥ 40	465 (50.71)	33 916 (17.79)		421 (53.63)	39 754 (27.95)	
eGFR			<.0001			.0015
eGFR ≥ 60	676 (73.72)	153 953 (80.77)		595 (75.8)	114 268 (80.33)	
eGFR < 60	241 (26.28)	36 655 (19.23)		190 (24.2)	27 987 (19.67)	
Diseases						
Diabetes mellitus	351 (38.28)	44 736 (23.47)	<.0001	334 (42.55)	42 748 (30.05)	<.0001
HBV	107 (11.67)	5175 (2.71)	<.0001	86 (10.96)	3528 (2.48)	<.0001
HCV	93 (10.14)	2345 (1.23)	<.0001	61 (7.77)	1571 (1.10)	<.0001
Alcoholism	35 (3.82)	686 (0.36)	<.0001	21 (2.68)	540 (0.38)	<.0001
Complications after index_d						
Ascites	29 (3.16)	22 (0.01)	<.0001	25 (3.18)	15 (0.01)	<.0001
Hepatic encephalopathy	13 (1.42)	7 (0.00)	<.0001	12 (1.53)	3 (0.00)	<.0001
SBP	6 (0.65)	102 (0.05)	<.0001	11 (1.40)	90 (0.06)	<.0001
HCC	65 (7.09)	163 (0.09)	<.0001	46 (5.86)	105 (0.07)	<.0001
Oesophageal bleeding	5 (0.55)	13 (0.01)	<.0001	7 (0.89)	8 (0.01)	<.0001
Gastric varices bleeding	27 (2.94)	1237 (0.65)	<.0001	23 (2.93)	959 (0.67)	<.0001

Index_d, Index date; GPT, glutamic-Pyruvic Transaminase; eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HBC, hepatitis C virus; SBP, systolic blood pressure; HCC, hepatocellular carcinoma.

Glutamic-pyruvic transferase (GPT) ≥40 U/L were found as risk factors cirrhosis. The odds ratios were 5.627 (95% CI: 5.065-6.250) and 4.200 (95% CI: 3.773-4.676) in overweight and obese men and 7.245 (95% CI: 6.159-8.524) and 5.211 (95% CI: 4.470-6.075), respectively, in their female counterparts. A higher odds of experiencing cirrhosis was found in HCV compared with HBV individuals. (i.e., 4.785 vs 3.479 and 4.977 vs 3.510 in overweight and obese men, respectively, and 5.610 vs 2.932 and 5.799 vs 2.869 in women).

TABLE 2 Demographic, anthropometric, and clinical and laboratory characteristics of female participants

