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Dose-response relationship between physical activity and nonalcoholic fatty liver disease: A prospective cohort study

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To the Editor: Nonalcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases globally, and this systemic disease carries a substantial economic burden and will result in a greater disease burden in the future.[1]

Mass screening of asymptomatic individuals using ultrasonography is not cost-effective. Therefore, simple, noninvasive tests are required to identify patients with NAFLD. The fatty liver index (FLI) and hepatic steatosis index (HSI) are accurate and easy to obtain, and offer practical, economical, and noninvasive means of identifying NAFLD in a database study.[2]

Physical activity (PA) is an important lifestyle modification used to treat NAFLD. However, evidence of an etiological relationship between PA and NAFLD from cohort study is lacking. Accordingly, in the present study, we estimated the association between leisure-time PA and the risk for NAFLD defined by two noninvasive markers—FLI and HSI—in a large prospective cohort in Taiwan, China. Here, we describe our findings and provide advice for preventing NAFLD.

Participants were selected from a population that had taken part in health examinations at MJ Health Management Institution in Taiwan, China. Information on demographics, lifestyle, socioeconomic status, and medical history was acquired using a self-administered questionnaire. Medical examinations were conducted according to the willingness and the membership class of the participants. Signed informed consent was provided by every participant before beginning the examination. Ethical approval for this study was obtained from the Ethical Committee from the Peking University Health Science Center (No. IRB00001052-20026).

The flowchart of participant selection is shown in [Supplementary Figure 1, http://links.lww.com/CM9/B498]. A total of 668,806 participants aged ≥18 years whose health was-examined between 1996 and 2010 were recruited into the study. Exclusion criteria included: (1) missing data for of crucial variables; (2) daily alcohol consumption >30 g for males and 20 g for females; (3) a previous diagnosis of hepatitis, cirrhosis, or acute liver disease; (4) the presence of NAFLD at baseline; and (5) data from only one medical examination.

Data on PA were collected using a self-administered questionnaire. We used metabolic equivalent of task (MET) to standardize the intensity of different types of exercise, assigning a MET of 2.5 for light (e.g., walking), 4.5 for moderate (e.g., brisk walking), 6.5 for medium-vigorous (e.g., jogging), and 8.5 for high-vigorous (e.g., running) exercise. Then we calculated hours of MET (MET-h) based on the type, frequency, and duration of PA. We divided MET-h per week into five categories in accordance with classifications in PA guidelines for Americans[3]: very low (<3.75 MET-h), low (3.75–7.49 MET-h), moderate (7.50–16.49 MET-h), high (16.50–25. 49 MET-h), and very high (≥25.50 MET-h).

FLI and HSI were introduced to help researchers identify patients with fatty liver;[4,5] FLI is calculated as

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$$FLI = 100 \times \frac{e^{0.953 \times \ln(\text{triglycerides}) + 0.139 \times BMI + 0.718 \times \ln(GGT) + 0.053 \times WC - 15.745}}{1 + e^{0.953 \times \ln(\text{triglycerides}) + 0.139 \times BMI + 0.718 \times \ln(GGT) + 0.053 \times WC - 15.745}},$$

where GGT stands for gamma-glutamyl transferase, WC stands for waist circumference, and BMI stands for body mass index. We set the cut point at 30.

HSI is calculated as

$$HSI = 8 \times \frac{ALT}{AST} ratio + BMI (+2, \text{if diabetes mellitus}; +2, \text{if female}),$$

where ALT stands for alanine aminotransferase, and AST stands for aspartate aminotransferase. The cut point was set at 36.

We performed Cox regression with time-dependent covariates to investigate the association between PA and NAFLD. All independent variables except for demographic variables were treated as time-dependent variables to account for change during the study period. We ran three models that introduced the covariates in a stepwise manner. The full model was adjusted for age, sex, education, BMI, fruit intake, vegetable intake, fried food intake, season, smoking, alcohol consumption, strenuousness of work, occupational exposure, hypertension, diabetes, dyslipidemia, cancer, and cardiovascular disease. Trend tests were performed across PA categories. We also conducted subgroup analyses based on metabolic syndrome (MS) to explore the different effects of PA on NAFLD in specific populations. Statistical analyses were performed in R 4.0.2 (The R Foundation). A two-tailed $P < 0.05$ was considered statistically significant.

