Physical activity is inversely associated with hepatic fibro-inflammation: A population-based cohort study using UK Biobank data

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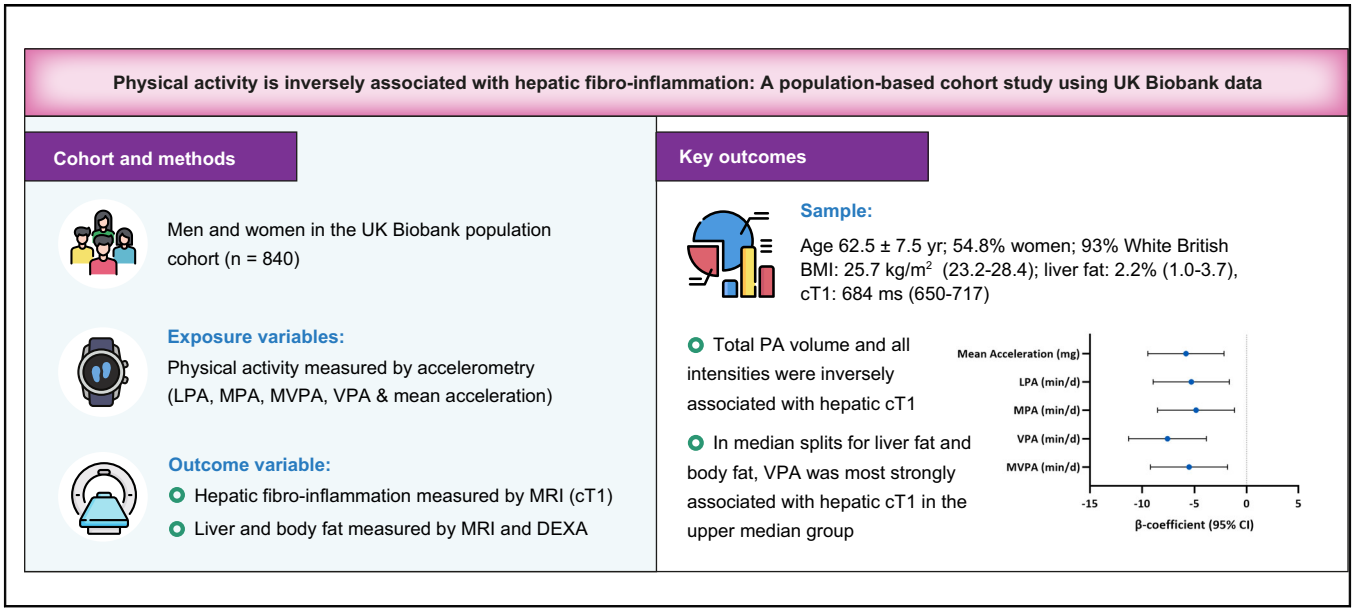
Graphical abstract



Highlights

- Physical activity is inversely related to hepatic fibro-inflammation.
- This inverse association is strongest for vigorous-intensity physical activity.
- The relationship is most visible in people with elevated liver and body fat.

Lay summary

This study has shown that people who regularly perform greater amounts of physical activity have a reduced level of inflammation and fibrosis in their liver. This beneficial relationship is particularly strong when more intense physical activity is undertaken (*i.e.*, vigorous-intensity), and is most visible in individuals with higher levels of liver fat and body fat.

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Research article

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Physical activity is inversely associated with hepatic fibro-inflammation: A population-based cohort study using UK Biobank data

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Background & Aims: Physical activity (PA) is recommended in the management of non-alcoholic fatty liver disease (NAFLD) given its beneficial effects on liver fat and cardiometabolic risk. Using data from the UK Biobank population-cohort, this study examined associations between habitual PA and hepatic fibro-inflammation.

Methods: A total of 840 men and women aged 55-70 years were included in this cross-sectional study. Hepatic fibro-inflammation (iron-corrected T1 [cT1]) and liver fat were measured using MRI, whilst body fat was measured using dual-energy X-ray absorptiometry. PA was measured using accelerometry. Generalised linear models examined associations between PA (light [LPA], moderate [MPA], vigorous [VPA], moderate-to-vigorous [MVPA] and mean acceleration) and hepatic cT1. Models were fitted for the whole sample and separately for upper and lower median groups for body and liver fat. Models were adjusted for sociodemographic and lifestyle variables.

