

# World Journal of *Gastroenterology*

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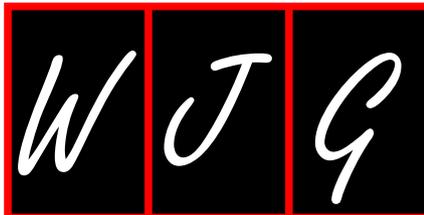
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Retrospective Study

## Chronic hepatitis B, nonalcoholic steatohepatitis and physical fitness of military males: CHIEF study

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### Abstract

#### AIM

To investigate the association of chronic hepatitis B and nonalcoholic steatohepatitis with physical fitness in a

Taiwanese military male cohort.

## METHODS

We made a cross-sectional examination of this association using 3669 young adult military males according to cardiorespiratory fitness and hospitalization events recorded in the Taiwan Armed Forces study. Cases of chronic hepatitis B ( $n = 121$ ) were defined by personal history and positive detection of hepatitis B surface antigen. Cases of nonalcoholic steatohepatitis ( $n = 129$ ) were defined by alanine transaminase level  $> 60$  U/L, liver ultrasound finding of steatosis, and absence of viral hepatitis A, B or C infection. All other study participants were defined as unaffected ( $n = 3419$ ). Physical fitness was evaluated by performance in 3000-m run, 2-min sit-ups, and 2-min push-ups exercises, with all the procedures standardized by a computerized scoring system. Multiple linear regression analysis was used to determine the relationship.

## RESULTS

Chronic hepatitis B negatively correlated with 2-min push-up numbers ( $\beta = -2.49$ ,  $P = 0.019$ ) after adjusting for age, service specialty, body mass index, systolic and diastolic blood pressures, current cigarette smoking, alcohol intake status, serum hemoglobin, and average weekly exercise times. Nonalcoholic steatohepatitis was borderline positively correlated with 3000-m running time ( $\beta = 11.96$ ,  $P = 0.084$ ) and negatively correlated with 2-min sit-up numbers ( $\beta = -1.47$ ,  $P = 0.040$ ).

## CONCLUSION

Chronic hepatitis B viral infection and nonalcoholic steatohepatitis affects different physical performances in young adult military males, and future study should determine the underlying mechanism.

**Key words:** Chronic hepatitis B; Military cohort; Physical fitness; Nonalcoholic steatohepatitis

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**Core tip:** We investigated the association of chronic hepatitis B and nonalcoholic steatohepatitis with physical fitness in a large population of young adult Taiwanese military males. The results demonstrated that men with chronic hepatitis B had fewer 2-min push-up numbers than unaffected men, whereas men with nonalcoholic steatohepatitis had longer time to complete a 3000-m run and fewer 2-min sit-up numbers than unaffected men. Our findings suggest that chronic hepatitis B and nonalcoholic steatohepatitis might influence different physical performances. The mechanisms underlying the relationship between hepatitis and physical fitness are not fully understood and further investigations are needed.

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## INTRODUCTION

According to the Taiwan Health and Welfare Report in 2015<sup>[1]</sup>, there were 2.5 million adult carriers of hepatitis B in Taiwan, with a prevalence of 15%-20%. In 1984, Taiwan launched a nationwide vaccination program to control the form of hepatitis caused by hepatitis B virus<sup>[2]</sup>. Over the next 10 years, this program successfully reduced the rate of hepatitis B carriers among children, from 10% to  $< 1\%$ <sup>[3]</sup>.

As is well known, chronic hepatitis B is associated with higher risk of liver cirrhosis and hepatocellular carcinoma. In addition, hepatitis B infection in the presence of liver dysfunction has been associated with higher risk of hemorrhagic stroke, but with lower risk of myocardial infarction and ischemic stroke<sup>[4]</sup>. However, the association between hepatitis B and incident cardiovascular events is null as long as liver function is preserved<sup>[4]</sup>.

