**RESEARCH**

# Accelerometer-derived moderate-to-vigorous physical activity and incident nonalcoholic fatty liver disease

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## Abstract

**Background** The liver effects of concentrated vs. more evenly distributed moderate-to-vigorous physical activity (MVPA) patterns remain unclear. We aimed to examine the association of accelerometer-measured MVPA and different MVPA patterns with liver outcomes.

**Methods** Eighty-eight thousand six hundred fifty-six participants without prior liver diseases from UK Biobank were included. MVPA was measured by a wrist-worn accelerometer. Based on the guideline-based threshold ($\geq 150$ min/week), MVPA patterns were defined as inactive ($< 150$ min/week), active weekend warrior (WW; $\geq 150$ min/week with $\geq 50\%$ of total MVPA achieved within 1–2 days), and regularly active ($\geq 150$ min/week but not active WW) patterns. The primary outcome was incident nonalcoholic fatty liver disease (NAFLD).

**Results** During a median follow-up of 6.8 years, 562 participants developed NAFLD. Overall, there was a nonlinear inverse association of total MVPA with incident NAFLD ($P$ for nonlinearity $= 0.009$): the risk of NAFLD rapidly decreased with the increment of MVPA (per 100 min/week increment: HR $= 0.68$; 95%CI, 0.57–0.81) when MVPA $< 208$ min/week, while moderately declined (HR $= 0.91$; 95%CI, 0.84–0.99) when MVPA $\geq 208$ min/week. For MVPA patterns, compared with inactive group, both active WW (HR $= 0.55$, 95%CI, 0.44–0.67) and active regular (HR $= 0.49$, 95%CI, 0.38–0.63) group were associated with a similar lower risk of NAFLD. Similar results were observed for each secondary outcome, including incident severe liver diseases, incident liver cirrhosis, and liver magnetic resonance imaging-based liver steatosis and fibrosis.

**Conclusions** Regardless of whether MVPA was concentrated within 1 to 2 days or spread over most days of the week, more MVPA was associated with a lower risk of incident liver outcomes, including NAFLD, liver cirrhosis, liver steatosis, and fibrosis, to MVPA more evenly distributed.

**Keywords** Physical activity, Weekend warrior, Liver diseases, Accelerometer

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## Background

Nonalcoholic fatty liver disease (NAFLD) is already the most common liver disease worldwide, affecting 32% of the global population [1, 2]. NAFLD may not only eventually progress to cirrhosis and hepatocellular carcinoma [1, 2] but also is a risk factor for cardiovascular disease [3]. Because of the limited targeted therapies currently

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available [4], identifying more modifiable risk factors is critical for the prevention and management of NAFLD.

Physical activity (PA) is a crucial modifiable lifestyle, and guidelines from the World Health Organization and American Heart Association recommend 150 min or more of moderate-to-vigorous physical activity (MVPA) per week [5, 6]. PA has been identified as a therapeutic strategy to prevent liver diseases by increasing fatty acid oxidation, decreasing fatty acid synthesis, and preventing mitochondrial and hepatocellular damage by reducing the release of damage-associated molecular patterns [7]. However, most previous studies on the relationship of PA and incident NAFLD relied on one-time self-reported measures of PA [8–10], which is subject to bias. To date, only one study has reported an inverse longitudinal association between accelerometer-measured PA and NAFLD [11]. Of note, this study did not assess the dose–response association between PA and NAFLD incidence, which may provide more granular information and allow for the possibility of a non-linear association PA and NAFLD incidence, and thereby help inform public health guidelines and personalized approaches to exercise prescription for primary prevention of NAFLD. Moreover, this study [11] focused on the total volume of PA, rather than the pattern of PA that considers both the duration and frequency of PA. While it is recommended to accumulate PA over most days of the week, weekend warrior (WW) PA pattern, characterized by concentrating PA into one or two sessions or days per week, is a more convenient option for many people and has become increasingly popular [12, 13]. Although previous evidence suggested that WW and regularly active PA patterns had similar cardiovascular and mortality benefits [13, 14], it remains unclear whether WW activity pattern confers similar liver benefits compared with more evenly distributed activity.

To address the above gaps in knowledge, using data from the UK Biobank, we aimed to examine the associations of accelerometer-measured MVPA and different MVPA patterns, including inactive, active WW, and regularly active MVPA patterns, with the risk of incident NAFLD and a series of liver outcomes in the general population.

## Methods
### Study design and participants
As previously described [15], the UK Biobank is a large, observational, population-based cohort recruiting half a million adult residents, aged 37–73 years, from 1 of 22 assessment centers across the UK (England, Wales, and Scotland) between 2006 and 2010. At baseline, participants were asked to complete a comprehensive questionnaire assessing sociodemographic, lifestyle, and health-related information, receive physical examinations, and provide biological samples. The UK Biobank was approved by the North West Research Ethics Committee (11/NW/0382) and all participants signed an informed consent.

