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Association between questionnaire- and accelerometer-measured physical activity and incidence of cardiovascular disease in subjects with metabolic dysfunction-associated steatotic liver disease

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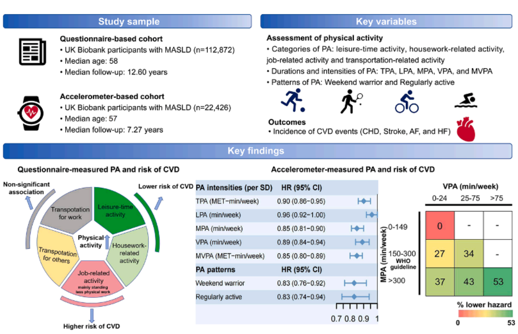
GRAPHICAL ABSTRACT



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ABSTRACT

Background: Evidence regarding the effect of physical activity (PA) on the risk of cardiovascular disease (CVD) among patients with metabolic dysfunction-associated steatotic liver disease (MASLD) is scarce. We aimed to clarify the role of PA in preventing CVD in patients with MASLD and provide insights into PA recommendations specific to this patient group.

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Methods: This study conducted two cohort studies of 112,872 subjects with MASLD using questionnaire-measured PA data and 22,426 subjects with MASLD using accelerometer-measured PA data. Incident CVD was ascertained from linked hospital and death records. Cox proportional hazard regression was used to investigate the associations.
Results: In the questionnaire-based cohort, performing more leisure-time PA and housework-related activity was associated with lower CVD risk in patients with MASLD. In the accelerometer-based cohort, total PA showed a linear inverse association with CVD risk, whereas a non-linear dose-response relationship was detected for moderate-intensity PA (MPA), vigorous-intensity PA (VPA) and moderate-to-vigorous-intensity PA (MVPA). Compared to inactive patients, those performing 150–300 min/week of MPA (HR 0.73, 95% CI 0.63–0.84) and >75 min/week of VPA (HR 0.70, 95% CI 0.55–0.89) were at lower CVD risk. Achieving 600 MET-min/week of MVPA in both weekend warrior and regularly active patterns showed similar cardiovascular benefits. Performing MPA beyond PA guidelines was associated with a further CVD risk reduction among patients with MASLD.
Conclusions: Our findings broadly support the effect of current PA guidelines in preventing CVD events among subjects with MASLD and suggest that the recommendation of MPA could be even more ambitious for the population.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) represents the leading liver disease, with a global prevalence increasing from 25.3 % in 1990–2006 to 38.0 % in 2016–2019 [1]. In 2023, a large multinational liver society proposed the nomenclature shift from NAFLD to “metabolic dysfunction-associated steatotic liver disease (MASLD)”, reflecting a more precise description of hepatic steatosis and incorporating definitive diagnostic criteria linked to cardiometabolic risk factors [2–4]. The definition significantly related MASLD to the elevated risk of incidence and mortality of cardiovascular disease (CVD) [4,5]. Indeed, CVD represents a more prevalent cause of mortality than liver disease in patients with NAFLD [6]. Therefore, it is of paramount importance to put forward robust strategies to mitigate the CVD burden in patients with MASLD.

Lifestyle interventions have been underscored as pivotal prevention in several clinical management approaches to attenuate disease progression in both NAFLD and MASLD [7,8]. For example, the 2024 EASL-EASD-EASO guideline recommends 150–200 min/week of moderate-intensity physical activity (MPA) for patients with MASLD to reduce steatosis and hepatic inflammation. Recent systematic reviews have also provided specific physical activity (PA) recommendations for patients with MASLD on cardiovascular risk reduction, such as 150–300 min/week of MPA or 75–150 min/week of vigorous-intensity physical activity (VPA) [9,10]. While existing literature suggests performing habitual PA to reduce CVD risk in NAFLD and MASLD populations, a limited number of cohort studies examined the associations between PA and CVD incidence in the patient group. The other important issue in this field is that the aforementioned PA recommendations are derived from the World Health Organization (WHO) guidelines designed for the general population [11,12], raising concerns regarding the efficacy and applicability for preventing CVD in patients with MASLD.

To date, only one retrospective cohort study reported that higher leisure-time PA (LTPA) was independently associated with a decreased odds ratio of atherosclerotic CVD among patients with NAFLD [13]. However, this study is constrained from drawing firm conclusions due to several limitations. Firstly, this study exclusively encompassed LTPA rather than a full range of PA categories and specific activities within each category. Secondly, the atherosclerotic CVD risk in this study was assessed by a pooled cohort risk equation, which is known to have poor validity in comparison to the actual incidence of CVD. Moreover, PA data in this study were collected through self-reported questionnaires, which could introduce recall bias and inaccuracies in estimating activity volume. In contrast, accelerometry is now the most commonly used objective measurement of PA in estimating energy expenditure, exercise patterns, duration and intensity with high precision [14,15]. Despite its utility, the association between accelerometer-measured PA and incident CVD in patients with MASLD remains unexplored in longitudinal cohort studies. An analysis of 5207 US adults with NAFLD showed protective correlations of accelerometer-measured total volume PA (TPA) and moderate-to-vigorous-intensity PA (MVPA) with lower CVD mortality risk [16]. However, their results considered neither light-intensity PA (LPA), MPA and VPA, nor the combination of duration and intensity of PA, and did not provide detailed PA recommendations for the NAFLD population.

To fill the research gaps mentioned above, we conducted a comprehensive analysis across a questionnaire-based and an accelerometer-based cohort using data from the UK Biobank. In the questionnaire-based cohort, we investigated the associations between various categories of daily PA as measured by questionnaires and the incidence of CVD in patients with MASLD. In the accelerometer-based cohort, we investigated the associations between various durations, intensities and patterns of PA as measured by accelerometers and the incidence of CVD and major CVD subtypes [coronary heart disease (CHD), stroke, atrial fibrillation (AF) and heart failure (HF)], providing a more accurate depiction of the magnitude and nature of this relationship in patients with MASLD. By integrating the evidence from both questionnaire-based and accelerometer-based cohorts, this study aims to clarify the role of PA in preventing CVD events in subjects with MASLD and provide insights into PA recommendations tailored for CVD prevention in MASLD management.

