Exercise might prevent cirrhosis in overweight and obese adults

Cheng-Feng Jan1 | Oswald Ndi Nfor2 | Jing-Yang Huang2 | Shu-Yi Hsu2 | Pei-Chieh Ko2 | Min-Chen Wu1 | Chien-Chang Ho3 | Yung-Po Liaw2,4

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 disease; NHIRD, National Health Insurance Research Database; ORs, odds ratio; TB, tuberculosis.

Trial registration number: Not applicable.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2017 The Authors. Liver International Published by John Wiley & Sons Ltd.
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 21\(^{st}\) 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.

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.

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.

2.2 | 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.
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/m² (overweight) included 917 men and 669 women while those with a BMI ≥27 kg/m² (Obese) included 785 men and 740 women.
Glutamic-pyruvic transferase (GPT) $\geq 40$ 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: 3.773-4.674) 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 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)              | 447 (56.94)      | 72 846 (51.21) |
| <150 min/w           | 306 (33.37)              | 262 (33.38)      | 50 516 (35.51) |
| >150 min/w           | 129 (14.07)              | 76 (9.68)        | 18 893 (13.28) |
| Low income           | 17 (1.85)                | 14 (1.78)        | 1678 (1.18)   |
| Age (y)              | <.0001                   | <.0001           |
| 40 ≤ Age < 60        | 282 (30.75)              | 270 (34.39)      | 67 316 (47.32) |
| 60 ≤ Age < 80        | 517 (56.38)              | 424 (54.01)      | 63 820 (44.86) |
| 80 < Age             | 118 (12.87)              | 91 (11.59)       | 11 119 (7.82) |
| Smoking              | <.0001                   | .1224            |
| Never                | 656 (71.54)              | 577 (73.5)       | 10 8647 (76.37) |
| ≤1 pack/d            | 197 (21.48)              | 148 (18.85)      | 24 690 (17.36) |
| >1 pack/d            | 64 (6.98)                | 60 (7.64)        | 8918 (6.27)   |
| Drinking             | <.0001                   | <.0001           |
| Never                | 650 (70.88)              | 531 (67.64)      | 98 847 (69.49) |
| Sometime             | 185 (20.17)              | 174 (22.17)      | 35 819 (25.18) |
| Frequent             | 82 (8.94)                | 80 (10.19)       | 7589 (5.33)   |
| GPT (U/L)            | <.0001                   | <.0001           |
| GPT < 40             | 452 (49.29)              | 364 (46.37)      | 102 501 (72.05) |
| GPT ≥ 40             | 465 (50.71)              | 421 (53.63)      | 39 754 (27.95) |
| eGFR ≥ 60            | 676 (73.72)              | 595 (75.8)       | 114 268 (80.33) |
| eGFR < 60            | 241 (26.28)              | 190 (24.2)       | 27 987 (19.67) |
| Diseases             |                          |                  |               |
| Diabetes mellitus    | 351 (38.28)              | 334 (42.55)      | 42 748 (30.05) |
| HBV                  | 107 (11.67)              | 86 (10.96)       | 352 (28.46)   |
| HCV                  | 93 (10.14)               | 61 (7.77)        | 1571 (11.00)  |
| Alcoholism           | 35 (3.82)                | 21 (2.68)        | 540 (0.38)    |
| Complications after index_d |                |                  |               |
| Ascites              | 29 (3.16)                | 22 (0.01)        | 25 (3.18)     | 15 (0.01)    |
| Hepatic encephalopathy | 13 (1.42)               | 7 (0.00)        | 12 (1.53)     | 3 (0.00)     |
| SBP                  | 6 (0.65)                 | 11 (1.40)        | 90 (0.06)     |
| HCC                  | 65 (7.09)                | 46 (5.86)        | 105 (0.07)    |
| Oesophageal bleeding | 5 (0.55)                 | 7 (0.89)         | 8 (0.01)      |
| Gastric varices bleeding | 27 (2.94)            | 23 (2.93)        | 959 (0.67)    |

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

|               | Overweight 24 ≤ BMI < 27 | No cirrhosis N = 207162 | P-value | Obesity BMI ≥ 27 | No cirrhosis N = 178415 | P-value |
|---------------|---------------------------|-------------------------|---------|------------------|-------------------------|---------|
| **Follow-up time (mo)** | 10.71                     |                         |         | 10.68            |                         |         |
| **Exercise**  |                           |                         |         |                  |                         |         |
| No            | 384 (57.4)                | 107 047 (51.67)         | <.0001  | 436 (58.92)      | 98 949 (55.46)          | .0696   |
| <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 (0.66)              | <.0001  | 46 (6.22)        | 100 (0.66)              | <.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...
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 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**                           |                          |                |
| 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.
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. 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.