The current analysis was restricted to a sub-sample of 103,661 participants who responded to emails for the accelerometer sub-study between 2013 and 2015. Individuals with insufficient accelerometer data quality or less than a full week of available acceleration data ($n=12{,}175$) were excluded. Additionally, we excluded participants who had NAFLD or severe liver diseases or other liver diseases or alcohol/drug use disorders at/before the time of accelerometer measurements ($n=2829$), resulting in a final analysis of 88,656 participants (Additional file 1: Figure S1).

### Exposure assessment
Between February 2013 and December 2015 (Additional file 1: Figure S2), participants who provided a valid email address to UK Biobank were invited at random to wear a wrist-worn accelerometer (Axivity AX3). Participants were instructed to wear the device on their dominant wrist continuously for 1 week while continuing with their usual activities. The accelerometer captures triaxial acceleration data over 7 days at 100 Hz with a dynamic range of ± 8 gravity. Proportions of time spent across sleep (non-awake behavior), sedentary behavior (SB) (awake behavior at ≤ 1.5 metabolic equivalent of task (METs), such as driving or watching television), light physical activity (LPA) (awake behavior at < 3 METs not meeting the sedentary behavior definition, such as cooking or self-care), and MVPA (awake behavior at ≥ 3 METs, such as walking the dog or jogging) per day were identified from raw accelerometer data using a previously published random forest and hidden Markov model machine-learning methods that were trained using wearable cameras and time-use diaries among 152 individuals in free-living conditions [16]. Briefly, accelerometer data was annotated with activities from the Compendium of Physical Activities. [17] A balanced Random Forest (RF) with 100 decision trees was trained to classify the behavior in 30-s time windows using 50 rotation-invariant time and frequency domain features of the accelerometer signal. Then, a hidden Markov model was employed to use time sequence information to improve the RF-assigned label sequence.

Because the optimal level of accelerometer-measured MVPA for prevention of incident NAFLD is unknown [18], in the primary analyses, based on the guideline-based threshold (≥ 150 min/week) [6], individuals were classified as active WW (equal to or above the MVPA threshold and ≥ 50% of total MVPA achieved within

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1–2 days) [13], regularly active (equal to or above MVPA threshold but not active WW), and inactive (below MVPA threshold) MVPA patterns.

### Covariates assessment
Detailed information on covariates at baseline was available through standardized questionnaires at baseline, including age, sex, ethnicities, Townsend deprivation index (TDI), income, education levels, employment, smoking, and alcohol drinking (Additional file 1: Figure S2). Body mass index (BMI) was measured and calculated as weight (in kilograms (kg)) divided by the square of height (in meters (m)).

### Study outcome assessment
The primary outcome was incident NAFLD [19], ascertained through links to hospital inpatient data and death register records. In accordance with the Expert Panel Consensus statement, NAFLD (including non-alcoholic steatohepatitis (NASH)) was identified as ICD-10 K76.0, K75.8, and ICD-9 571.8. Hospital admissions data were available until September 30, 2021, for centers in England, July 31, 2021, for centers in Scotland, and February 28, 2018, for centers in Wales, and mortality data were available until October 2021(Additional file 1: Figure S2). The follow-up person-time for each participant was calculated from the final date of accelerometer wear until the date of death, the first date of outcome diagnosis, the date of loss to follow-up, or the end of follow-up, whichever came first.

Since NAFLD is the most important cause of cirrhotic complications, hepatocellular carcinoma, and liver-related mortality [20], to avoid missing NAFLD events that can lead to adverse liver outcomes, we used incident severe liver diseases (a composite of liver cirrhosis, liver failure, hepatocellular carcinoma, and liver-related death) and incident liver cirrhosis as secondary outcomes (Additional file 1: Table S1).

Moreover, liver magnetic resonance imaging (MRI) was performed between January 2016 and February 2020 in the UK Biobank imaging sub-study (Additional file 1: Figure S2), and the proton density fat fraction (PDFF) and iron-corrected T1 mapping (cT1) was extracted as a measurement of liver steatosis and liver fibrosis, respectively [21]. In this sub-study, liver steatosis, defined as PDFF ≥ 5.5% [22], and liver fibrosis, defined as cT1 ≥ 800 ms (ms) [21], were also identified as secondary outcomes to capture undiagnosed relatively mild cases of chronic liver disease. In the current sub-analysis, 15,455 participants had available data of PDFF, while 12,393 participants had available data of cT1 (Additional file 1: Figure S1).

### Statistical analysis
Population characteristics were presented as mean (SD) for continuous variables or proportions for categorical variables. Difference of characteristics according to incident NAFLD (yes vs. no) were tested by *t*-tests and chi-square tests for continuous and categorical variables, respectively.