2. Materials and methods

2.1. Data source and study cohorts

UK Biobank is a population-based prospective study with more than 500,000 participants aged 40–69 years recruited between 2006 and 2010 throughout the UK [17–19]. The study was approved by the North-West Multi-Centre Research Ethics Committee (reference 11/NW/0382), and all participants provided written consent. In this study, we investigated the associations between PA and incident CVD in two cohorts: a questionnaire-based cohort using questionnaire-measured PA data and an accelerometer-based cohort using objective accelerometer-measured PA data. Inclusion and exclusion criteria are presented in Supplementary Methods, Table S1 and Fig 1.

2.2. Definition of masld

Patients with MASLD were identified using the standard definitions: the presence of steatotic liver disease and at least one of the following cardiometabolic risk factors, including (1) body mass index (BMI) ≥25 kg/m^2 or waist circumference >94 cm for male and >80 cm for female; (2) fasting serum glucose ≥5.6 mmol/L or 2-hour post-load glucose levels ≥7.8 mmol/L or HbA1c≥5.7 % or type 2 diabetes or its treatment; (3) blood pressure ≥130/85 mmHg or its treatment; (4) plasma triglyceride (TG) ≥150 mg/dL or lipid lowering treatment; or (5) plasma high-density lipoprotein (HDL) cholesterol ≤40 mg/dL for male and ≤50 mg/dL for female or lipid lowering treatment [4,20]. According to other epidemiological studies using the UK Biobank data, steatotic liver disease is indicated by a fatty liver index (FLI) ≥60, which yields a sensitivity of 61 % and specificity of 86 % [21–24].

2.3. Assessment of PA

In the questionnaire-based cohort, PA data were collected from 2006 to 2010 using the International Physical Activity Questionnaire [25,26]. Detailed information for questions in the questionnaire is provided in Supplementary Table S2. Five categories of PA are covered in the questionnaire, namely LTPA (stair climbing, strenuous sports, walking for pleasure and other exercises), housework-related activity [heavy do-it-yourself (DIY) and light DIY], job-related activity (job involves heavy manual or physical work and job involves mainly walking or standing), transportation for work (by car, walk, public transport and cycle) and transportation for others (by car, walk, public transport and cycle). Participants reported their frequency (day/week) and duration (min/day) for specific PA within the first two categories, their frequency for job-related activity, and their types of transportation for specific PA within the last two categories. We further categorized the questionnaire-measured PA data into TPA, LPA, MPA, VPA and MVPA. According to the WHO PA guidelines, the metabolic equivalent of task (MET) is a physiological measure expressing the intensity of PA, and one MET is the energy equivalent expended by an individual while seated at rest [11]. In the present study, LPA, MPA and VPA were determined as the time spent at 30–125 mg, 125–400 mg and >400 mg per week, respectively [14,27]. To take both intensity and duration into consideration simultaneously, TPA and the MVPA were expressed by combining MET and minutes (MET-min/week).

Accelerometer-based PA data were collected from 2013 to 2015 using the Axivity AX3 wrist-worn triaxial accelerometer (Axivity Ltd., Newcastle, UK) in milli-gravity units (mg). Participants were required to wear the accelerometer continuously and to carry on with their normal activities for seven days. Five indicators are selected, including TPA, LPA, MPA, VPA and MVPA. The duration of MVPA in this study was determined by calculating the daily proportion of time spent engaging in MVPA. The participants were categorized according to their level and pattern of PA following the WHO PA guidelines, including inactive (MVPA <600 MET-min/week) and physically active (MVPA ≥600 MET-min/week) groups. The physically active group was further divided based on the highest volume of PA over a 2-day period, which did not necessarily need to be on a weekend: the weekend warrior group (in which at least 50 % of total MVPA occurred within 1–2 days) and the regularly active group (in which at least 50 % of total MVPA was distributed over >2 days).

2.4. Ascertainment of CVD

The outcomes of this study were the incidence of composite CVD events, including CHD, stroke, AF and HF, which were obtained from hospital admissions and disease-specific death registers. We defined these outcomes according to the International Classification of Diseases edition 10 (ICD-10) codes: I20–I25 for CHD, I60-I64 for stroke, I48 for AF and I50 for HF. The follow-up time began at the date of enrollment or accelerometer wearing and ended at the date of hospital admission, death or the end of follow-up (December 31, 2021, for England and Wales; February 28, 2022, for Scotland), whichever came first.

2.5. Covariates

Details of covariates are described in Supplementary Methods [19,28,29]. If there was missing covariate information (including participants who responded “do not know” or “prefer not to answer”), missing values were imputed using multiple imputations. The percentage of missing covariates was 8.93 %.