Results: In the full sample, LPA (-0.08 ms [-0.12 to -0.03]), MPA, (-0.13 ms [-0.21 to -0.05]), VPA (-1.16 ms [-1.81 to -0.51]), MVPA (-0.14 ms [-0.21 to -0.06]) and mean acceleration (-0.67 ms [-1.05 to-0.28]) were inversely associated with hepatic cT1. With the sample split by median liver or body fat, only VPA was inversely associated with hepatic cT1 in the upper median groups for body (-2.68 ms [-4.24 to -1.13]) and liver fat (-2.33 [-3.73 to -0.93]). PA was unrelated to hepatic cT1 in the lower median groups.

Conclusions: Within a population-based cohort, device-measured PA is inversely associated with hepatic fibro-inflammation. This relationship is strongest with VPA and is greater in people with higher levels of body and liver fat.

Lay summary: This study has shown that people who regularly perform greater amounts of physical activity have a reduced level of inflammation and fibrosis in their liver. This beneficial relationship is particularly strong when more intense physical activity is undertaken (*i.e.*, vigorous-intensity), and is most visible in individuals with higher levels of liver fat and body fat.
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Introduction

The dual comorbidities of obesity and type 2 diabetes have fuelled a rise in chronic liver disease, owing to a surge in the prevalence of non-alcoholic fatty liver disease (NAFLD). Globally, 32% of adults have NAFLD,[1] which is an increasingly prominent indication for liver transplantation.[2] NAFLD is a term that describes a spectrum of liver pathologies, beginning with hepatic steatosis, and in an increasing proportion of individuals, progressing to hepatic inflammation (non-alcoholic steatohepatitis [NASH]), fibrosis and cirrhosis.[3] Whilst hepatic steatosis is associated with insulin resistance and heightened cardiovascular risk,[4,5] it often progresses slowly.[6] Conversely, the presence of NASH, characterised by hepatic inflammation and hepatocyte injury, is associated with a more rapid and advanced disease progression.[7,8] Furthermore, the staging of hepatic fibrosis is the strongest predictor of cardiovascular and liver-related morbidity and mortality.[9,10] Therefore, hepatic fibro-inflammation is a crucial target within the management of NAFLD.

The increasing public health burden of NAFLD has focused efforts on the development of therapies. Although clinical efficacy for NASH resolution has been demonstrated for some anti-diabetic agents,[11,12] no medications are currently licenced for NAFLD. Lifestyle therapies remain integral for NAFLD, with guidelines emphasising the importance of weight loss (7-10%) to reduce NASH and hepatic fibrosis.[13] The therapeutic benefits of physical activity (PA) are also recognised,[14] with meta-analyses demonstrating that exercise training reduces hepatic steatosis.[15] Evidence is less clear about whether PA beneficially

Keywords: Exercise; Non-alcoholic steatohepatitis; Obesity; Liver fat.
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influences advanced features of NAFLD, particularly hepatic inflammation and fibrosis.

The potential for PA to beneficially impact hepatic fibro-inflammatory activity has been demonstrated in rodent studies,[16–20] with some evidence that vigorous PA (VPA) confers greater benefit than moderate PA (MPA).[16] These findings are supported by observational data showing that VPA is associated with a reduced odds of developing NASH and advanced hepatic fibrosis in people with NAFLD.[21] Given the practical challenges with liver biopsies, evidence from human PA interventions is limited and presently conflicting. Recently, 12 weeks of moderate-to-vigorous aerobic exercise training was found to improve hepatic fibrosis and hepatocyte ballooning in people with NAFLD.[22] However, histological benefits have not been seen in other interventions.[23,24]