To test the actual association of MVPA in relation to other movement behaviors, a compositional data analysis (CODA) approach was used [16]. For CODA, the activity composition was created by expressing the time spent on each activity (i.e., MVPA, sleep, SB, and LPA) as a proportion of a 24-h day. The activity composition was then expressed as isometric log-ratio (ilr) coordinates to account for the interdependency of the activity domains. Then, Cox proportional hazards regression models estimating survival were built using the corresponding set of three ilr coordinates for MVPA.

Restricted cubic spline (RCS) Cox regression was performed to test for linearity and explore the shape of the dose–response relationship of total MVPA with incident NAFLD. A two-piecewise Cox regression model was used to examine the threshold effect of total MVPA on incident NAFLD using a smoothing function. The inflection point (i.e., threshold) was determined using the likelihood-ratio test and bootstrap resampling methods. Cox proportional hazards models were used to estimate the relationship of total MVPA or MVPA patterns with study outcomes, except for liver MRI-related outcomes which was estimated using binomial regression models. In multivariable models, several potential confounders were controlled for, including demographics (age, sex, ethnicities, recruitment center, TDI, educational attainment, household income, employment), anthropometric and lifestyle factors (smoking status, alcohol consumption, and BMI), and the total time and season of accelerometer wear. The proportional hazards assumption was checked using the Schoenfeld residuals, and no violation was found. Percentages of missing values of covariates were less than 1% except for income (10.3%). Missing data were coded as a missing indicator category for categorical variables and with mean values for continuous variables.

To test the robustness of our findings, several sensitivity analyses were also performed for the association between MVPA patterns and primary outcome. Firstly, the MVPA patterns was defined using threshold derived from the threshold effect analyses (≥ 208 min/week) at which the rapid decline in NAFLD risk lessened or leveled off as MVPA increased. Secondly, we assessed alternative definitions of the WW pattern, including ≥ 50% of total MVPA over 1–2 consecutive days and ≥ 50% of total MVPA over 1–2 weekend days. Third, all participants

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within 2 years of follow-up were excluded to minimize reverse causation. Fourth, participants with missing covariates were excluded. Fifth, we further adjusted for pre-existing hypertension and diabetes, defined as baseline self-reported medical history or health records taken before the time of accelerometer measurement, and healthy diet scores, evaluated using a more recent dietary recommendation for cardiovascular health which considered adequate consumption of fruits, vegetables, whole grains, fish, shellfish, dairy products, and vegetable oils, and reduced consumption of refined grains, processed meats, unprocessed meats, and sugar sweetened beverages. Sixth, we further limited the main analysis to participants with low-to-intermediate predicted NAFLD risk as estimated by the Dallas Steatosis Index (DSI). DSI is a superior tool to predict NAFLD as inferred using MR spectroscopy. Based on DSI, NAFLD can be excluded with a negative predictive value of 80% at a threshold of < 50% risk [23, 24]. Seventh, as NAFLD is an important cardiovascular risk factor, we also assessed the association between MVPA pattern and cardiovascular disease.

As additional exploratory analyses, possible modifications of the association of MVPA patterns with incident NAFLD were also assessed for the following variables: age ($< 60$ or $\geq 60$ years), sex (females or males), BMI ($< 25$ or $\geq 25$ kg/m$^2$), smoking status (never or ever), and alcohol drinking ($< 1$ or $\geq 1$ times/week).

A two-tailed $P < 0.05$ was considered to be statistically significant in all analyses. Analyses were performed using R 4.1.1 software (http://www.R-project.org/).

## Results

### Study participants and population characteristics
Of the 88,656 participants included, the mean age was 56.1 (SD, 7.8) years, and 50,303 (56.7%) were female. All participants wore accelerometer for 7 days, and the mean times spent in MVPA were 290 (SD, 242) min/week.

During a median follow-up of 6.8 years (interquartile range, 6.2–7.3 years), 562 (0.6%) participants developed NAFLD. As shown in Table 1, compared with participants without incident NAFLD, those with incident NAFLD were more likely to be smokers, tended to have disadvantaged socioeconomic status, lower alcohol consumption, and higher BMI.

### Association of total MVPA with incident NAFLD
The CODA approach showed that time spent in MVPA relative to the other movement behaviors (sleep, SB, and LPA) was associated with a reduction in the risk of incident NAFLD (HR, 0.84; 95% CI, 0.78–0.91, $P < 0.001$).

Subsequently, RCS showed a nonlinear inverse association of total MVPA with incident NAFLD ($P$ for nonlinearity = 0.009; Fig. 1). Accordingly, in the threshold effect

analysis, in participants with total MVPA < 208 min/week, the risk of incident NAFLD rapidly decreased as the total MVPA increased (per 100 min/week increment: HR, 0.68; 95% CI, 0.57–0.81), while in participants with total MVPA ≥ 208 min/week, the risk of incident NAFLD only relatively slowly decreased with the increase of the total MVPA (per 100 min/week increment: HR, 0.91; 95% CI, 0.84–0.99) (Table 2).