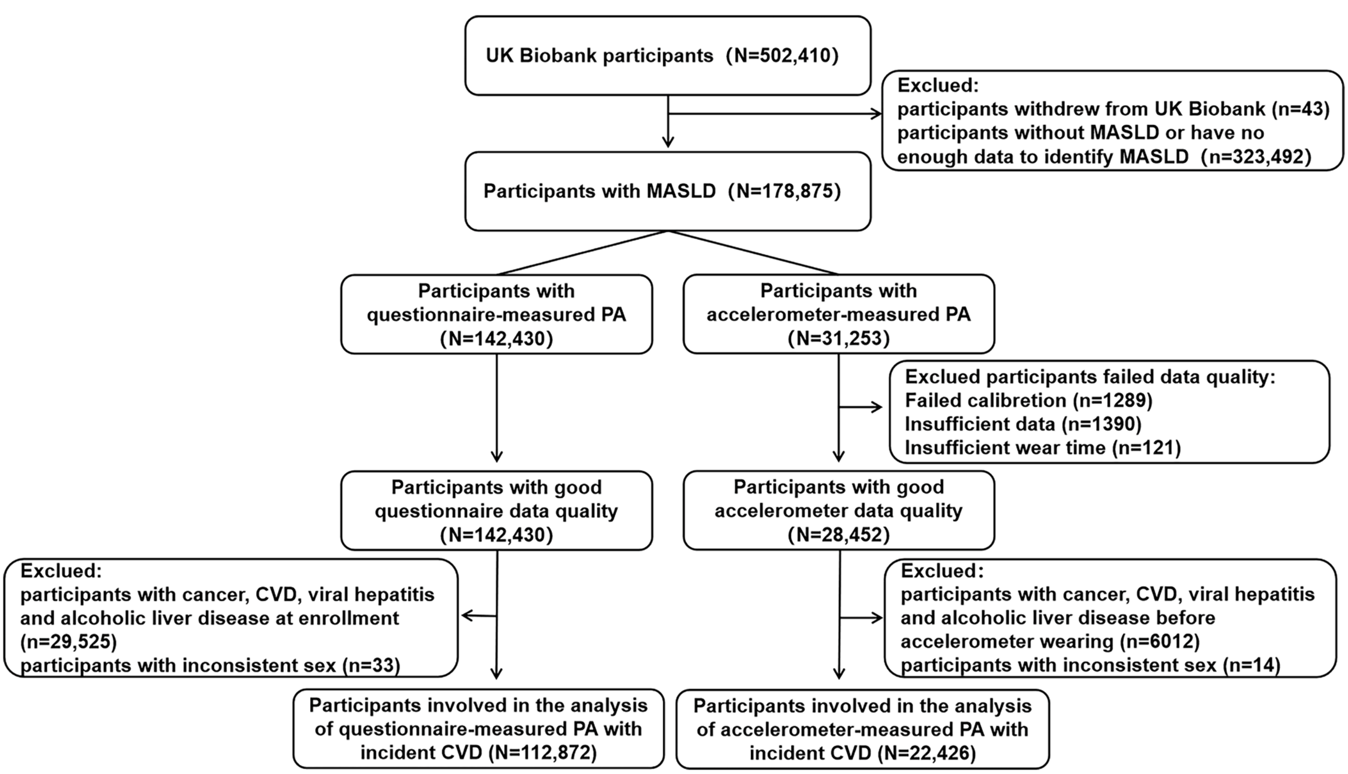

Fig. 1. Flowchart illustrating the selection of the study population from UK Biobank participants. CVD, cardiovascular disease; MASLD, metabolic dysfunction-associated steatotic liver disease; PA, physical activity.

2.6. Statistical analysis

In the questionnaire-based cohort, baseline characteristics were reported as mean [standard deviation (SD)], median [interquartile range (IQR)] or percentages as appropriate by incident CVD or not. With the time at recruitment as the start of follow-up, we investigated the associations of various PA categories, durations and intensities with incident CVD in patients with MASLD using Cox proportional hazard models adjusted for age, sex, ethnicity, education, Townsend deprivation index, diet, smoking status, alcohol consumption, sedentary behavior, obesity, diabetes, hypertension, high TG and low HDL cholesterol. We also categorized TPA and LPA into quarters, MPA into <150, 150–300, 300–600 and ≥600 min/week, VPA into <25, 25–50, 50–75 and ≥75 min/week, and MVPA into <600, 600–1200, 1200–1800 and ≥1800 MET-min/week. These cut-offs were chosen based on the WHO PA guidelines (150–300 min/week of MPA, 75–150 min/week of VPA, an equivalent combination of MPA and VPA) [11]. Results were reported as hazard ratios (HRs) and 95 % confidence intervals (CIs). The proportional hazards assumption was tested using Schoenfeld residuals and no violation was found. In the accelerometer-based cohort, baseline characteristics were reported as mean (SD), median (IQR) or percentages as appropriate by quarters of TPA and by incident CVD or not. With the time accelerometer wear finished as the start of follow-up, we investigated the associations of various PA durations, intensities and patterns with incident CVD in patients with MASLD using Cox proportional hazard models, adjusting as in questionnaire-based analysis and additionally for the season of accelerometer wear.

We examined the non-linear relationship between accelerometer-measured PA and incident CVD using penalized cubic splines. We further constructed a risk matrix to illustrate the joint associations of MPA and VPA with incident CVD, where MPA was categorized into <150, 150–300 and >300 min/week and VPA into <25, 25–75 and >75 min/week. A compositional isotemporal substitution analysis was performed to estimate the effect on CVD by reallocating time between sedentary behavior (SB), LPA and MVPA. To reveal the effects of PA on cardiovascular health in a more comprehensive and precise way, we conducted the above analyses for major CVD subtypes (CHD, stroke, AF and HF). Moreover, preventable fractions for the study population (PFP) were calculated to estimate the proportions of all incident CVD cases that could have been prevented if the individuals in specific MPA, VPA and MVPA levels were as active as the most active group, assuming that the associations were causal. More detailed information for statistical analysis is provided in Supplementary Methods.

Several sensitivity analyses were conducted in the accelerometer-based cohort to ensure the robustness and validity of the findings: 1) incorporating LPA, MPA and VPA into one model to mutually adjust for each other; 2) restricting analysis exclusively among participants with complete covariate data; 3) excluding CVD events that occurred within two years of accelerometer wear; 4) employing a competing risk model which considered death as a competing risk for incident CVD; 5) further adjusted for lipid-lowering medication, antihypertensive medication and estimated glomerular filtration rate (eGFR); and 6) conducting analysis using FLI ≥30 and ≥45 as cut-offs. Subgroup analyses were stratified by age (<65 years/≥65 years), sex (female/male), diabetes (yes/no), hypertension (yes/no), high TG (yes/no) and low HDL cholesterol (yes/no). A likelihood ratio test was conducted to assess the statistical significance of interactions between the subgroup categories and PA. All statistical analyses were performed using R software, version 4.4.0. All P values were two-sided and $P < 0.05$ was considered statistically significant.

3. Results

3.1. Population characteristics

Baseline characteristics of 112,872 participants with MASLD stratified by incident CVD in the questionnaire-based cohort are shown in Supplementary Table S3. The median age of the participants was 58 (IQR, 50–63) years and 65.5 % were male. During a median follow-up of 12.60 years, 19,683 participants were diagnosed with CVD. Compared to participants without CVD, those with CVD were more likely to be older, male, smokers, less educated, higher deprived, have a poor diet, perform more SB and have more cardiometabolic risk factors at baseline. Baseline characteristics of the 22,426 participants with MASLD involved in the accelerometer-based cohort by quarters of TPA are shown in Supplementary Table S4. The median age of the participants was 57 (50–62) years and 62.9 % were male. During a median follow-up time of 7.27 years, 2311 participants were diagnosed with CVD. Compared to participants adopting a high level of TPA, those with a low level were more likely to be older, male, less educated, more drank, higher deprived, have a poor diet, perform more SB and have more cardiometabolic risk factors. The characteristics of the excluded participants in the accelerometer-based cohort were similar to those of the included (Supplementary Table S5). Baseline characteristics by CVD events of the accelerometer-based cohort are shown in Supplementary Table S6.