Besides viral hepatitis, liver damage is usually related to non-viral etiologies, such as cholestasis, steatosis, drugs or alcohol, and systemic hypoperfusion. These hazardous agents may cause hepatic necrosis, leading to increased liver enzymes in circulation, including that of aspartate transaminase (AST) and alanine transaminase (ALT). However, elevated AST levels are not only found with liver parenchymal damage but also occur upon cardiac or skeletal muscle injury. Elevated ALT levels, on the other hand, are much more specific to liver damage<sup>[5]</sup>. In general,  $> 1.5$ -fold increase over the upper normal limit of ALT is indicative of active hepatitis<sup>[6]</sup>.

Nonalcoholic steatohepatitis (NASH), a severe type of nonalcoholic fatty liver disease (NAFLD), is a growing endemic liver disease, especially in developed countries. Characterized by elevated ALT levels and fat infiltration of the liver, NASH and NAFLD are highly related to metabolic diseases, such as obesity, dyslipidemia, hyperuricemia and type 2 diabetes<sup>[7]</sup>. In East Asian countries, the prevalence of NAFLD in middle-aged adults varies from 11.5% to 23.3% and that in children or teenagers ranges from 3.4% to 5.2%<sup>[8,9]</sup>. High levels of ALT are correlated with a higher risk of NASH<sup>[10,11]</sup>, and similar to chronic hepatitis B-NASH is one of the major causes of liver cirrhosis and hepatoma in Taiwan. NASH is also a risk factor of ischemic cardiovascular disease<sup>[12]</sup>.

Previous studies have demonstrated that both chronic hepatitis B and NASH or NAFLD are associated with a pre-sarcopenia and sarcopenia status in middle- and old-aged populations<sup>[13-15]</sup>. However,

few epidemiologic studies reported in the publicly available literature have examined the association of chronic hepatitis B and NASH with physical fitness (characterized by endurance and resistance exercises) in young adults. And, none of those studies has addressed the issue in Asian populations<sup>[16-18]</sup>. Therefore, we investigated the associations in a large cohort of young adult men in Taiwan working under a regimented physical fitness program (military).

## MATERIALS AND METHODS

### Study population

The study of cardiorespiratory fitness and hospitalization events in armed forces (known as the "CHIEF Study") provides a historical cohort consisting of 4080 professional military members, of ages between 18 and 50 years. All participants completed the annual health examination in eastern Taiwan during 2014, in which they underwent any one of three exercise tests, including 2-min push-ups, 2-min sit-ups, and 3000-m non-weight-bearing running. The CHIEF study design has been described in detail previously<sup>[19]</sup>.

Of the 4080 total participants, we excluded 411 women because none fulfilled the criterion for acute hepatitis [as defined by an ALT level > 60 U/L, equating to 1.5-times the upper limit (40 U/L) of the normal levels of ALT]. Of the remaining 3669 study subjects (all male), 121 (3.3%) were diagnosed with chronic hepatitis B according to personal history and detection of hepatitis B virus surface antigen. Among the 3548 persons without chronic hepatitis B, a total of 129 (3.5%) were clinically diagnosed with NASH based on ALT level > 60 U/L, liver ultrasound showing steatosis, absence of other viral hepatitis (A and C), and without excessive alcohol intake.

It was noted that two men had both chronic hepatitis B and an ALT level > 60 U/L. Those men who were free of chronic hepatitis B and had ALT ≤ 60 U/L were classified as the "unaffected" group ( $n = 3419$ , 93.2%). The composition of the three groups (chronic hepatitis B, NASH, and unaffected) are shown in Table 1.

### Measurements

Participants' medical history taking and annual health examination were performed in the Hualien Armed Forces General Hospital of Hualien County in Eastern Taiwan. Each participant was asked to complete a self-report questionnaire to provide details of his medical history, including chronic viral hepatitis B carrier status, cigarette smoking status (never, former, and current), alcohol intake status (never and current), frequency of > 30-min exercise in leisure time, and medications taken in the past 6 mo.