### Association of MVPA patterns with incident NAFLD
Based on the guideline-based threshold (≥ 150 min/week), 36,765 (41.5%) participants were in the active WW group, 22,506 (25.4%) participants were in the active regular group, and 29,385 (33.1%) participants were in the inactive group.

Overall, there was a similar inverse dose–response association of time spent in MVPA and the risk of incident NAFLD for both WW and regular activity participants across the entire range of MVPA (Fig. 2). Accordingly, compared with the inactive group, both active WW (HR, 0.55, 95% CI, 0.44–0.67) and active regular (HR, 0.49, 95% CI, 0.38–0.63) group were associated with a similar lower risk of incident NAFLD (Table 3). Compared with the active regular group, the active WW group was not significantly associated with a higher risk of incident NAFLD (HR, 1.12, 95% CI, 0.86–1.46).

In the sensitivity analyses, using threshold derived from the threshold effect analyses (≥ 208 min/week) (Sensitivity analysis 1), using different WW definitions (Sensitivity analysis 2 and 3), excluding participants within 2 years of follow-up (Sensitivity analysis 4), excluding participants with missing covariates (Sensitivity analysis 5), further adjusting for pre-existing hypertension and diabetes, and healthy diet scores (Sensitivity analysis 6), or further restricting the main analysis to participants with a low-to-intermediate predicted NAFLD risk (Sensitivity analysis 7) did not substantially change our findings (Additional file 1: Table S2). Moreover, both active WW and active regular group were associated with a similar lower risk of cardiovascular disease among the total population or among those with low-to-intermediate or high predicted NAFLD risk (Additional file 1: Table S3).

In the stratified analyses, there were no significant interactions of MVPA patterns with age, sex, BMI, smoking status, and alcohol drinking on the risk of incident NAFLD (all $P$ for interaction > 0.05; Additional file 1: Table S4).

### Association of MVPA patterns with secondary outcomes
During the follow-up, 504 (0.6%) incident severe liver diseases and 436 (0.5%) liver cirrhosis were documented. Compared with inactive group, both active WW group (severe liver diseases: HR, 0.75, 95% CI, 0.61–0.93;

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**Table 1** General characteristics of study participants by incident nonalcoholic fatty liver disease status (NAFLD)

| Characteristics | All participants | Incident NAFLD | | P value |
|---|---|---|---|---|
| | | No | Yes | |
| N | 88,656 | 88,094 | 562 | |
| Age, years | 56.1 (7.8) | 56.1 (7.8) | 56.3 (7.6) | 0.596 |
| Male, *n* (%) | 38,353 (43.3) | 38,099 (43.2) | 254 (45.2) | 0.353 |
| White, *n* (%) | 85,587 (96.5) | 85,053 (96.5) | 534 (95) | 0.037 |
| Recruitment centers, *n* (%) | | | | < 0.001 |
| England | 79,519 (89.7) | 78,975 (89.6) | 544 (96.8) | |
| Scotland | 5787 (6.5) | 5774 (6.6) | 13 (2.3) | |
| Wales | 3350 (3.8) | 3345 (3.8) | 5 (0.9) | |
| Townsend deprivation index | − 1.7 (2.8) | − 1.8 (2.8) | − 0.8 (3.2) | < 0.001 |
| Employed, *n* (%) | 83,710 (94.4) | 83,199 (94.4) | 511 (90.9) | < 0.001 |
| Income (< £31,000), *n* (%) | 30,726 (34.7) | 30,491 (34.6) | 235 (41.8) | < 0.001 |
| Education (college or university), *n* (%) | 38,353 (43.3) | 38,183 (43.3) | 170 (30.2) | < 0.001 |
| Smoking status, *n* (%) | | | | < 0.001 |
| Current | 5903 (6.7) | 5850 (6.7) | 53 (9.5) | |
| Previous | 31,501 (35.6) | 31,263 (35.6) | 238 (42.6) | |
| Never | 51,012 (57.7) | 50,744 (57.8) | 268 (47.9) | |
| Alcohol drinking, *n* (%) | | | | < 0.001 |
| > 4 times/week | 20,077 (22.6) | 19,957 (22.7) | 120 (21.4) | |
| 3–4 times/week | 23,057 (26.0) | 22,957 (26.1) | 100 (17.8) | |
| 1–2 times/week | 22,345 (25.2) | 22,214 (25.2) | 131 (23.3) | |
| < 1 time/week | 18,211 (20.5) | 18,057 (20.5) | 154 (27.4) | |
| Never | 4898 (5.5) | 4842 (5.5) | 56 (10.0) | |
| Body mass index, kg/m$^2$ | 26.7 (4.5) | 26.6 (4.5) | 31 (5.5) | < 0.001 |
| Season of accelerometer wear, *n* (%) | | | | 0.195 |
| Spring | 20,875 (23.5) | 20,761 (23.6) | 114 (20.3) | |
| Summer | 24,037 (27.1) | 23,876 (27.1) | 161 (28.6) | |
| Autumn | 24,456 (27.6) | 24,305 (27.6) | 151 (26.9) | |
| Winter | 19,288 (21.8) | 19,152 (21.7) | 136 (24.2) | |
| Total time of accelerometer wear, days | 6.7 (0.6) | 6.7 (0.6) | 6.7 (0.6) | 0.513 |
| Moderate-to-vigorous physical activity, min/week | 290.5 (242.9) | 291.2 (243) | 179.3 (186.1) | < 0.001 |
| Moderate-to-vigorous physical activity patterns, *n* (%) | | | | < 0.001 |
| Inactive | 40,059 (45.2) | 39,673 (45) | 386 (68.7) | |
| Active weekend warrior | 28,094 (31.7) | 27,996 (31.8) | 98 (17.4) | |
| Active regular | 20,503 (23.1) | 20,425 (23.2) | 78 (13.9) | |