3.2. Association between questionnaire-based PA and incidence of CVD in subjects with masld

Compared to participants with MASLD who did not engage in the specific types of LTPA, those who performed stair climbing, strenuous sports, walking for pleasure or other exercises demonstrated a protective effect against CVD regardless of frequency and duration (Fig 2 and Supplementary Table S7). Similarly, both heavy and light DIY housework helped protect against CVD regardless of frequency and duration, compared to participants who did not engage in these housework-related activities. For job-related activity, job involving heavy manual or physical work showed a negative impact on CVD risk when performed sometimes and job involving mainly walking or standing showed a

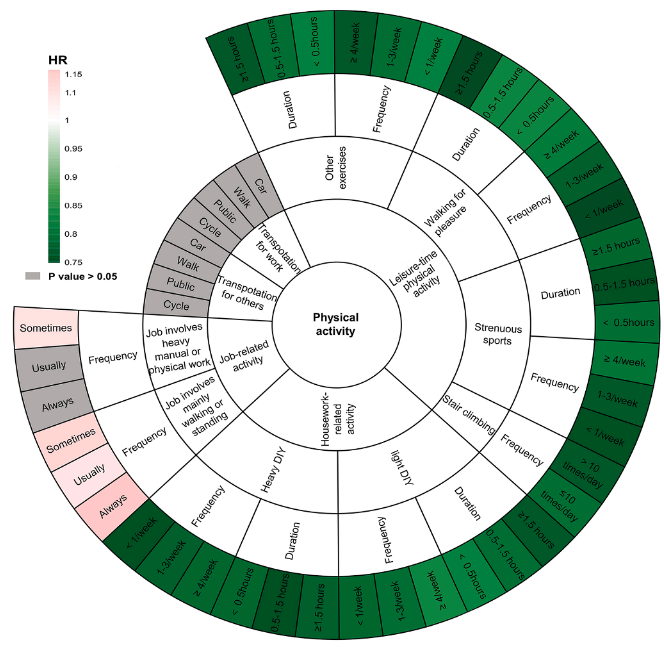

Fig. 2. Associations between various categories of questionnaire-based PA and incident CVD in subjects with MASLD. Analyses were conducted using the Cox model adjusted for age, sex, ethnicity, education, Townsend deprivation index, diet, smoking status, alcohol consumption, sedentary behavior, obesity, diabetes, hypertension, high TG and low HDL cholesterol. CVD, cardiovascular disease; MASLD, metabolic dysfunction-associated steatotic liver disease; DIY, do-it-yourself; HDL, high-density lipoprotein; HR, hazard ratio; TG, triglyceride.

negative impact on CVD across all frequencies (sometimes, usually and always). Additionally, neither transportation for work nor transportation for other reasons demonstrated a significant effect on CVD risk in this population. Regarding various PA durations and intensities, we noted significant inverse associations between overall TPA and LPA quartiles, low levels of VPA and moderate levels of MVPA with incident CVD in patients with MASLD (Supplementary Table S8).

3.3. Associations between accelerometer-based PA and incidence of CVD in subjects with masld

We observed statistically significant inverse associations between TPA, LPA, MPA, VPA and MVPA with incident CVD in patients with MASLD (Fig 3 and Supplementary Table S9). In particular, MPA, VPA and MVPA were significantly linked to reduced risk of CVD at all levels, whereas LPA was correlated with lower CVD risk only at the highest quarter. A per-SD increment in TPA, LPA, MPA, VPA and MVPA was