The physical health examination included: anthropometric measurements of height, weight, and body mass index (weight, kg/height, m<sup>2</sup>; assessed in a standing position); hemodynamic data of pulse

rate and blood pressures [in the right upper arm; measured in a sitting position after rest for at least for 15 min, using the FT-201 automated blood pressure monitor (Parama-Tech Co Ltd, Fukuoka, Japan)]; and laboratory data of hemoglobin, AST, ALT, and hepatitis B surface antigen (by standard blood testing). As part of the annual health survey routine, cases of elevated ALT level of unknown cause undergo work-up that includes a liver ultrasound and serologic testing for anti-hepatitis A virus IgM, anti-hepatitis C virus IgG, and alpha-fetoprotein. Liver ultrasounds were performed by experienced sonographers, and diffuse hepatic steatosis was defined by the presence of significant liver-kidney contrast<sup>[20]</sup>.

The three exercise tests were administered by trained experts at the Military Physical Training and Testing Center in Eastern Taiwan under stringent and consistent regimens and the corresponding measurements of physical fitness were standardized. Both the 2-min push-up and 2-min sit-up tests were scored using computerized monitoring, and the entire test course was recorded by video. For the former, a push-up was scored only when the participant's body upward movement achieved the initial resting set height levels of shoulder and buttock, as detected simultaneously by infrared sensors. The test was aborted immediately upon either elbows or knees touching down on the ground before the time out. For the latter, a sit-up was scored only when the participant's body bent forward and elbows contacted the touch sensors on both thighs. For the 3000-m non-weight-bearing running test, the entire course was recorded by video. All runs occurred at 4:00 pm on a day without rain, when the risk coefficient of heat stroke [the product of outdoor temperature (°C) and relative humidity (%) × 0.1] was < 40.

### Statistical analysis

The participants' baseline characteristics were summarized as mean ± SD for continuous data and as numbers and percentages for categorical data. The outcome of interest was evaluated by the performance of exercises. Cardiorespiratory fitness and lower extremity muscle strength were mainly evaluated by the 3000-m running time (in s). Abdominal and psoas muscles strength was evaluated by the 2-min sit-up numbers. Upper extremity muscle strength was evaluated by the 2-min push-up numbers.

The effect of chronic hepatitis B, NASH and unaffected status on performance of each exercise (*i.e.*, timed duration of 3000-m running race, numbers of 2-min sit-ups, and numbers of 2-min push-ups) was estimated by using analysis of covariance (ANCOVA), and the results are presented as mean ± SE. A linear regression of each exercise performance with chronic hepatitis B and NASH, in reference to the unaffected group, was also performed. In addition, logistic regression was used to determine the odds of the best (top 10<sup>th</sup> percentile) and the worst (last 10<sup>th</sup> percentile)

**Table 1** Baseline characteristics of military men with chronic hepatitis B or nonalcoholic steatohepatitis, and the unaffected

	Chronic hepatitis B, <i>n</i> = 121	Nonalcoholic steatohepatitis, <i>n</i> = 129	Unaffected, <i>n</i> = 3419	<i>P</i> value
Age in years	33.5 ± 4.1	30.2 ± 5.1	29.2 ± 5.9	< 0.0001
Service specialty				0.29
Air force	36 (29.75)	38 (29.46)	953 (27.87)	
Army	55 (45.45)	56 (43.41)	1743 (50.98)	
Navy	30 (24.79)	35 (27.13)	723 (21.15)	
BMI in kg/m <sup>2</sup>	25.5 ± 2.7	27.6 ± 2.5	24.7 ± 3.1	< 0.0001
Waist circumference in cm	85.4 ± 6.4	90.0 ± 5.9	83.1 ± 8.0	< 0.0001
SBP in mmHg	117.2 ± 12.7	123.4 ± 12.6	118.2 ± 13.1	< 0.0001
DBP in mmHg	71.6 ± 10.7	73.6 ± 10.4	70.4 ± 10.1	0.0009
Heart rate in beats/min	74.9 ± 10.8	74.0 ± 11.7	72.0 ± 10.8	0.0021
Hypertension	11 (9.09)	17 (13.18)	294 (8.60)	0.19
AST in U/L	24.1 ± 13.7	43.4 ± 16.4	19.8 ± 6.8	< 0.0001
ALT in U/L	32.7 ± 27.8	85.4 ± 29.9	20.4 ± 10.8	< 0.0001
Hb in g/dL	15.2 ± 1.0	15.4 ± 1.1	15.2 ± 1.0	0.016
Cigarette smoking	38 (31.40)	43 (33.86)	1295 (38.46)	0.18
Alcohol drinking	62 (51.24)	47 (36.43)	1507 (44.08)	0.062
Exercise frequency				0.55
Never or occasionally	23 (19.01)	27 (20.93)	719 (21.03)	
1-2 times/wk	43 (35.54)	56 (43.41)	1279 (37.41)	
> 3-5 times/wk	55 (45.45)	46 (35.66)	1421 (41.56)	