Data are expressed as mean (SD) or *n* (%), accordingly

cirrhosis: HR, 0.80, 95% CI, 0.64–0.99) and active regular group (severe liver diseases: HR, 0.76, 95% CI, 0.59–0.97; cirrhosis: HR, 0.76, 95% CI, 0.58–0.99) were associated with a similar lower risk of incident severe liver diseases and cirrhosis (Table 3).

Among 15,455 participants with available data of PDFF, 3,416 have liver steatosis (PDFF ≥ 5.5%), and 559 have liver fibrosis (cT1 ≥ 800 ms) among 12,393 participants with available data of cT1. Consistently, compared with inactive group, both active WW group (liver steatosis: OR, 0.74, 95% CI, 0.67–0.81; liver fibrosis: OR, 0.62, 95%

CI, 0.51–0.76) and active regular (liver steatosis: OR, 0.60, 95% CI, 0.53–0.67; liver fibrosis: OR, 0.48, 95% CI, 0.37–0.62) group were associated with a similar lower prevalence of liver steatosis and liver fibrosis (Table 3).

## Discussion

Using a large prospective cohort study, we showed that there was a nonlinear inverse association between the duration of MVPA with the risk of NAFLD, with a threshold of 208 min/week. More importantly, MVPA concentrated within 1 to 2 days was associated with a similarly

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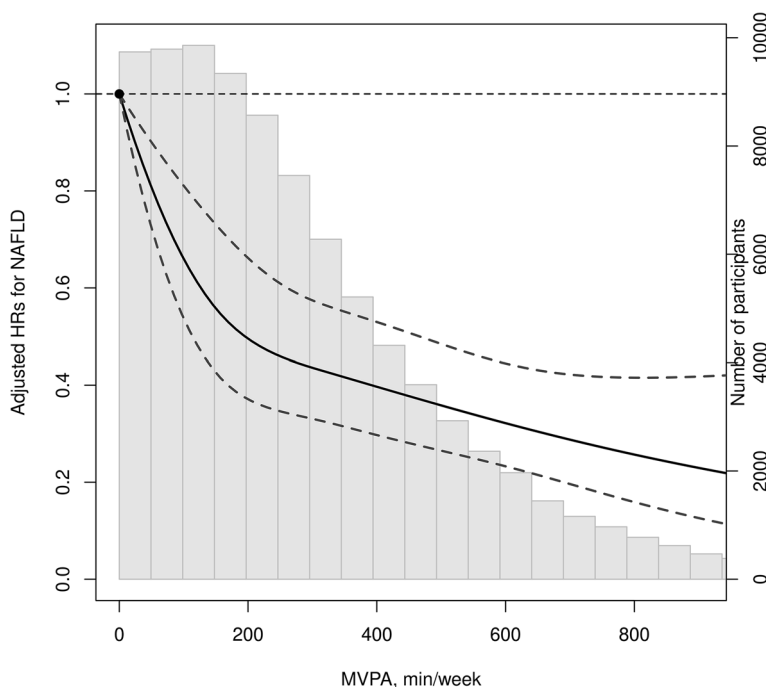


**Fig. 1** The dose–response association of total moderate-to-vigorous physical activity with the risk of incident nonalcoholic fatty liver disease. The histogram indicated distribution of total moderate-to-vigorous physical activity. Results were adjusted for age, sex, ethnicities, recruitment center, Townsend Deprivation Index, educational attainment, household income, employment, smoking status, alcohol consumption, body mass index, and the total time and season of accelerometer wear