	Overweight 24 ≤ BMI < 27			Obesity BMI ≥ 27		
	Cirrhosis N = 669	No cirrhosis N = 207 162	*P*-value	Cirrhosis N = 740	No cirrhosis N = 178 415	*P*-value
Follow-up time (mo)	10.71			10.68		
Exercise			<.0001			.0696
No	384 (57.4)	107 047 (51.67)		436 (58.92)	98 949 (55.46)	
<150 min/w	238 (35.58)	73 378 (35.42)		242 (32.7)	60 575 (33.95)	
>150 min/w	47 (7.03)	26 737 (12.91)		62 (8.38)	18 891 (10.59)	
Age (y)			<.0001			<.0001
40 ≤ Age < 60	98 (14.65)	79 647 (38.45)		114 (15.41)	66 296 (37.16)	
60 ≤ Age < 80	465 (69.51)	110 071 (53.13)		526 (71.08)	98 550 (55.24)	
80 < Age	106 (15.84)	17 444 (8.42)		100 (13.51)	13 569 (7.61)	
Smoking			.1210			.9460
Never	643 (96.11)	201 430 (97.23)		719 (97.16)	173 076 (97.01)	
≤1 pack/d	16 (2.39)	3991 (1.93)		15 (2.03)	3932 (2.20)	
>1 pack/d	10 (1.49)	1741 (0.84)		6 (0.81)	1407 (0.79)	
Drinking			.0729			.8474
Never	632 (94.47)	195 168 (94.21)		699 (94.46)	167 699 (93.99)	
Ever	26 (3.89)	10 102 (4.88)		36 (4.86)	9279 (5.20)	
Frequent	11 (1.64)	1892 (0.91)		5 (0.68)	1437 (0.81)	
GPT			<.0001			<.0001
GPT < 40	306 (45.74)	182 495 (88.09)		335 (45.27)	146 495 (82.11)	
GPT ≥ 40	363 (54.26)	24 667 (11.91)		405 (54.73)	31 920 (17.89)	
eGFR			<.0001			<.0001
eGFR ≥ 60	461 (68.91)	168 193 (81.19)		489 (66.08)	139 658 (78.28)	
eGFR < 60	208 (31.09)	38 969 (18.81)		251 (33.92)	38 757 (21.72)	
Diseases						
Diabetes mellitus	251 (37.52)	45 669 (22.05)	<.0001	336 (45.41)	53 907 (30.21)	<.0001
HBV	49 (7.32)	3626 (1.75)	<.0001	49 (6.62)	2900 (1.63)	<.0001
HCV	125 (18.68)	2836 (1.37)	<.0001	118 (15.95)	2403 (1.35)	<.0001
Alcoholism	4 (0.60)	154 (0.07)	<.0001	5 (0.68)	191 (0.11)	<.0001
Complications after index_d						
Ascites	19 (2.84)	38 (0.02)	<.0001	11 (1.49)	13 (0.01)	<.0001
Hepatic encephalopathy	12 (1.79)	3 (0.00)	<.0001	7 (0.95)	3 (0.00)	<.0001
SBP	5 (0.75)	108 (0.05)	<.0001	4 (0.54)	86 (0.05)	<.0001
HCC	38 (5.68)	124 (0.06)	<.0001	46 (6.22)	100 (0.06)	<.0001
Oesophageal bleeding	4 (0.60)	17 (0.01)	<.0001	-	-	-
Gastric varices bleeding	15 (2.24)	953 (0.46)	<.0001	18 (2.43)	905 (0.51)	<.0001

Index_d, Index date; GPT, glutamic-Pyruvic Transaminase; eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HBC, hepatitis C virus; SBP, systolic blood pressure; HCC, hepatocellular carcinoma.

4 | DISCUSSION

To our knowledge, this is the first study that has employed a large sample size to show that physical exercise might significantly prevent obese and overweight adults from developing cirrhosis. Full adjustments were made for several variables including low-income, age, lipid-lowering medications, commodity, lipid profile etc. Weekly exercise >150 minutes was found to be more protective for cirrhosis. We also found a dose–response relationship between exercise and protection from cirrhosis was evident in obese individuals and

TABLE 3 Association between exercise and cirrhosis in male participants using multiple logistic regression analysis

	Overweight 24 ≤ BMI < 27			Obese BMI ≥ 27		
	OR	95% C.I.	*P*-value	OR	95% C.I.	*P*-value
Exercise (ref = No)						
<150 min/w	0.879	0.788-0.980	.0206	0.874	0.782-0.977	.0177
>150 min/w	0.734	0.622-0.866	.0003	0.701	0.584-0.841	.0001
P-trend			.0757			.0005
Low income (ref = No)	1.872	1.264-2.771	.0017	1.198	0.746-1.925	.4551
Age (ref = 40 ≤ Age < 60)						
60 ≤ Age < 80	2.244	1.962-2.567	<.0001	2.414	2.111-2.761	<.0001
80 < Age	2.983	2.458-3.621	<.0001	3.689	3.018-4.508	<.0001
Smoking (ref = Never)						
≤1 pack/d	1.493	1.258-1.772	<.0001	1.177	0.975-1.421	.0890
>1 pack/d	1.310	0.977-1.756	.0716	1.034	0.768-1.392	.8257
Drinking (ref = Never)						
Ever	0.916	0.775-1.083	.3052	1.004	0.847-1.189	.9640
Frequent	1.454	1.112-1.902	.0062	1.527	1.161-2.008	.0024
GPT (ref = ≤40)						
GPT ≥ 40	5.627	5.065-6.250	<.0001	4.200	3.773-4.676	<.0001
eGFR (ref = ≥60)						
eGFR < 60	1.404	1.247-1.581	<.0001	1.282	1.137-1.445	<.0001
HBV	3.479	2.920-4.146	<.0001	3.51	2.907-4.238	<.0001
HCV	4.785	4.090-5.599	<.0001	4.977	4.198-5.902	<.0001
Alcoholism	6.428	4.531-9.119	<.0001	4.061	2.650-6.224	<.0001