The generalisability of the aforementioned evidence beyond secondary care is uncertain, as an indication for liver biopsy was necessary for participant enrolment. Furthermore, the available observational evidence is limited by the self-reported assessments of PA, which are constrained to leisure-time (recreational activity). To address these limitations, we used data available within the UK Biobank population-cohort to examine the relationship between device-measured PA (accelerometry) and hepatic fibro-inflammation, determined by MRI (hepatic cT1). Notably, hepatic cT1 is a continuous score corresponding to hepatic inflammation and fibrosis, adjusted for hepatic iron content. This MRI-derived metric has been validated against liver histology[25–28] and has demonstrated clinical utility prospectively.[29] Based on current evidence, we hypothesised that PA would be inversely associated with hepatic fibro-inflammation, with stronger relationships apparent for more intense forms of PA. Moreover, given the non-clinical population demographic, we anticipated that stronger associations would be seen between PA and hepatic fibro-inflammation in people with higher levels of liver fat and body fat.

Materials and methods

Data source and study population

The present study used data obtained from the UK Biobank (project number 36371), a large prospective cohort study of over 500,000 men and women aged between 37-73 years. The study protocol has been reported in detail.[30] Briefly, individuals living within a 25-mile radius of the 22 assessment centres based in England, Scotland and Wales were invited to attend a baseline assessment visit. These visits were conducted between March 2006 and July 2010 and involved a comprehensive assessment of a range of sociodemographic, lifestyle, biological and clinical outcomes. Ethical approval was granted by the Northwest Multi-Centre Research Ethics Committee (Ref: 11/NW/0382). The research was conducted in accordance with the Declarations of Helsinki and Istanbul, and all participants provided written informed consent before taking part.

For this analysis, participants were included if they had valid MRI (cT1, proton density fat fraction [PDFF]), body composition (dual-energy X-ray absorptiometry; [DXA]), and PA data (at least 5 days of accelerometry). Those reporting excessive alcohol intake (men >21 units/week, women >14 units/week), a diagnosis of cancer (any form), or secondary causes of chronic liver disease, were excluded.

Liver magnetic resonance imaging and analysis

Since April 2014, the UK Biobank imaging enhancement protocol has sought to re-invite ~100,000 participants for multi-modal imaging including brain, cardiac and abdominal MRI, DXA and carotid ultrasound.[31] As part of the Liver*MultiScan*® protocol (Perspectum Diagnostics, Oxford, UK), liver MRI scans were acquired from a single transverse slice at the porta hepatis using a Siemens 1.5 T MAGNETOM Aera scanner (Siemens AG, Munich, Germany). All acquisitions were performed during end-expiration breath-holds in the absence of contrast agents. A cardiac-gated ShMOLLI (Shortened Modified Look-Locker Inversion) sequence was used to quantify liver T1, whilst a multi-echo spoiled-gradient-echo was used to quantify liver iron and PDFF. Liver T1 can then be corrected for the opposing effect of iron to produce an iron-corrected T1 (cT1) score (unit expressed in milliseconds), an indirect marker of hepatic fibro-inflammatory activity.

Liver MRI data were analysed in a blinded fashion using Liver*MultiScan*® Discover software (Version 4.0, Perspectum Diagnostics, Oxford, UK). Liver T2*, cT1 and PDFF image maps were generated from an automated delineation of the liver excluding major vessels using a deep learning approach.[32] Three 15 mm circular regions of interest were manually selected for each image by trained image analysts and a mean average was calculated for liver T2*, cT1 and PDFF. Further details of the liver MRI and analysis protocols have been published previously.[31,33] In this study, hepatic cT1 score was the outcome variable.

Device-measured PA assessment (exposures)

Between May 2013 and December 2015, a sub-set of participants (~100,000) were provided with an Axivity AX3 triaxial accelerometer (Axivity Ltd., Newcastle, UK) to objectively assess their habitual PA levels. Invitation letters were sent at random, and accelerometers were distributed in order of acceptance. Participants were instructed to wear the accelerometer continuously on their dominant wrist for 7 consecutive days. Raw triaxial acceleration data were captured at 100 Hz with a dynamic range of ± 8 *g*, with cut-points set at 5-second epochs. Device calibration was in accordance with van Hees *et al.*.[34]

Periods of wear time were identified using the pre-processing methods outlined by Doherty *et al.*,[35] whilst periods of non-wear (consecutive stationary episodes lasting for at least 60 min) were removed. Individuals who either had less than 5 days of data, did not have data in each 1 h period of the 24 h cycle, or had data recording errors, were excluded from the analysis.[35,36] A valid wear time of at least 3 days was considered; however, only a small difference between the number of participants providing at least 3 and at least 5 days of wear time (n = 44 participants) was observed. This observation, combined with at least 5 days of wear time data providing a better representation of free-living PA, led to the valid wear criteria for this study being set to at least 5 days of data.