**Table 2** Threshold effect analyses of total moderate-to-vigorous physical activity (MVPA) on the risk of incident nonalcoholic fatty liver disease (NAFLD) using two-piecewise regression models

| Total MVPA, min/week | Total | Events(rate[a]) | Crude model | | Adjusted model[b] | |
|---|---|---|---|---|---|---|
| | | | HR (95% CI) | P value | HR (95% CI) | P value |
| < 208 | 40,059 | 386 (1.4) | 0.51 (0.43, 0.61) | < 0.001 | 0.68 (0.57, 0.81) | < 0.001 |
| ≥ 208 | 48,597 | 176 (0.5) | 0.89 (0.82, 0.96) | 0.004 | 0.91 (0.84, 0.99) | 0.028 |

[a] Incidence rates were expressed as per 10,000 person-years

[b] Adjusted for age, sex, ethnicities, recruitment center, Townsend deprivation index, educational attainment, household income, employment, smoking status, alcohol consumption, body mass index, and the total time and season of accelerometer wear

lower risk of NAFLD, severe liver diseases, liver cirrhosis, liver steatosis, and fibrosis to more regular MVPA.

Although there was some evidence based on questionnaire-assessed PA to support an inverse association between PA and NAFLD risk [8–11], evidence using objective measures of PA is very limited. To date, only one study of PA measured using accelerometers [11] found that an increase of 10 milligravity per hour of accelerometer average, estimated to equal 45 min of additional walking per day for a fictive 80-kg male participant, was associated with a 47% (HR 0.53; 95% CI 0.41–0.70) reduction in NAFLD development. Nevertheless, the study was conducted under the assumption that PA is linearly related with NAFLD risk, and it is still unclear whether

there is a non-linear relationship between PA and the risk of NAFLD. Our study extends this area meaningfully, showing a nonlinear inverse association between the duration of MVPA with the risk of NAFLD. Cubic spline analysis and threshold effect analyses showed a rapid decline in the risk of NAFLD with the increase in MVPA in participants with total MVPA < 208 min/week, while only a relatively slow decline in participants with total MVPA ≥ 208 min/week. Those findings support the current recommendations for MVPA (≥ 150 min/week) to improve health, while providing additional evidence that longer MVPA duration (≥ 208 min/week) may have greater benefits in preventing NAFLD. Of note, consistent with other accelerometer-based studies [25–28], the

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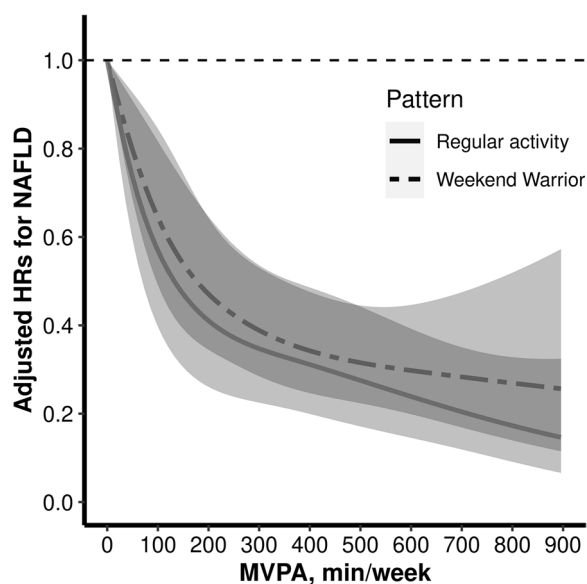


**Fig. 2** The dose–response association of moderate-to-vigorous physical activity with the risk of incident nonalcoholic fatty liver disease stratified by activity patterns. There was a similar inverse dose–response association of time spent in MVPA and the risk of incident NAFLD for both WW and regular activity participants across the entire range of MVPA. HR indicates hazard ratio. The solid line indicates how NAFLD incidence varies as a function of time spent in MVPA, while the dashed lines are confidence intervals. All results were adjusted for age, sex, ethnicities, recruitment center, Townsend Deprivation Index, educational attainment, household income, employment, smoking status, alcohol consumption, body mass index, and the total time and season of accelerometer wear

average MVPA time in the current study was significantly higher (290 min/week) compared with self-reported data. This may be partially explained by the fact that questionnaire-assessed MVPA may be subjective and predominantly accounts for bouted MVPA (typically lasting more than 10 min), whereas accelerometer measurements capture both bouted and unbouted MVPA.

Another striking finding in the present study is that WW and regularly active participants had similar lower risks across a broad spectrum of liver diseases, suggesting that spreading MVPA over more days or concentrating MVPA into 1 to 2 days may not influence liver benefit. Indeed, data from the Meiji Yasuda Longitudinal Study showed that engaging in at least three times/week moderate-intensity PA or at least two times/week vigorous-intensity PA was associated with a lower hazard of incident fatty liver in never-moderate alcohol drinkers [29]. Moreover, in an occupational health screening program, any increase in the number of weekly exercise sessions was associated with a decrease in risk of incident fatty liver [30]. However, these two studies only assessed the frequency of PA, and the benefit may be contributed to the duration of PA. Our study further extends previous

findings by considering both the duration and frequency of PA and found that WW and regular active participants had similar liver benefits across the entire range of activity levels, not just those who met PA guideline recommendations.