Continuous variables are expressed as mean ± SD, and categorical variables as *n* (%). ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; DBP: Diastolic blood pressure; Hb: Hemoglobin; SBP: Systolic blood pressure.

performance in each exercise with chronic hepatitis B and NASH, in reference to the unaffected.

In model 1, age and service specialty were adjusted. In model 2, body mass index was additionally adjusted. In model 3, systolic and diastolic blood pressures, pulse rate, current smoking status, current alcohol intake status, hemoglobin, and average exercise frequency per wk were further adjusted. These potential confounders were chosen for the models according to prior published associations with physical fitness<sup>[21-23]</sup>.

A 2-tailed value of *P* < 0.05 was considered significant. SAS statistical software (SAS System for Windows, version 9.4; SAS Institute, Cary, NC, United States) was used for all statistical analyses.

## RESULTS

### Baseline group characteristics

The baseline characteristics of each study group are shown in Table 1. Participants with chronic hepatitis B had modestly older age, higher pulse rate, and greater proportion of current alcohol drinkers than those with NASH and the unaffected participants. In addition, participants with NASH had greater AST and ALT levels, greater body mass index, and higher blood pressures and hemoglobin levels.

### Group means comparisons

There was a significant difference between the means of performances for each exercise among the study groups (across the three models, overall *P* value < 0.0001; Table 2). With regard to the 3000-m run and 2-min sit-up tests, the performance of those with NASH was the worst among the study groups and

significantly worse than that in the unaffected group (in models 1-3, despite the difference in the running test being modestly reduced after the adjustments for all covariates in model 3, *P* = 0.069). With regard to the 2-min push-up test, the performance of those with chronic hepatitis B was the worst among the study groups and worse than that in the unaffected group (in models 1-3).

### Multiple linear regression

The results of multiple linear regression of each physical performance, with chronic hepatitis B and NASH relative to the unaffected group, in models 1-3 are shown in Table 3. The relationship between the three groups and each exercise performance are in line with the findings presented in Table 2. Chronic hepatitis B was negatively correlated with the 2-min push-up numbers in model 3 ( $\beta$  = -2.49, *P* = 0.019). In addition, NASH was positively correlated with 3000-m running time ( $\beta$  = 15.48, *P* = 0.026) and negatively correlated with the 2-min sit-up numbers ( $\beta$  = -1.79, *P* = 0.013) after adjusting for age, specialty, and body mass index (Table 2). The association with 2-min sit-up numbers remained significant, but that with the 3000-m running time was modestly reduced ( $\beta$  = 11.96, *P* = 0.084).