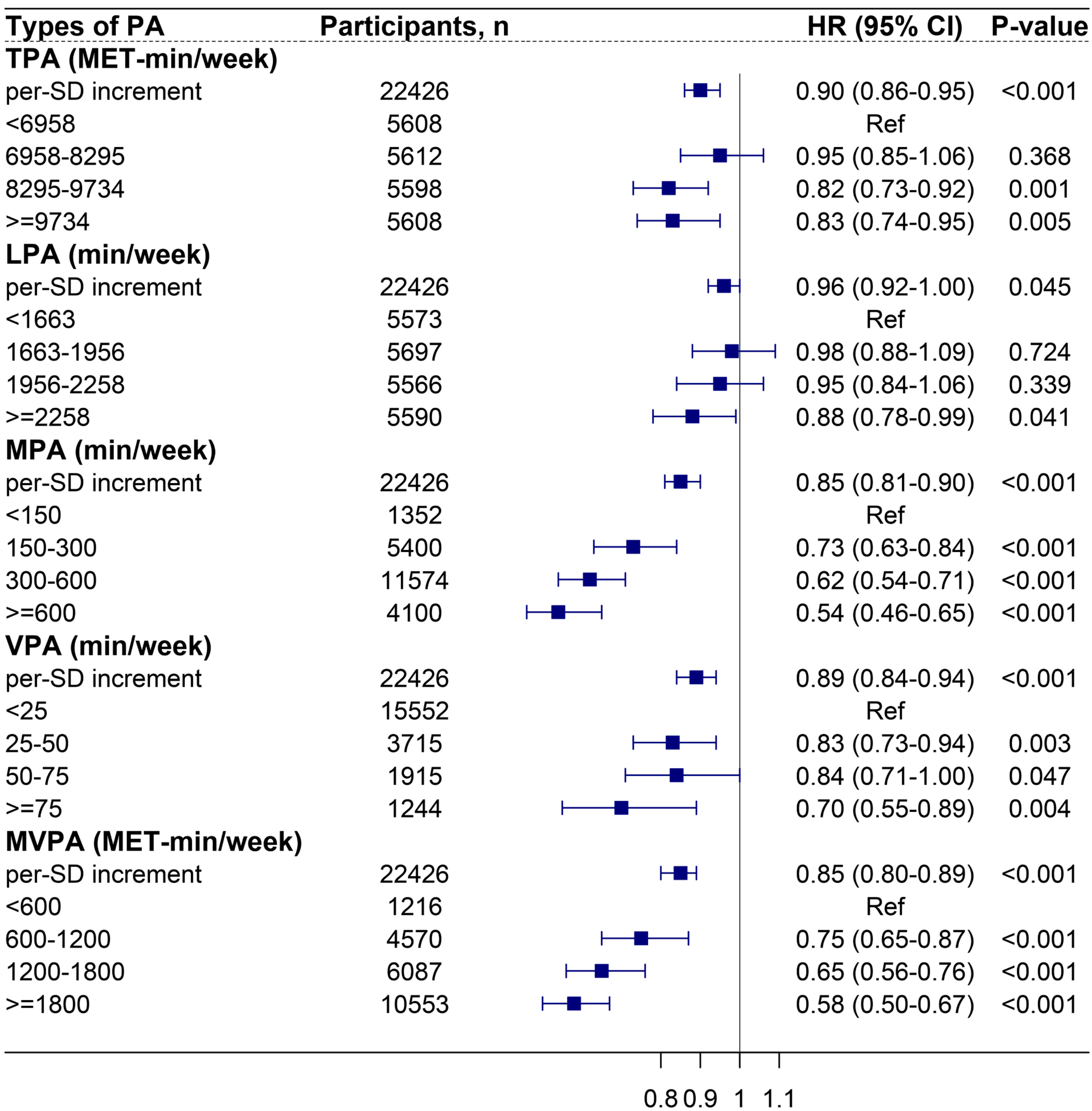

Fig. 3. Associations between various durations and intensities of accelerometer-measured PA and incident CVD in subjects with MASLD. Analyses were conducted using the Cox model adjusted for age, sex, ethnicity, education, Townsend deprivation index, season of accelerometer wear, diet, smoking status, alcohol consumption, sedentary behavior, obesity, diabetes, hypertension, high TG and low HDL cholesterol. CVD, cardiovascular disease; MASLD, metabolic dysfunction-associated steatotic liver disease; CI, confidence interval; HDL, high-density lipoprotein; HR, hazard ratio; LPA, light-intensity physical activity; MET, metabolic equivalent of tasks; MPA, moderate-intensity physical activity; MVPA, moderate-to-vigorous-intensity physical activity; Ref, reference; SD, standard deviation; TG, triglyceride; TPA, total volume physical activity; VPA, vigorous-intensity physical activity.

associated with lower risk of CVD, with adjusted HRs (95 % CIs) of 0.90 (0.86–0.95), 0.96 (0.92–1.00), 0.85 (0.81–0.90), 0.89 (0.81–0.90) and 0.85 (0.80–0.89), respectively. We only observed a non-linear dose-response relationship in MPA (P for non-linear: 0.0009), VPA (P for non-linear: 0.0071) and MVPA (P for non-linear: 0.0025), where the curves were L-shaped for MPA and MVPA and U-shaped for VPA (Fig 4). Compared to patients with MASLD who performed the lowest PA level, those performing the WHO PA guideline (150–300 min/week of MPA, 75–150 min/week of VPA and ≥600 MET-min/week of MVPA) were at lower CVD risk (Fig 4C-E). Notably, the risk of CVD sharply declined within the WHO-recommended range of MPA, continuing up to 600 min/week (Fig 4C). However, the lowest CVD risk was achieved within the WHO-recommended range of VPA (Fig 4D). For MVPA, a sharp decrease was observed within the WHO-recommended range, followed by a relatively flat decline without an observable plateau (Fig 4E). We then performed a risk matrix and illustrated that simultaneously meeting both recommended MPA and VPA was associated with an additional reduced CVD risk (Fig 5 and Supplementary Table S10). Jointly performing >300 min/week of MPA and >75 min/week of VPA was associated with a 53 % risk reduction of CVD. In the compositional isotemporal substitution analysis (Fig 6), reallocating time from LPA and SB to MVPA was associated with reduced risk of CVD. Compared to physically inactive patients, multivariable-adjusted HRs for CVD were 0.83 (95 % CI, 0.76–0.92) for weekend warriors and 0.83 (95 % CI, 0.74–0.94) for regularly active participants (Supplementary Table S11). The HR for weekend warriors versus regularly active participants was 1.00 (95 % CI, 0.88–1.13).

Assuming that the associations were causal, 4.71 %, 27.78 % and 3.71 % of incident CVD cases in the study population were attributed to a low level of MPA (<150 min/week), VPA (<75 min/week) and MVPA (<600 MET-min/week), respectively (Supplementary Table S12). The differences in preventable fractions were mainly due to a low prevalence of MPA (6.03 %; <150 min/week) and MVPA (5.42 %; <600 MET-min/week) and an extremely high prevalence of VPA (94.45 %; <75 min/week), that below the PA guidelines in the study population. It was

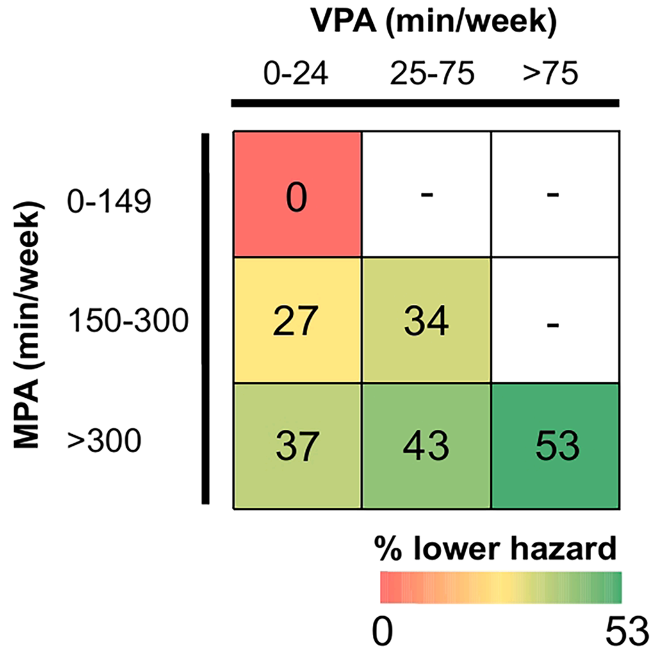

Fig. 5. Risk matrix for the joint associations of MPA and VPA with incident CVD in subjects with MASLD. Analyses were conducted using the Cox model adjusted for age, sex, ethnicity, education, Townsend deprivation index, season of accelerometer wear, diet, smoking status, alcohol consumption, sedentary behavior, obesity, diabetes, hypertension, high TG and low HDL cholesterol. The numbers presented are the associated reduction in the hazard ratio (percent) compared with the least active group. There was not a sufficient number of participants to estimate HRs in the blanked cells. CVD, cardiovascular disease; HDL, high-density lipoprotein; HR, hazard ratio; MASLD, metabolic dysfunction-associated steatotic liver disease; MPA, moderate-intensity physical activity; TG, triglyceride; VPA, vigorous-intensity physical activity.