Using accelerometer-based quantified PA data in community-based setting, the foremost findings of this study highlight that participation in even less MVPA is more beneficial in preventing NAFLD than non-participation in MVPA. Furthermore, our study first showed that, for the same amount of MVPA, spread out for more days or concentrated for fewer days over a week may have similar liver benefits. Given that the WW MVPA pattern may be a more convenient and acceptable option for many people due to an accelerating pace of life and increased work demands, these findings may be useful for clinical or individual counseling, as well as for public health policies and interventions.

This study has some limitations. Firstly, despite comprehensive adjustments for a range of covariates, residual confounding cannot be completely ruled out due to the inherent limitation of observational study design, and causality needs to be further confirmed. Secondly, the design of the UK biobank allowed for the assessment of associations of many different exposures with a wide range of health outcomes, but was not explicitly designed to assess the relationship of accelerometer-measured exercise behaviors with liver outcomes, thus introducing selection bias that could be even more true for the follow-up studies as the accelerometer wearing. In particular, UK Biobank had a low response rate (5.5%) in the baseline assessment, and participants were predominantly of European descent from England and healthier than the general UK population [31]. For example, the incidence of NAFLD in this study was 10.1/10,000 person-years in England, 3.3/10,000 person-years in Scotland, and 4.4/10,000 person-years in Wales, which was lower than reported in the general population [20]. However, because the exposures of interest have sufficient variance and the study sample is large, the generalizability of the association between risk factors and health outcomes can be assured [32]. Thirdly, consistent with a previous study [33], in our current study, covariates were mainly assessed at baseline (between 2006 and 2010), while the accelerometry sub-study was conducted from 2013 to 2015. Although most of the covariates assessed at baseline remained generally stable [33], there is potential multiple biases and further research with more comprehensive design and representative samples is needed to confirm those findings. Fourthly, although 7-day monitoring periods have been routinely used in previous studies [13, 34] because they provide an opportunity to sample PA on both weekdays and weekend days

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**Table 3** Association of moderate-to-vigorous physical activity (MVPA) patterns with study outcomes

| MVPA patterns | Events(rate[a]) | Crude model | | Adjusted model[b] | |
|---|---|---|---|---|---|
| | | HR/OR(95% CI) | *P* value | HR/OR(95% CI) | *P* value |
| Primary outcome: incident nonalcoholic fatty liver disease | | | | | |
| Inactive | 322 (16.7) | Ref | | Ref | |
| Active weekend warrior | 154 (6.3) | 0.37 (0.31, 0.45) | < 0.001 | 0.55 (0.44, 0.67) | < 0.001 |
| Active regular | 86 (5.7) | 0.34 (0.27, 0.43) | < 0.001 | 0.49 (0.38, 0.63) | < 0.001 |
| Secondary outcomes | | | | | |
| *Incident severe liver diseases* | | | | | |
| Inactive | 220 (11.4) | Ref | | Ref | |
| Active weekend warrior | 178 (7.3) | 0.64 (0.52, 0.77) | < 0.001 | 0.75 (0.61, 0.93) | 0.008 |
| Active regular | 106 (7.0) | 0.61 (0.49, 0.77) | < 0.001 | 0.76 (0.59, 0.97) | 0.025 |
| *Incident liver cirrhosis* | | | | | |
| Inactive | 186 (9.6) | Ref | | Ref | |
| Active weekend warrior | 159 (6.5) | 0.67 (0.54, 0.83) | < 0.001 | 0.80 (0.64, 0.99) | 0.045 |
| Active regular | 91 (6.0) | 0.62 (0.48, 0.80) | < 0.001 | 0.76 (0.58, 0.99) | 0.041 |
| *Liversteatosis* | | | | | |
| Inactive | 1352 (29.5) | Ref | | Ref | |
| Active weekend warrior | 1410 (20.1) | 0.60 (0.55,0.65) | < 0.001 | 0.74 (0.67,0.81) | < 0.001 |
| Active regular | 654 (17.0) | 0.49 (0.44,0.54) | < 0.001 | 0.60 (0.53,0.67) | < 0.001 |
| *Liver fibrosis* | | | | | |
| Inactive | 264 (7.4) | Ref | | Ref | |
| Active weekend warrior | 206 (3.6) | 0.47 (0.39,0.57) | < 0.001 | 0.62 (0.51,0.76) | < 0.001 |
| Active regular | 89 (2.8) | 0.36 (0.28,0.46) | < 0.001 | 0.48 (0.37,0.62) | < 0.001 |

[a] Incidence rates were expressed as per 10,000 person-years for incident nonalcoholic fatty liver disease, incident severe liver diseases, and incident liver cirrhosis, while rates were expressed as percentage for liver fat and liver fibrosis