The summary PA variables used as exposures in the present analysis include the total mean acceleration across the 7-day period (marker of total PA), and the average time spent (mins per day) at different PA intensities, as defined by specific ranges of mean acceleration values.[37,38] These include light PA (LPA, 30-99 mg), MPA (100–399 mg), VPA (≥400 mg) and moderate-vigorous PA (MVPA, ≥100 mg).

Covariates

The following covariates were used in the present analysis: socio-demographics (age, sex, ethnicity, number of medications taken, education, household income, employment status, social deprivation), lifestyle factors (smoking status, units of alcohol intake per week, processed meat intake, daily fruit and vegetable intake). Age was calculated from date of birth to date of attendance at the baseline assessment visit, whilst sex, ethnicity (white British, other), smoking status (never, past, current) and number of medications per day were self-reported. Self-report questionnaires were also used for education (university or college degree, other), household income (<£52,000, ≥£52,000, other) and employment status (employment, retired, not in paid work). The Townsend deprivation index was used as a measure of social deprivation.[39] Food frequency questionnaires determined the intake of processed meat, fruit and vegetables (portions per day), and alcohol (the unit sum of average weekly intake of red wine, champagne and white wine, beer and cider, spirits, and fortified wine). Total body fat percentage was measured using an iDXA instrument (GE-Lunar, Madison, WI, USA).[31]

Statistical analysis

Sample characteristics are presented as mean (SD) for normally distributed data, median (IQR) for non-normally distributed data, and count (%) for categorical data. Liver (cT1 score, liver fat percentage) and adiposity (BMI, body fat percentage) outcomes were reported as continuous variables. Normality of distribution of the outcome variable was assessed using histograms of standardised residuals. Normality was assessed and confirmed. General linear regression models were used to examine the associations of PA exposure variables (mean acceleration, LPA, MPA, VPA and MVPA) with hepatic cT1 score. Unadjusted models were fitted, whilst model 1 was adjusted for sociodemographic variables including sex, age, ethnicity, education, employment status, household income and Townsend deprivation index. Model 2 was additionally adjusted for clinical and lifestyle factors, including number of medications, smoking status, alcohol intake, fruit and vegetable intake and processed meat intake. Models were not further adjusted for measures of liver fat or adiposity given the potential for these factors to act as mediators rather than confounders. However, to explore whether the associations between PA exposures and cT1 score are modified by liver fat and body fat, sub-analyses were performed by repeating the models with the sample split by median liver fat percentage and median body fat percentage. Linear relationships between