When we used FLI to measure NAFLD, 121,607 participants were ultimately included in the cohort. The incidence of NAFLD in the cohort was 13.03% over a median duration of 3.50 years of follow-up (interquartile range: 1.94–6.62 years). Participants took part in a health examination every 1.17 (interquartile range: 0.89–1.80) years in the cohort. Supplementary Table 1, http://links.lww.com/CM9/B498 displays the baseline characteristics of the FLI cohort. Baseline characteristics of the FLI cohort by PA category are shown in Supplementary Table 2, http://links.lww.com/CM9/B498.

The association between PA and FLI-defined NAFLD is shown in Figure 1A. After adjusting all potential covariates, the low PA group had a hazard ratio (HR) of 0.91 (95% confidence interval [CI]: 0.88, 0.95), the moderate PA group had an HR of 0.88 (95% CI: 0.84, 0.91), the high PA group had an HR of 0.79 (95% CI: 0.74, 0.84), and the very high PA group had an HR of 0.71 (95% CI: 0.66, 0.77). A trend test further showed a statistically significant association between PA and FLI-defined NAFLD ($P < 0.001$).

When we treated PA as a continuous variable, we found that higher PA was associated with a lower risk for FLI-defined NAFLD. Each 5 MET-h/week increase in PA was associated with a 4% (95% CI: 3%, 5%) decrease in the risk for FLI-defined NAFLD. The dose–response association between PA and FLI-defined NAFLD is shown in Figure 1B.

The results of subgroup analyses are shown in Figure 1A. In the MS group, moderate PA and high PA had a significant effect on NAFLD, which indicates that MS patients should engage in moderate to high PA to protect themselves from NAFLD. No evidence of significant interaction between MS and PA was found (P for interaction >0.05).

When we used HSI to measure NAFLD, 118,946 participants were included in the cohort. Supplementary Table 1 (http://links.lww.com/CM9/B498) shows the baseline characteristics of the HSI cohort. Baseline characteristics of the HSI cohort by PA category are shown in Supplementary Table 3 (http://links.lww.com/CM9/B498).

The association between PA and HSI-defined NAFLD is shown in Figure 1C. The results are similar to those of the FLI cohort. Each 5 MET-h/week increase in PA was associated with a 3% (95% CI: 2%, 4%) decrease in the risk for HSI-defined NAFLD. When we plotted the dose–response association between PA and NAFLD, a similar curve was observed [Figure 1D]. Subgroup analyses showed similar results to those of the FLI subgroup analyses [Figure 1C].

The present prospective cohort study from Taiwan, China, showed an inverse dose–response association between PA and the risk for NAFLD, indicating that higher PA is related to a lower risk for NAFLD after adjustment for a wide range of covariates. Subgroup analyses revealed that in MS populations, compared with very low PA, high PA was associated with a significantly lower risk for NAFLD. If we assign specific amounts of MET to different types of exercise, our results can be further interpreted as follows: An additional 120 min light, or 67 min moderate, or 47 min medium-vigorous, or 36 min high-vigorous exercise per week can reduce the risk for NAFLD by 3–4%.

Our results are comparable to those of other completed studies. Sung *et al*[6] conducted a large-scale cohort study with a 5-year follow-up in a Korean population, which suggested that exercising more than 5 times/week reduces the risk of developing NAFLD by 12%. However, the researchers only measured the frequency of exercise and did not take into account change in PA. We calculated the volume of PA using a combination of frequency, intensity, and duration. Further, because PA was a modifiable lifestyle behavior throughout the follow-up period, we treated it as a time-dependent variable in the Cox regression. Thus, our results precisely capture the association between PA and the risk for NAFLD. A meta-analysis summarized cohort studies and case-control studies to capture the dose–response association between PA and NAFLD.[7] It indicated that every 500 MET-min/week increase in PA is associated with an 18% reduction in the risk for NAFLD, which is higher than our results. Such a difference could be explained by the longer mean follow-up period in the meta-analysis.