### Logistic regression

Table 4 presents the results of logistic regression of the best 10% and the worst 10% performance in each exercise, with chronic hepatitis B and NASH in reference to the unaffected. In model 1, participants with NASH had 1.5-fold to 2.0-fold increased risk of achieving performance in the worst 10% for the

**Table 2 Relationship of chronic hepatitis B, nonalcoholic steatohepatitis, and unaffected status with exercise performances**

	3-m run			2-min sit-ups			2-min push-ups		
	<i>n</i>	mean ± SE	<i>P</i> value	<i>n</i>	mean ± SE	<i>P</i> value	<i>n</i>	mean ± SE	<i>P</i> value
Model 1			< 0.0001 <sup>1</sup>			< 0.0001 <sup>1</sup>			< 0.0001 <sup>1</sup>
Chronic hepatitis B	106	862.90 (6.88)	0.007 <sup>2</sup>	120	47.04 (0.73)	0.13 <sup>2</sup>	120	46.71 (1.07)	0.58 <sup>2</sup>
Nonalcoholic steatohepatitis	102	889.18 (6.95)	< 0.0001 <sup>3</sup>	128	45.52 (0.70)	0.0032 <sup>3</sup>	127	45.90 (1.03)	0.0007 <sup>3</sup>
Unaffected	3088	858.41 (1.34)	0.52 <sup>4</sup>	3403	47.61 (0.14)	0.44 <sup>4</sup>	3394	49.44 (0.21)	0.012 <sup>4</sup>
Model 2			< 0.0001 <sup>1</sup>			< 0.0001 <sup>1</sup>			< 0.0001 <sup>1</sup>
Chronic hepatitis B	106	861.15 (6.69)	0.17 <sup>2</sup>	120	47.05 (0.73)	0.22 <sup>2</sup>	120	46.86 (1.06)	0.56 <sup>2</sup>
Nonalcoholic steatohepatitis	102	874.35 (6.83)	0.0025 <sup>3</sup>	128	47.80 (0.71)	0.0013 <sup>3</sup>	127	47.71 (1.03)	0.11 <sup>3</sup>
Unaffected	3081	858.75 (1.31)	0.72 <sup>4</sup>	3395	47.60 (0.14)	0.46 <sup>4</sup>	3385	49.40 (0.21)	0.018 <sup>4</sup>
Model 3			< 0.0001 <sup>1</sup>			< 0.0001 <sup>1</sup>			< 0.0001 <sup>1</sup>
Chronic hepatitis B	105	866.74 (6.54)	0.30 <sup>2</sup>	119	46.68 (0.72)	0.33 <sup>2</sup>	119	46.37 (1.05)	0.35 <sup>2</sup>
Nonalcoholic steatohepatitis	100	876.41 (6.70)	0.069 <sup>3</sup>	125	45.71 (0.71)	0.043 <sup>3</sup>	124	47.74 (1.04)	0.29 <sup>3</sup>
Unaffected	3029	864.07 (1.38)	0.69 <sup>4</sup>	3340	47.16 (0.15)	0.51 <sup>4</sup>	3330	48.86 (0.22)	0.020 <sup>4</sup>

<sup>1</sup>Overall *P* value; <sup>2</sup>Chronic hepatitis B *vs* nonalcoholic steatohepatitis; <sup>3</sup>Nonalcoholic steatohepatitis *vs* unaffected; <sup>4</sup>Chronic hepatitis B *vs* unaffected. Model 1: Adjusted for age and service specialty; Model 2: Adjusted for age, service specialty, and body mass index; Model 3: Adjusted for age, service specialty, body mass index, systolic blood pressure, diastolic blood pressure, heart rate, current smoking, alcohol intake, hemoglobin, and exercise frequency.

**Table 3 Linear regression of chronic hepatitis B and nonalcoholic steatohepatitis with exercise performances**

	Chronic hepatitis B		Nonalcoholic steatohepatitis	
	β (SE)	<i>P</i> value	β (SE)	<i>P</i> value
Model 1				
Running	4.59 (6.98)	0.51	30.65 (7.05)	< 0.0001
Sit-ups	-0.58 (0.74)	0.43	-2.09 (0.71)	0.0033
Push-ups	-2.75 (1.09)	0.01	-3.49 (1.05)	0.009
Model 2				
Running	2.54 (6.79)	0.71	15.48 (6.94)	0.026
Sit-ups	-0.55 (0.74)	0.45	-1.79 (0.72)	0.013
Push-ups	-2.57 (1.07)	0.017	-1.65 (1.05)	0.12
Model 3				
Running	1.98 (6.68)	0.10	11.96 (6.91)	0.084
Sit-ups	-0.45 (0.73)	0.53	-1.47 (0.72)	0.04
Push-ups	-2.49 (1.06)	0.019	-1.10 (1.05)	0.30