The multiple logistic regression model included the following variables: exercise, low-income, age, smoking, drinking, glutamic-pyruvic transaminase (GPT), estimated glomerular filtration rate (eGFR), hepatitis B and C virus (HBV and HCV), alcoholism, hospitalization, medication (statin and fibrate), betel nut chewing, Cho/HDL, LDL/HDL, diabetes mellitus, and comorbidity (metabolic syndrome, asthma, chronic obstructive pulmonary disease [COPD], tuberculosis [TB], acute coronary syndrome [ACS], cerebrovascular accidents [CVA], and hypertension [HTN]).
Interaction (BMI*Exercise) *P* = .6625.

overweight women. Nonetheless, the *P*-value for trend approached the borderline of significance in overweight men. In addition, viral hepatitis B and C (HBV and HCV), GPT ≥40, diabetes mellitus, alcoholism, and age older than 60 were found to be the significant risk factors of cirrhosis. Our study was designed based on the global recommendations on physical activity for health which state that adults aged 18-64 years require at least 150 minutes of moderate-intensity aerobic physical activity each week.[12]

Until now, previous publications have focused mainly on the benefits of exercise in patients with coronary heart disease (CHD), diabetes, and cancer. In a recently published study conducted in Korea, authors found that any amount of moderate weekly exercise lasting at least 10 minutes was beneficial in either reducing the risk of new fatty liver or in improving the resolution of existing fatty liver.[9] An evidence-based review reported that light and moderate exercise are protective for liver disease and inflammatory bowel disease.[13] We have demonstrated that physical exercise is beneficial in reducing the risk of cirrhosis as evident in obese and overweight adults. It is also reassuring to note that a modest weight reduction and an increase in weekly exercise may have the potential to prevent the development of cirrhosis.[14] Moderate to vigorous intensity physical activity ≥250 minutes per week has significantly benefited obese individuals with nonalcoholic fatty liver disease (NAFLD)[7] which is expected to be the leading cause of cirrhosis in the coming years.[15,16] Different mechanisms have been described to show how aerobic exercise can improve NAFLD.[17] Studies to define the most beneficial form and duration of exercise treatment are warranted.[18]

As stated earlier, cirrhosis results from different mechanisms of liver injury that lead to necroinflammation. The possible mechanism by which exercise may protect against cirrhosis is still unclear. Elevation of cytokines has been reported in the peritoneal fluid and blood of patients with cirrhosis.[19] Ruben and colleagues found that physically active individuals had lower plasma concentrations of cytokines when compared to age- and gender-matched inactive groups.[20]

TABLE 4 Association between exercise and cirrhosis in female participants using multiple logistic regression analysis