ORCID

Yung-Po Liaw  http://orcid.org/0000-0003-2046-4964

REFERENCES

1. Sari AA, Karyani AK, Alavian SM, Arab M, Gholmohamadi FR, Rezaei S. The economic burden of liver cirrhosis in Iran: a cost of illness study. Iran J Public Health. 2015;44:512.
2. Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. Lancet. 2014;383:1749-1761.
3. Schuppan D, Afdhal NH. Liver cirrhosis. Lancet. 2008;371:838-851.
4. Davis GL, Alter MJ, El-Serag H, Poynard T, Jennings LW. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. Gastroenterology. 2010;138:513-521.e6.
5. Neff GW, Duncan CW, Schiff ER. The current economic burden of cirrhosis. Gastroenterol Hepatol (NY). 2011;7:661-671.
6. Hickman I, Jonsson J, Prins J, et al. Modest weight loss and physical activity in overweight patients with chronic liver disease results in sustained improvements in alanine aminotransferase, fasting insulin, and quality of life. Gut. 2004;53:413-419.
7. Oh S, So R, Shida T, et al. High-intensity aerobic exercise improves both hepatic fat content and stiffness in sedentary obese men with nonalcoholic fatty liver disease. Sci Rep. 2017;7:43029.
8. Jones JC, Coombes JS, Macdonald GA. Exercise capacity and muscle strength in patients with cirrhosis. Liver Transpl. 2012;18:146-151.
9. Sung K-C, Ryu S, Lee J-Y, Kim J-Y, Wild SH, Byrne CD. Effect of exercise on the development of new fatty liver and the resolution of existing fatty liver. J Hepatol. 2016;65:791-797.
10. Berzigotti A, Saran U, Dufour JF. Physical activity and liver diseases. Hepatology. 2016;63:1026-1040.
11. Hallsworth K, Thoma C, Moore S, et al. Non-alcoholic fatty liver disease is associated with higher levels of objectively measured sedentary behaviour and lower levels of physical activity than matched healthy controls. Frontline Gastroenterol. 2015;6:44-51.
12. World Health Organization. Global Recommendations on Physical Activity for Health. Geneva: World Health Organization; 2010.
13. Bi L, Triadafilopoulos G. Exercise and gastrointestinal function and disease: an evidence-based review of risks and benefits. Clin Gastroenterol Hepatol. 2003;1:345-355.
14. Keating SE, Adams LA. Exercise in NAFLD: just do it. J Hepatol. 2016;65:671-673.
15. Booth FW, Roberts CK, Laye MJ. Lack of exercise is a major cause of chronic diseases. Compr Physiol. 2012;2:1143-1211.
16. Franciscus A. Disease progression: what is cirrhosis HCS$ version 2010:3.
17. Guo R, Liong EC, So KF, Fung M-L, Tipoe GL. Beneficial mechanisms of aerobic exercise on hepatic lipid metabolism in non-alcoholic fatty liver disease. Hepatobiliary Pancreat Dis Int. 2015;14:139-144.
18. Whitsett M, Vanwagner LB. Physical activity as a treatment for non-alcoholic fatty liver disease: a systematic review. World J Hepatol. 2015;7:2041.
19. Eriksson A, Gretzer C, Wallerstedt S. Elevation of cytokines in peritoneal fluid and blood in patients with liver cirrhosis. Hepatogastroenterology. 2003;51:505-509.
20. Reuben DB, Judd-Hamilton L, Harris TB, Seeman TE. The associations between physical activity and inflammatory markers in high-functioning older persons: MacArthur studies of successful aging. J Am Geriatr Soc. 2003;51:1125-1130.
21. Benvegnù L, Fattovich G, Noventa F, et al. Concurrent hepatitis B and C virus infection and risk of hepatocellular carcinoma in cirrhosis. A prospective study. Cancer. 1994;74:2442-2448.
22. Walker M, El-Serag H, Sada Y, et al. Cirrhosis is under-recognised in patients subsequent diagnosed with hepatocellular cancer. Aliment Pharmacol Ther. 2016;43:621-630.

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