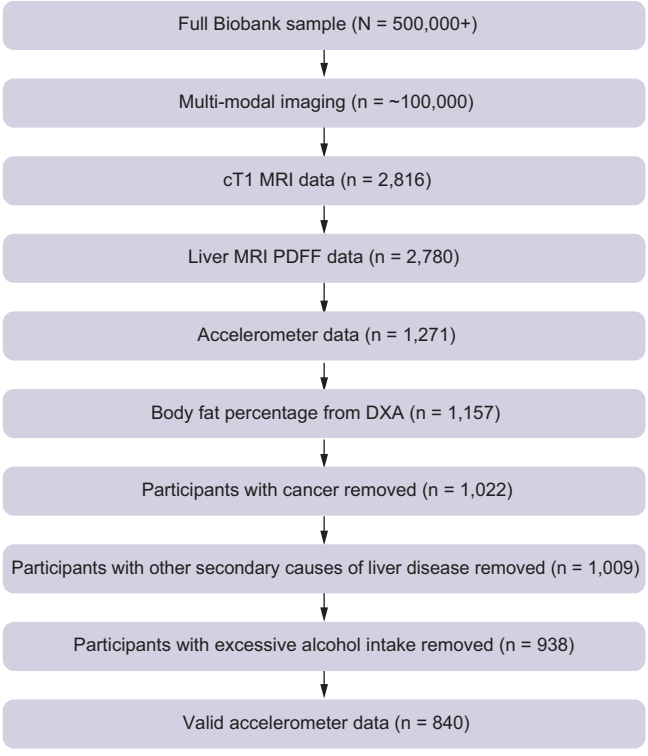

Fig. 1. Sample reduction process. cT1, iron-corrected T1; DXA, dual-energy X-ray absorptiometry; PDFF, proton density fat fraction.

Table 1. Baseline characteristics for full sample (n = 840).

Demographics	
Age, years	62.5 (7.5)
Sex	
Men	380 (45.2%)
Women	460 (54.8%)
Ethnicity	
White British	784 (93.3)
Other	56 (6.7)
Education	
College or University degree	359 (42.7)
Other	481 (57.3)
Employment status	
Employed	356 (42.8)
Retired	439 (52.3)
Not in paid work	45 (4.9)
Household income	
<£52,000	540 (64.3)
£52,000 or more	214 (25.5)
Unknown	86 (10.2)
Townsend deprivation index	-2.6 (-4.1–1.1)
Lifestyle factors	
Number of medications, median (range)	1.0 (0.0–2.5)
Alcohol intake, units/week	5.0 (2.0–9.0)
Smoking status	
Never	565 (67.3%)
Previous	250 (29.8%)
Current	25 (2.9%)
Fruit and vegetable intake, portions/day	7.0 (4.5–9.5)
Processed meat intake	
Never	79 (9.5)
Less than weekly	223 (26.5)
Weekly	538 (64.0)
Liver and adiposity outcomes	
cT1 score, ms	683.9 (650.3–717.0)
Liver fat, %	2.2 (1.0–3.7)
Body fat, %	34.5 (28.3–40.6)
BMI, kg/m^2	25.7 (23.2–28.4)
Participants with NAFLD	148 (17.6%)
Physical activity outcomes	
Valid days	6.9 (6.8–7.1)
Mean acceleration, mg	27.3 (22.1–32.3)
LPA (30-99 mg), mins/day	366.0 (84.0)
MPA (100-399 mg), mins/day	105.9 (44.5)
VPA (≥400 mg), mins/day	2.9 (0.7–5.0)
MVPA (≥100 mg), mins/day	110.6 (46.9)

Sample characteristics are presented as mean (SD) for normally distributed data, median (IQR) for non-normally distributed data, and count (%) for categorical data, unless otherwise specified.
BMI, body mass index; LPA, light physical activity; MPA, moderate physical activity; MVPA, moderate-to-vigorous physical activity; NAFLD, non-alcoholic fatty liver disease; VPA, vigorous physical activity.

PA exposure variables and the cT1 outcome variable were tested by dividing all PA exposure variables into tertiles and performing model 2 adjustments. This analysis confirmed a graded effect and therefore a linear relationship between exposure and outcome variables (see Table S1). Statistical analyses were performed using SPSS version 27 (SPSS Inc., Chicago, Illinois).

Results

Fig. 1 details the sample reduction process. Overall, 840 participants were included in this cross-sectional study who were predominantly white British, middle-to-older-aged, and female (Table 1). The hepatic cT1 score and liver fat content were generally low, with less than one-fifth of participants possessing NAFLD (liver fat ≥5.56%). Eleven participants (1.3%) had NASH according to hepatic cT1 score (≥857 ms). Most participants (57.6%) had a BMI ≥25 kg/m^2, with 17.4% living with obesity (BMI ≥30 kg/m^2). All participants provided at least 5 days of valid wear time data, whilst 794 (94.5%) provided at least 6 days, and 285 (33.9%) provided the full 7 days of valid accelerometer data. PA means/medians are reported in Table 1. Most participants reported high daily minutes of LPA (75% achieved >300 min/day) and MPA (86% achieved > 60 min/day), and low daily minutes of VPA (70% performed <5 min/day).