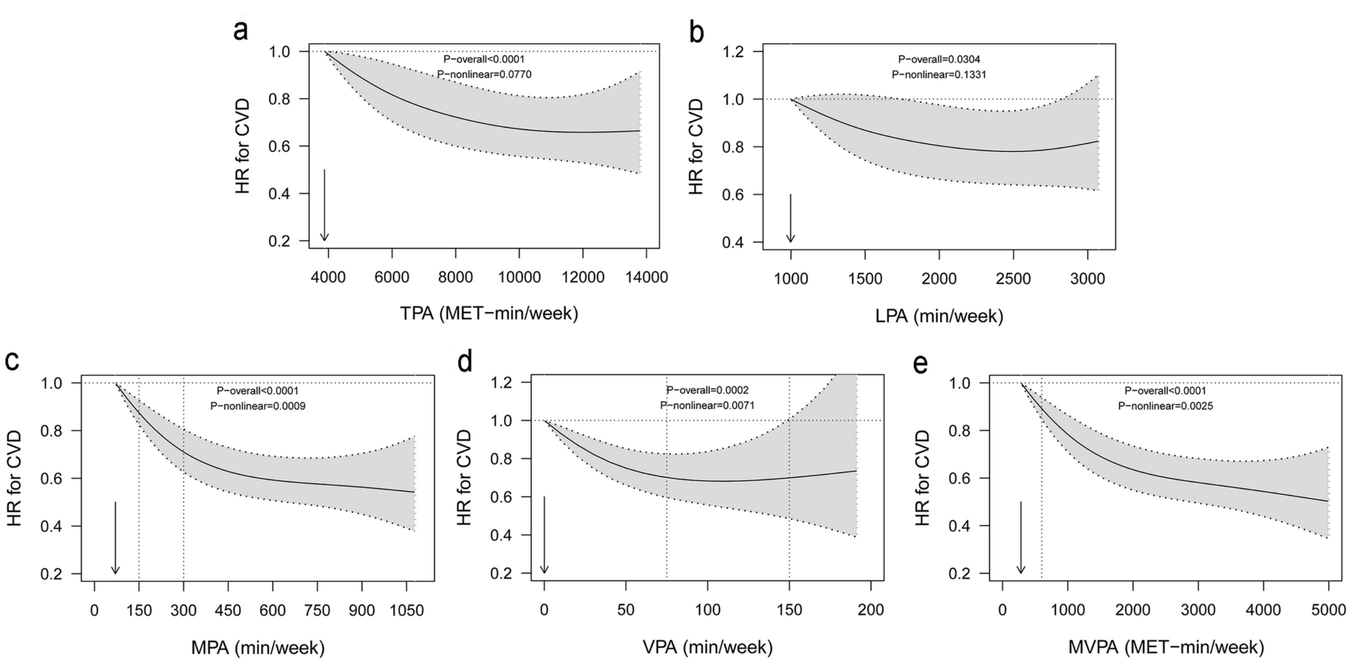

Fig. 4. Penalized cubic splines for the associations between accelerometer-measured PA and incident CVD in subjects with MASLD. A for TPA, B for LPA, C for MPA, D for VPA and E for MVPA. Analyses were conducted using the Cox model adjusted for age, sex, ethnicity, education, Townsend deprivation index, season of accelerometer wear, diet, smoking status, alcohol consumption, sedentary behavior, obesity, diabetes, hypertension, high TG and low HDL cholesterol. The ribbon indicates the 95 % confidence interval. CVD, cardiovascular disease; MASLD, metabolic dysfunction-associated steatotic liver disease; HDL, high-density lipoprotein; HR, hazard ratio; LPA, light-intensity physical activity; MET, metabolic equivalent of tasks; MPA, moderate-intensity physical activity; MVPA, moderate-to-vigorous-intensity physical activity; TG, triglyceride; TPA, total volume physical activity; VPA, vigorous-intensity physical activity.

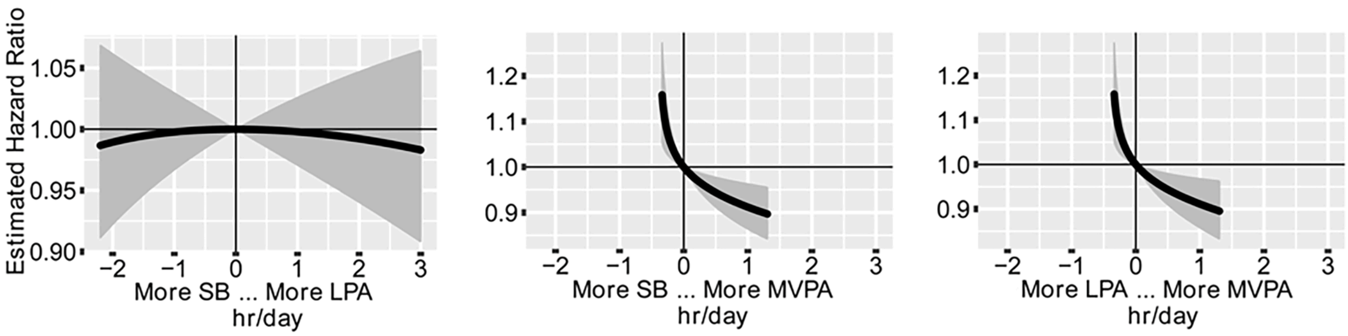

Fig. 6. HRs for the incidence of CVD associated with a balance between movement behaviors in the participants. All relative to the mean behavior composition (hours of SB, LPA and MVPA per day). Model used age as the timescale and was additionally adjusted for sex, ethnicity, education, Townsend deprivation index, season of accelerometer wear, diet, smoking status, alcohol consumption, sedentary behavior, obesity, diabetes, hypertension, high TG and low HDL cholesterol. The ribbon indicates the 95 % confidence interval. HDL, high-density lipoprotein; HR, hazard ratio; CVD, cardiovascular disease; LPA, light-intensity physical activity; MVPA, moderate-to-vigorous-intensity physical activity; SB, sedentary behavior; TG, triglyceride.

noteworthy that more than 12 % of CVD events in the study population could have been prevented if all participants had undertaken 300–600 min/week of MPA or ≥1800 MET-min/week of MVPA.

Pearson correlation coefficients between types of PA are shown in Supplementary Table S13. Multicollinearity diagnostics by employing variance inflation factors (VIF) confirmed that LPA, MPA and VPA were non-collinear, with respective VIFs of 1.28, 1.66, and 1.35. When LPA, MPA and VPA were incorporated in the same model to adjust for each other mutually, the association between LPA and CVD incidence became insignificant and VPA was significantly linked to lower risk of CVD only at the highest quartile; the association of MPA remained stable (Supplementary Table S14). The findings remained robust and consistent across the sensitivity analyses, including using competing risk regression, restricting the analysis to participants with complete covariate data, excluding CVD events within the first two years of follow-up, further adjusting for lipid-lowering medication, antihypertensive medication and eGFR, and using FLI ≥30 and ≥45 as cut-offs (Supplementary Tables S15–S20). Subgroup analyses stratified by age, sex, with or without diabetes, hypertension, high TG or low HDL cholesterol revealed similarly aligned with our main results (Supplementary Tables S21–S26).