Model 1: Adjusted for age and service specialty; Model 2: Adjusted for age, service specialty, and body mass index; Model 3: Adjusted for age, service specialty, body mass index, systolic blood pressure, diastolic blood pressure, heart rate, current smoking, alcohol intake, hemoglobin, and exercise frequency.

3000-m run, the 2-min sit-ups and the 2-min push-ups tests, as compared to the unaffected group (OR = 1.86, 1.55 and 1.80, respectively). However, the associations were remarkably reduced and became insignificant in model 2 and model 3 (OR = 1.14, 1.24 and 1.08, respectively). In contrast, chronic hepatitis B was not associated with worst 10% performance for any of the three exercise tests, in models 1-3. In addition, neither chronic hepatitis B or NASH were associated with the best 10% performance for any of the three exercise tests, in models 1-3.

## DISCUSSION

Our principal findings were that both chronic hepatitis B and NASH were associated with worse physical

performance in a young adult military male cohort in Taiwan. The men with chronic hepatitis B achieved fewer numbers of push-ups in 2 min, possibly having to do with lower strength of the upper extremities. The men with NASH spent a longer time completing the 3000-m run and had fewer numbers of sit-ups in 2 min, reflecting their cardiorespiratory fitness and strength of lower extremities and psoas muscles being lower than those of the unaffected men.

Both chronic hepatitis B and NASH have been reported as associated with skeletal muscle atrophy, probably leading to decreased physical fitness. In an abdominal computed tomography imaging study, Hiraoka *et al.*<sup>[13]</sup> found the prevalence of pre-sarcopenia in patients with chronic hepatitis due to hepatitis B or C virus, or with alcoholic hepatitis, as about 15.3%, which was higher than that of the normal controls, regardless of age. In addition, NASH and NAFLD are closely related to obesity and insulin resistance. Some studies have demonstrated the effect of insulin resistance on mitochondrial dysfunction, suggesting that NASH or NAFLD may be related to muscle mass wasting (*i.e.*, sarcopenia)<sup>[15]</sup>. Along these lines, Hong *et al.*<sup>[14]</sup> found a significant correlation between NAFLD and sarcopenia, according to strict evaluation by dual-energy X-ray absorptiometry in middle- to old-aged men.

The histological severity of NAFLD ranges from steatosis and steatohepatitis, to advanced fibrosis and even cirrhosis. The risk factors of NAFLD are male sex, increased age, and the main components of metabolic syndrome (*i.e.*, higher body mass index, triglycerides and total cholesterol). NAFLD is, thus, considered as a hepatic manifestation of metabolic syndrome<sup>[24]</sup>. In addition, multiple metabolic abnormalities have been characterized as strongly predictive of NASH.

The prevalence of metabolic syndrome is reportedly

**Table 4 Association of chronic hepatitis B and nonalcoholic steatohepatitis with best 10% and worst 10% of exercise performances**