[b] Adjusted for age, sex, ethnicities, recruitment center, Townsend deprivation index, educational attainment, household income, employment, smoking status, alcohol consumption, body mass index, and the total time and season of accelerometer wear

and achieve a greater than 80% intra-class correlations in most populations [35], it may not fully capture habitual physical activity behaviors, making it difficult to identify possible real-world weekend warriors. Moreover, a single time-point limited any potential inferences related to within-person changes or variability in PA over time. Fifth, in our study, the study outcomes were ascertained by hospital inpatient data, cancer registry, and death register records. The exact diagnostic data for each NAFLD case were unavailable. While it is important to acknowledge this limitation, continuous monitoring of NAFLD onset by instrumentation is unpractical in a large sample population. Obtaining NAFLD through electronic health records is an acceptable alternative and has been widely used in epidemiological studies [19, 36–39]. Moreover, our primary analysis trended to include more advanced or severe cases of NAFLD and may have missed some relatively mild NAFLD, thus underestimating the true association. On the one hand, advanced NAFLD may be more clinically important, given that the severity of NAFLD was positively related to the risk of subsequent adverse outcomes [3]. Furthermore, to address this issue, we used new-onset severe liver diseases as a secondary

outcome to avoid missing NAFLD events that could lead to adverse liver outcomes and found similar results. In addition, as NAFLD is an important cardiovascular risk factor, we also assessed the association between MVPA pattern and cardiovascular disease and observed similar results among those with low-to-intermediate or high predicted NAFLD risk. On the other hand, we further restricted the primary analysis to participants with a low-to-intermediate predicted NAFLD risk and found similar results, suggesting that underdiagnosis cases of mild NAFLD produced little bias in estimating the association between exposure and NAFLD risk. Additionally, we used MRI-derived liver PDFF and cT1 to potentially capture undiagnosed relatively mild cases of NAFLD or liver fibrosis and found similar results, suggesting that MVPA pattern could not only contribute to advanced cases of NAFLD but also less advanced cases. Sixth, reverse causality is possible because participants included in the current study may have fatty liver even if not diagnosed. However, we further excluded participants within 2 years of follow-up or excluded participants with higher predicted NAFLD risk and observed similar results. Seventh, although diagnostic criteria for NAFLD excluded

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excessive alcohol use, alcohol use may still be a potential confounding factor. However, we have carefully controlled for alcohol consumption and did not find any modification effects for alcohol consumption.

## Conclusions

In summary, our results showed a dose-dependent protective association between accelerometer-measured MVPA and incident NAFLD, suggesting that physical inactivity is unhealthy for the liver. Our further exploratory analysis indicated that MVPA concentrated within 1 to 2 days and spread over most days of the week had a similar significantly reduced risk of liver outcomes. Although further confirmation is needed, our study highlights the benefits of MVPA on the liver and the "more than one road leads to Rome" in terms of MVPA frequency.

## Abbreviations

| | |
|---|---|
| BMI | Body mass index |
| CI | Confidence interval |
| CODA | Compositional data analysis |
| cT1 | Iron-corrected T1 mapping |
| DSI | Dallas Steatosis Index |
| HR | Hazard ratio |
| ilr | Isometric log-ratio |
| LPA | Light physical activity |
| METs | Metabolic equivalent of task |
| MRI | Magnetic resonance imaging |
| MVPA | Moderate-to-vigorous physical activity |
| NAFLD | Nonalcoholic fatty liver disease |
| NASH | Non-alcoholic steatohepatitis |
| PA | Physical activity |
| PDFF | Proton density fat fraction |
| SB | Sedentary behavior |
| TDI | Townsend deprivation index |
| WW | Weekend warrior |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-024-03618-2.

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Additional file 1: Figures S1-S2 and Table S1-S3. Figure S1. Flow chart of the participants in the current analysis. Figure S2. Timeline of variables collection. Table S1. Disease definitions used in the UK Biobank study. Table S2. Sensitivity analyses for the association of moderate-to-vigorous physical activity patterns with incident nonalcoholic fatty liver disease. Table S3. Association of moderate-to-vigorous physical activity (MVPA) patterns with incident cardiovascular disease.

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## Authors' contributions
LMY and QXH designed and conducted the research. LMY and YZL performed the data management and statistical analyses. LMY and QXH Qin wrote the manuscript. LMY, YZL, ZYY, HPP, ZC, YSS, ZYJ, GXQ, and QXH reviewed/edited the manuscript for important intellectual content. All authors read and approved the final manuscript.

## Availability of data and materials
The UK Biobank data are available on application to the UK Biobank, and the analytic methods and study materials that support the findings of this study will be available from the corresponding authors on request.

## Declarations

### Ethics approval and consent to participate
The UK Biobank was approved by the North West Research Ethics Committee (11/NW/0382) and all participants signed an informed consent.

### Consent for publication
Not applicable.

### Competing interests
The authors declare that they have no competing interests.

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