3.4. Associations between accelerometer-based PA and incidence of CVD subtypes in subjects with MASLD

We observed significant inverse associations between TPA, MPA, VPA and MVPA and the incidence of CVD subtypes in patients with MASLD (Supplementary Tables S27-S30). Higher levels of MPA and MVPA were significantly linked to lower risk of stroke, and higher levels of VPA were correlated with lower risk of CHD and HF. We only detected a significant non-linear dose-response relationship in MPA, VPA and MVPA with the incidence of stroke, AF and HF (Supplementary Fig S1). Performing 150–300 min/week of MPA and ≥600 MET-min/week of MVPA showed reduced risks in all four subtypes (Supplementary Fig S1C and Fig S1E). A rapid decrease in the risk of stroke, AF and HF was observed with increased MPA and MVPA levels within the WHO-recommended range. We observed a U-shaped relationship between VPA and incident HF but no statistically significant associations were observed for incident stroke or AF (Supplementary Fig S1D). It was worth noting that continuously decreasing risk of CHD (P for non-linear >0.05) was observed across MPA, VPA and MVPA, even exceeding the WHO-recommended range. Consistently, jointly performing >300 min/week of MPA and >75 min/week of VPA was associated with the greatest reduction in the risk of CHD (Supplementary Fig S2A and Table S10). However, the lowest risk of stroke, AF and HF was observed when >300 min/week of MPA combined with 25–75 min/week of VPA (Supplementary Fig S2B-D and Table S10). In the compositional isotemporal substitution analysis, reallocating time from SB to LPA was not associated with significant reductions in the risk of four CVD subtypes (Supplementary Fig S3). Furthermore, reallocating time from SB and LPA to MVPA was associated with reduced risk of CHD, AF and HF but not stroke.

4. Discussion

In our study, the questionnaire- and accelerometer-measured PA were both significantly associated with incident CVD in patients with MASLD. In the questionnaire-based cohort, performing more LTPA and housework was correlated with lower risk of CVD in patients with MASLD. In the accelerometer-based cohort, significant dose-response relationships were found between TPA, MPA, VPA and MVPA and incident CVD in patients with MASLD. Participants who performed the WHO-recommended PA (150–300 min/week of MPA, 75–150 min/week of VPA and ≥600 MET-min/week of MVPA) were at lower CVD risk compared to those with the lowest level of PA. Jointly performing >300 min/week of MPA and >75 min/week of VPA was associated with the lowest CVD risk in patients with MASLD. Reallocating time to MVPA from LPA or SB was associated with reduced risk of CVD. Given the same amount of total MVPA, weekend warrior participants had a similar reduction in CVD risk as regularly active participants. These findings provide population-scale evidence that highlights the significance of PA, especially MPA and MVPA, in preventing CVD events and provide valuable insights into future PA recommendations for subjects with MASLD.

To our knowledge, our study is the first to systematically explore the associations between various categories of PA (LTPA, housework-related, job-related and transportation-related activity) and specific terms within each category with incident CVD in patients with MASLD. Previous studies in the general population have primarily examined the relationship between LTPA and incident CVD [30–32], and a retrospective cohort study in NAFLD patients reported that higher LTPA (>600 MET-min/week) was associated with lower odds of developing atherosclerotic CVD [13]. Our study supports and extends these findings by demonstrating that all specific terms of LTPA and housework-related activity confer a protective effect against CVD in patients with MASLD, whereas transportation-related activity does not. While in Donghee's study using the NHANES data, positive effects of both LTPA and transportation-related PA on CVD mortality were found [33]. Possible explanations for this inconsistency are recall bias and misclassification of PA measured by questionnaires, as well as the distinctive characteristics of the study population. Notably, job involving mainly walking or standing and job involving heavy manual work increased CVD risk by 9~16 %. These findings suggest that reducing prolonged standing or sedentary behaviors and engaging in multiple categories of PA in daily life may obtain many cardiovascular health benefits for patients with MASLD.

The methodologies employed for questionnaire-based PA assessment may introduce discrepancies that prevent accurate measurement of the associations between PA and incident CVD. By contrast, accelerometry can objectively measure the durations and intensities of PA. In the current study, the durations of questionnaire-measured TPA and LPA, as well as the proportion of participants meeting the WHO-recommended levels of MPA and MVPA, were much lower than those measured by accelerometry. Specifically, the questionnaire-based cohort showed only low levels of VPA and MVPA linked to liver health, while MPA presented insignificant results. However, previous accelerometer-based studies supported that engaging in more PA was associated with reduced risk of CVD or HF [34–36]. Our accelerometer-based cohort comprehensively assessed these findings in MASLD patients, demonstrating inverse associations between various durations and intensities of PA with incident CVD and four major subtypes, which aligned with prior studies in general populations [35–37]. The dose-response relationship in our study indicated that PA performed within the WHO-recommended range showed a positive effect against CVD, and performing more MPA and MVPA than recommended by the WHO may provide additional benefits to the population, such as a more than 25 % reduction in CVD risk. We also noted a 53 % risk reduction of CVD among those who jointly performed >300 min/week of MPA and >75 min/week of VPA. Although prior questionnaire-based research in the NAFLD population primarily highlighted that only VPA but not MPA was linked to reduced risk of steatohepatitis and mortality [38–40], Kim et al. corroborated our findings that accelerometer-measured MVPA (consisting primarily of MPA due to participants engaging in little VPA) lowered mortality in NAFLD patients [16]. Moreover, our findings supported that engaging in more MPA and MVPA could obtain positive effects against CHD, stroke, AF and HF. Compositional isotemporal substitution analysis indicated that reallocating time to MVPA from LPA or SB was associated with reduced risk of CVD [34,41], as well as CHD, AF and HF, suggesting that increasing MPA and MVPA should be encouraged in patients with MASLD to prevent the development of CVD events. In patients who performed MVPA ≥600 MET-min/week, both the weekend warrior and regularly active patterns were similarly linked to a 17 % lower risk of CVD, suggesting that when actively performing the same amount of MVPA, spreading it over more days or concentrating it into fewer days may not influence the obtained cardiovascular benefit.