	Chronic hepatitis B		Nonalcoholic steatohepatitis		Unaffected Ref.
	OR (95%CI)	P value	OR (95%CI)	P value	
For the top 10% performance level					
Model 1					
Running ≤ 783 s	0.85 (0.52-1.41)	0.53	1.26 (0.82-1.92)	0.29	1.00
Sit-ups ≥ 58/2 min	0.78 (0.37-1.62)	0.50	0.28 (0.10-0.77)	0.013	1.00
Push-ups ≥ 60/2 min	0.64 (0.31-1.33)	0.23	0.43 (0.20-0.93)	0.033	1.00
Model 2					
Running ≤ 783 s	0.85 (0.51-1.40)	0.52	1.20 (0.78-1.84)	0.41	1.00
Sit-ups ≥ 58/2 min	0.78 (0.38-1.63)	0.51	0.30 (0.11-0.83)	0.021	1.00
Push-ups ≥ 60/2 min	0.65 (0.31-1.36)	0.26	0.56 (0.26-1.22)	0.14	1.00
Model 3					
Running ≤ 783 s	0.85 (0.52-1.41)	0.53	1.16 (0.75-1.80)	0.50	1.00
Sit-ups ≥ 58/2 min	0.79 (0.38-1.66)	0.53	0.32 (0.12-0.89)	0.028	1.00
Push-ups ≥ 60/2 min	0.68 (0.32-1.42)	0.30	0.60 (0.28-1.32)	0.21	1.00
For the bottom 10% performance level					
Model 1					
Running ≥ 934 s	1.15 (0.63-2.07)	0.65	1.86 (1.14-3.04)	0.013	1.00
Sit-ups < 40/2 min	0.98 (0.59-1.62)	0.93	1.55 (0.92-2.61)	0.098	1.00
Push-ups < 37/2 min	1.50 (0.88-2.55)	0.13	1.80 (1.12-2.88)	0.015	1.00
Model 2					
Running ≥ 934 s	1.12 (0.62-2.03)	0.71	1.22 (0.74-2.02)	0.44	1.00
Sit-ups < 40/2 min	0.96 (0.58-1.60)	0.88	1.42 (0.84-2.41)	0.19	1.00
Push-ups < 37/2 min	1.48 (0.87-2.53)	0.15	1.24 (0.76-2.01)	0.39	1.00
Model 3					
Running ≥ 934 s	1.15 (0.63-2.10)	0.65	1.14 (0.68-1.92)	0.65	1.00
Sit-ups < 40/2 min	0.95 (0.56-1.59)	0.83	1.24 (0.71-2.15)	0.54	1.00
Push-ups < 37/2 min	1.46 (0.85-0.52)	0.17	1.08 (0.65-1.79)	0.76	1.00

Model 1: Adjusted for age and service specialty; Model 2: Adjusted for age, service specialty, and body mass index; Model 3: Adjusted for age, service specialty, body mass index, systolic blood pressure, diastolic blood pressure, heart rate, current smoking, alcohol intake, hemoglobin, and exercise frequency.

lower in individuals with higher levels of physical fitness<sup>[25]</sup>. Cardiorespiratory fitness and muscular strength are also inversely associated with metabolic syndrome prevalence<sup>[26,27]</sup>, as well as with intrahepatic fat content, but are independent of visceral and total body fat mass<sup>[28,29]</sup>. Krasnoff *et al.*<sup>[16]</sup> further found that patients with NAFLD of differing histological severity had suboptimal health-related fitness, and patients with NASH and those with lower NAFLD activity score had significantly lower cardiorespiratory fitness than their counterparts.

Westerbacka *et al.*<sup>[30]</sup> demonstrated that serum ALT was significantly correlated with percentage of liver fat, and further suggested that serum ALT might be a useful marker of liver fat in individuals lacking other causes of liver damage or insulin resistance. Indeed, several studies have used elevated serum ALT as a non-invasive indicator of NASH. Data from the 1988-1994 United States National Health and Nutrition Examination Survey (NHANES) indicated elevated ALT in 3% of the middle- to old-aged general population<sup>[31]</sup>, and the 1999-2002 NHANES data indicated elevated ALT in as high as 7% of the study population<sup>[32]</sup>.

Only few studies to date have investigated the relationship between ALT levels and physical fitness in young adults. In our present study, the prevalence of elevated ALT levels (> 60 U/L) in young adult military males was 3.5%, close to the percentage from

NHANES. The men with NASH had worse performances in the three exercise examinations, after controlling for age and service specialty. The association of NASH with 2-min push-up numbers was nullified upon adjustment for body mass index and other potential covariates, whereas the associations of NASH with 2-min sit-up numbers and 3000-m running time were only modestly reduced upon adjustment.