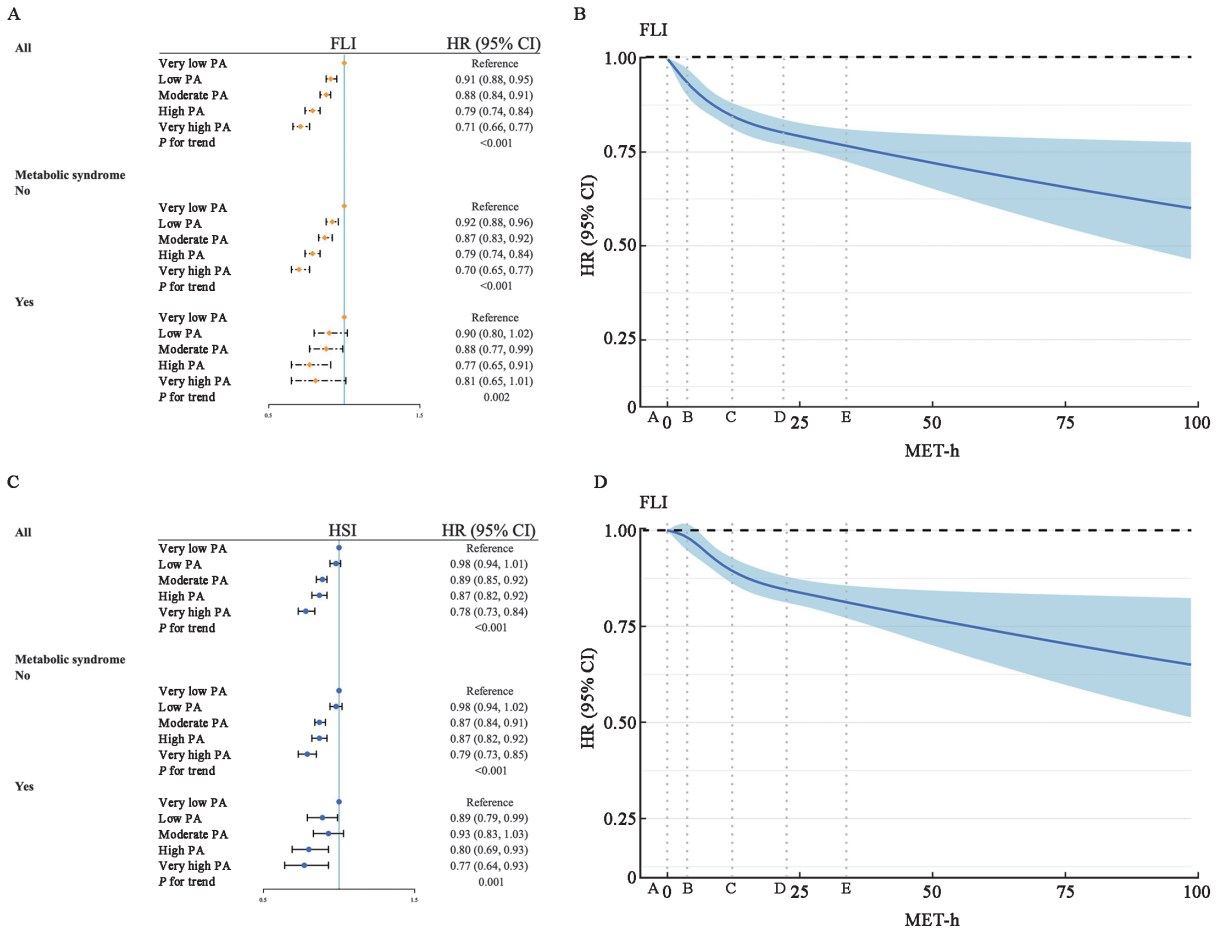

Figure 1: Association between PA and FLI- and HSI-defined NAFLD. (A) A forest plot capturing relationships between different levels of PA and FLI-defined NAFLD. The results of subgroup analysis stratified by MS and trend test are also illustrated. (B) Exposure–response curve for the relationship between PA and FLI-defined NAFLD. A: very low PA (<3.75 MET-h), B: low PA (3.75–7.49 MET-h), C: moderate PA (7.50–16.49 MET-h), D: high PA (16.50–25.49 MET-h), E: very high PA (≥25.50 MET-h). (C) A forest plot capturing relationships between different levels of PA and HSI-defined NAFLD. The results of subgroup analysis stratified by MS and trend test are also illustrated. (D) Exposure–response curve for the relationship between PA and HSI-defined NAFLD. a: very low PA (<3.75 MET-h), b: low PA (3.75–7.49 MET-h), c: moderate PA (7.50–16.49 MET-h), d: high PA (16.50–25.49 MET-h), e: very high PA (≥25.50 MET-h). CI: Confidence interval; FLI: Fatty liver index; HSI: Hepatic steatosis index; HR: Hazard ratio; MET-h: hours of MET; MET: Metabolic equivalent of task; MS: Metabolic syndrome; PA: Physical activity.

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Conflicts of interest

None.

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