	Overweight 24 ≤ BMI < 27			Obese BMI ≥ 27		
	OR	95% C.I.	*P*-value	OR	95% C.I.	*P*-value
Exercise (ref = No)						
<150 min/w	0.918	0.778-1.083	.3124	0.916	0.780-1.075	.2808
>150 min/w	0.503	0.370-0.684	<.0001	0.736	0.562-0.964	.0262
P-trend			<.0001			<.0001
Low income (ref = No)	2.703	1.418-5.153	.0025	0.828	0.306-2.239	.7106
Age (ref = 40 ≤ Age < 60)						
60 ≤ Age < 80	3.110	2.453-3.942	<.0001	2.885	2.318-3.589	<.0001
80 < Age	4.753	3.480-6.491	<.0001	4.546	3.371-6.132	<.0001
Smoking (ref = Never)						
≤1 pack/d	1.583	0.923-2.715	.0951	1.094	0.632-1.896	.7475
>1 pack/d	2.272	0.825-6.256	.1122	1.155	0.412-3.242	.7841
Drinking (ref = Never)						
Ever	0.961	0.616-1.501	.8618	0.888	0.598-1.319	.5575
Frequent	2.027	0.769-5.343	.1530	0.319	0.098-1.039	.0579
GPT (ref = GPT < 40)						
GPT ≥ 40	7.245	6.159-8.524	<.0001	5.211	4.47-6.075	<.0001
eGFR (ref = ≥60)						
eGFR < 60	1.402	1.175-1.674	.0002	1.397	1.185-1.647	<.0001
HBV	2.932	2.152-3.995	<.0001	2.869	2.108-3.903	<.0001
HCV	5.610	4.518-6.967	<.0001	5.799	4.671-7.200	<.0001
Alcoholism	3.391	1.142-10.071	.0279	3.625	1.417-9.271	.0072

The multiple logistic regression model included the following variables: exercise, low-income, age, smoking, drinking, glutamic-pyruvic transaminase (GPT), estimated glomerular filtration rate (eGFR), hepatitis B and C virus (HBV and HCV), alcoholism, hospitalization, medication (statin and fibrate), betel nut chewing, Cho/HDL, LDL/HDL, diabetes mellitus, and comorbidity (metabolic syndrome, asthma, chronic obstructive pulmonary disease [COPD], tuberculosis [TB], acute coronary syndrome [ACS], cerebrovascular accidents [CVA], and hypertension [HTN]).
Interaction (BMI*Exercise) *P* = .1267.

In our study, alcoholism was greatly associated with cirrhosis in both men and women. The odds for cirrhosis were significant mainly among frequent male drinkers compared to their female counterparts. It is worth noting that treating alcoholic liver disease remains challenging and the main therapy demands abstinence from alcohol.[5] Cirrhosis has also been associated with a higher risk of hepatocellular carcinoma.[21,22]

It is worth stating that an analysis in subjects with known liver disease such as HBV and HCV is necessary to clarify whether the effects of exercise are limited to subjects with presumed NAFLD associated to overweight/obesity, or keep existing in patients with liver disease because of other causes having as an additional cause of liver disease metabolic syndrome. Because of the small number of individuals with viral hepatitis in our study, a subanalysis was carried out only in men. However, the effect of exercise was not significant. The odds ratio for exercise <150 minutes per week was 1.046 (CI: 0.80-1.37) for HBV^+/HCV^- individuals and 0.966 (CI: 0.74-1.26) for HBV^-/HCV^+ individuals. For exercise >150 min/wk, the odds ratio was 0.772 (CI: 0.50-1.18) for HBV^+/HCV^- individuals and 1.073 (CI: 0.77-1.50) for HBV^-/HCV^+ individuals. Larger sample sizes are needed to properly address such associations.

Physical exercise may be advantageous for patients with cirrhosis and could reduce the need for liver transplantation. The strengths and limitation of our study should be addressed. This is the first study to investigate the effect of exercise and cirrhosis using multiple data sources in Taiwan. Second, we used a larger sample size and adjusted for several variables. However, we could not obtain detailed information describing exercise patterns from the databases, hence larger dedicated studies investigating cirrhosis should take into account exercise type and intensity.

In conclusion, moderate exercise might significantly prevent obese and overweight adults from developing cirrhosis. The benefits appear

to be greater in individuals who exercise more than 150 minutes per week. Future investigations require more biomedical evidence to support this causal relationship.

ACKNOWLEDGEMENTS

This study was supported in part by grants from the National Science Council (NSC 102-2119-M-040 -001) and the Ministry of Science and Technology (MOST 103-2119-M-040 -001, MOST 104-2119-M-040-002).

CONFLICT OF INTEREST

The authors do not have any disclosures to report.

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How to cite this article: Jan C-F, Nfor ON, Huang J-Y, et al. Exercise might prevent cirrhosis in overweight and obese adults. *Liver Int*. 2018;38:515–522. https://doi.org/10.1111/liv.13553