These findings were in line with results of previous studies. Church *et al.*<sup>[17]</sup> showed that serum ALT levels were inversely associated with physical fitness; although, the association was reduced after controlling for both body mass index and waist circumference. In addition, Trilk *et al.*<sup>[18]</sup> also found that teenagers and young adults with low cardiorespiratory fitness had higher ALT levels than those with adequate cardiorespiratory fitness.

Ironically, we showed that chronic hepatitis B may reduce muscle strengths of the upper extremities in the early thirties, but not affect the strength of lower extremities or of cardiorespiratory fitness. Notably, there were only two men in our cohort with both chronic hepatitis B and ALT levels > 60 U/L. We speculate that the decreased muscle strength of the upper extremities was not caused by chronic active hepatitis B. Although pre-sarcopenia might lead to weaker muscle strength of the upper extremities in the early stages of chronic hepatitis B, the sparing effect

of the lower extremities and cardiorespiratory fitness remains unclear and needs further investigation.

Finally, among the young men in our study who were within the top 10% of the exercise performances (showing outstanding physical fitness), there were no significant differences between the three exercise tests when those with NASH were compared to the unaffected individuals. This result suggests that the change in liver function did not significantly affect exercise performance in elite participants of physical fitness trainees. As for the bottom 10%, those with NASH had worse performance in all three exercise tests, even after adjusting for age and service specialty. However, the associations became remarkably reduced after adjusting for body mass index. These findings indicate that, in such a group, the main factors affecting physical performance may be derived from body weight or obesity rather than liver damage.

There are several strengths in this study's design. First, all procedures of the three exercise tests for evaluations of physical fitness were standardized and performed in a strictly regimented manner. Second, the sample size of this study was large enough to identify adequate numbers of participants with chronic hepatitis B or NASH for analysis. Nonetheless, there were some limitations to the study. First, the liver ultrasounds were not routinely performed for every participant with normal ALT levels, and thus the prevalence of NAFLD in the unaffected men might be a potential confounder. Since previous studies have shown that NAFLD was associated with poor physical fitness, the inverse association of NASH with the exercise performances might be underestimated. Second, the severity of NASH lacked pathologic evidence, despite our having identified individuals at risk through ultrasonic liver-kidney contrast and a strict ALT level. Third, there might be potential recall bias regarding the self-report questionnaire answers.

In conclusion, our findings suggest that chronic hepatitis B and NASH may affect different exercise performances in a young adult military male cohort. The mechanisms underlying the relationship between hepatitis and physical fitness are still not fully understood and require further investigation.

## COMMENTS

### Background

Previous studies have reported that both chronic hepatitis B and nonalcoholic steatohepatitis (NASH) are associated with pre-sarcopenia and sarcopenia status in middle- and old-aged populations. However, few epidemiologic studies are available to examine the association of chronic hepatitis B and NASH with physical fitness in young adults, particularly those of Asian race.

### Research frontiers

This study is the first, to our knowledge, to investigate the association of chronic hepatitis B and NASH with physical fitness in a large young adult military male cohort in Taiwan.

### Innovations and breakthroughs

Among young adult military males, those with chronic hepatitis B had fewer

numbers of 2-min push-ups than the unaffected men, whereas those with NASH had longer 3000-m running time and fewer 2-min sit-up numbers than the unaffected men. These findings suggest that chronic hepatitis B and NASH might influence different physical performances.

### Applications

Chronic hepatitis B and NASH may be targets for therapeutic intervention to improve physical fitness among these patient populations.

### Terminology

The cardiorespiratory fitness of each participant was mainly evaluated by the time it took to complete a 3000-m run, the number of standardized push-ups within 2 min, and the number of standardized sit-ups within 2 min. Chronic hepatitis B was defined by personal history and positive detection of hepatitis B surface antigen. NASH was defined by alanine transaminase level > 60 U/L, liver ultrasound finding of steatosis, and absence of viral hepatitis A, B or C infection.

### Peer-review

The article is very good, as it is the first one describing the relationship between liver functions and physical fitness in Taiwan.

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