While the lowest CVD risk was observed within the WHO-recommended VPA range in the accelerometer-based cohort, the protective effect of engaging in more VPA than the level recommended by the WHO guidelines against CVD in patients with MASLD should not be denied, as a linear relationship between VPA and incident CHD was observed and few participants in our study achieved the recommended VPA. Notably, we didn't find a significant dose-response relationship between VPA and incident stroke or AF, but observed a U-shaped curve between VPA and incident HF, suggesting that the protective effect of VPA on different CVD outcomes may vary in these patients. Supporting our study, the American Heart Association had raised concerns regarding these findings that high amounts of VPA were correlated with potential cardiac maladaptive responses, of which relationship resulted in a U- or reverse J-shaped dose-response curve, as well as an increased risk of acute cardiovascular event and sudden cardiac death in individuals with susceptible or diseased heart [42,43]. For example, older individuals with a history of coronary artery disease can suffer sudden cardiac death during strenuous exercise [44]. These results, along with our findings, supported engaging in moderate VPA to enhance cardiovascular fitness and prevent CVD in patients with MASLD at an early stage, whereas the approach to obtain additional cardiovascular benefits by continuously increasing amounts of VPA over time should be prudent for individuals with cardiac discomfort or underlying heart disease. Despite the potential health benefits of VPA, results should be interpreted cautiously and more research is warranted to determine its impact on cardiovascular risk, given that a few participants met the VPA recommendations in the accelerometer-based cohort.

Controlled intervention studies remain inconclusive regarding the effects of LPA on CVD incidence [45]. Our accelerometer-based cohort revealed that LPA at the highest level was associated with lower CVD incidence, but the association became insignificant after adjusting for MPA and VPA. Similar results were found in the other study based on UK Biobank [35]. While we identified a significant inverse association between LPA and incident HF, our results showed insignificance for HF or the other three CVD subtypes when reallocating time from SB to LPA. This contrasts with the findings of Andrea et al., who suggested that a 1-hour/day increment in LPA counted for the prevention of CVD and CHD in older women [46]. However, MVPA may introduce a confounding variable in these outcomes, given that individuals rarely engage solely in LPA. Although research evidence indicated that LPA could enhance cardiometabolic health [47], no studies have yet confirmed its role in CVD incidence or related mortality [48]. Therefore, these findings on LPA must be interpreted cautiously, and more studies are required to determine the effect of LPA. Nevertheless, the linear relationship of TPA with the incidence of CVD and major CVD subtypes observed in our study further supports that increasing overall PA volume at any intensity may optimize risk across a broad range of cardiovascular diseases in patients with MASLD.

Our study carries important implications for public health by preventing CVD in patients with MASLD, given the limitations of specific PA recommendations for this population. Firstly, we underscore the urgent need to reduce prolonged standing or sedentary behaviors and enhance the volume of PA in daily life. Secondly, the comparison of durations and intensities of PA between questionnaire- and accelerometer-based cohorts indicated that PA obtained through questionnaires was significantly underestimated. This oversight may weaken our understanding of PA levels on liver health, suggesting that PA recommendations based on objectively measured PA data are required. Thirdly, our findings broadly support current general PA recommendations as a potent strategy for reducing CVD in patients with MASLD in the accelerometer-based cohort and suggest that the MPA recommendation could be more ambitious. In our study population, approximately 18.36 % of CVD cases could be prevented by performing 600 min/week of MPA and 12.62 % by 1800 MET-min/week of MVPA. Moreover, for people with fewer opportunities for daily or regular physical activity, the weekend warrior pattern is a potential alternative in CVD preventive intervention strategies. Our findings can serve as large-scale clinical evidence that performing greater amounts of daily MPA and MVPA may lead to enhanced cardiovascular benefits. Lastly, we found that jointly performing more MPA (>300 min/week) and moderate VPA (>75 min/week) was associated with the lowest risk of CVD, approximately a 53 % risk reduction. These findings support new health insights advising to meet both MPA and VPA recommendations, where available, to maximize cardiovascular benefits in patients with MASLD. Notably, patients with susceptible heart risk and other unfit cardiovascular conditions are discouraged from exceeding the current VPA recommendation in clinical practice.

This study has several important advantages, including its prospective design, large sample size, and wide range of PA information that combines the questionnaire and accelerometer data. Detailed data allowed us to include PA that was not typically examined in other studies and comprehensively explore the potential associations between various categories and intensities of PA and the incidence of CVD in patients with MASLD. However, several limitations should be considered. First, the possibility of changes in PA during the measurement period of seven days at baseline may weaken the associations between long-term habitual PA and CVD incidence. Second, despite adjustment for a wide range of covariates, including social demographic factors, lifestyle factors and cardiometabolic risk factors, residual confounding and reverse causation cannot be ruled out in observational studies, and causal interpretation should be cautious. Third, the wrist accelerometer may not be suitable for characterizing resistance exercise or cycling and may not differentiate the time spent in SB and LPA. Fourth, the UK Biobank sample is not fully representative of the overall UK population, which may result in the findings of our study not being generalizable to a wider population.

In summary, engaging in more LTPA and housework-related activity, as well as increasing TPA, especially MPA and MVPA, were associated with lower risk of CVD in subjects with MASLD. Achieving 600 MET-min/week of MVPA, whether it is spread throughout the week or concentrated on a weekend, was effective in preventing CVD events in subjects with MASLD. Performing MPA beyond the current WHO recommendation (>150 min/week) was associated with a further risk reduction in MASLD subjects. The associations of VPA with specific CVD events should be carefully examined before the promotion of very high levels of VPA in the MASLD population is considered. These findings may provide a sound basis for the future development of PA guidelines for subjects with MASLD, thereby improving the health burden of CVD events.

CRediT authorship contribution statement

Yingxin Liao: Writing – original draft, Data curation. **Yuqing Deng:** Writing – review & editing, Writing – original draft, Project administration, Data curation, Conceptualization. **Chao Yu:** Writing – review & editing, Conceptualization. **Xuechen Chen:** Writing – review & editing, Formal analysis, Data curation. **Peiting Zhang:** Formal analysis. **Shijia Wang:** Writing – review & editing, Data curation. **Mengyu Zhou:** Formal analysis. **Wenhua Ling:** Supervision, Project administration, Conceptualization. **Xu Chen:** Project administration, Conceptualization. **Hongliang Xue:** Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

None.

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Ethics approval and consent to participate

The UK Biobank was approved by the North-West Multi-Centre Research Ethics Committee (reference 11/NW/0382) and all participants signed written consent.

Availability of data and materials

The data that support the findings of this study are available from UK Biobank (https://www.ukbiobank.ac.uk/).

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Declaration of generative AI

Not applicable.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2025.101272.

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