Fig. S1A-E shows the dispersion of PA exposure variables *vs.* hepatic cT1 in the full study sample. Generalised linear model analysis within the full sample revealed significant (p <0.05) inverse associations between hepatic cT1 and all PA exposure variables in the unadjusted models (β [95% CI]: mean acceleration, -0.67 ms [-1.05 to -0.28]; LPA, -0.08 ms [-0.12 to -0.03]; MPA, -0.13 ms [-0.21 to -0.05]; VPA, -1.16 ms [-1.81 to -0.51]; MVPA, -0.14 ms (-0.21 to -0.06]). These significant inverse associations remained after adjustment for sociodemographic factors (Model 1: mean acceleration, -0.74 ms [-1.13 to -0.35];

Table 2. Associations between hepatic cT1 score and physical activity outcomes in median split low and high body fat samples.

	β-coefficient	*p* value	Lower 95% CI	Upper 95% CI
Low body fat (n = 420)				
Mean acceleration (mg)				
Unadjusted model	-0.19	0.36	-0.59	0.21
Adjusted model 1	-0.13	0.53	-0.54	0.28
Adjusted model 2	-0.13	0.47	-0.54	0.28
LPA (mins/day)				
Unadjusted model	-0.02	0.44	-0.08	0.03
Adjusted model 1	0.00	0.93	-0.05	0.06
Adjusted model 2	0.00	0.90	-0.06	0.06
MPA (mins/day)				
Unadjusted model	-0.02	0.21	-0.08	0.03
Adjusted model 1	-0.04	0.50	-0.14	0.07
Adjusted model 2	-0.05	0.36	-0.15	0.06
VPA (mins/day)				
Unadjusted model	-0.37	0.27	-1.03	0.29
Adjusted model 1	-0.48	0.16	-1.16	0.19
Adjusted model 2	-0.45	0.17	-1.12	0.23
MVPA (mins/day)				
Unadjusted model	-0.06	0.18	-0.16	0.03
Adjusted model 1	-0.04	0.40	-0.14	0.06
Adjusted model 2	-0.05	0.29	-0.15	0.05
High body fat (n = 420)				
Mean acceleration (mg)				
Unadjusted model	**-1.27**	**<0.01**	**-2.08**	**-0.46**
Adjusted model 1	**-1.03**	**0.01**	**-1.83**	**-0.23**
Adjusted model 2	-0.79	0.07	-1.58	0.00
LPA (mins/day)				
Unadjusted model	**-0.11**	**<0.01**	**-0.18**	**-0.05**
Adjusted model 1	**-0.07**	**0.03**	**-0.14**	**-0.01**
Adjusted model 2	-0.06	0.13	-0.12	0.01
MPA (mins/day)				
Unadjusted model	**-0.15**	**0.03**	**-0.29**	**-0.02**
Adjusted model 1	-0.10	0.15	-0.23	0.03
Adjusted model 2	-0.06	0.48	-0.19	0.07
VPA (mins/day)				
Unadjusted model	**-2.33**	**<0.01**	**-3.97**	**-0.70**
Adjusted model 1	**-2.87**	**<0.01**	**-4.46**	**-1.29**
Adjusted model 2	**-2.68**	**<0.01**	**-4.24**	**-1.13**
MVPA (mins/day)				
Unadjusted model	**-0.15**	**0.02**	**-0.28**	**-0.03**
Adjusted model 1	-0.11	0.09	-0.24	0.02
Adjusted model 2	-0.07	0.35	-0.20	0.06

Data were analysed using generalised linear models with a normal distribution and identity link function, and are presented as β-coefficients and 95% CIs. *P* values <0.05 indicate statistical significance.
Model 1 adjusted for sex, age, ethnicity, education, employment status, household income, Townsend deprivation.
Model 2 adjusted for model 1 + number of medications, smoking status, alcohol intake, fruit and vegetable intake, processed meat intake.
LPA, light physical activity; MPA, moderate physical activity; MVPA, moderate-to-vigorous physical activity; VPA, vigorous physical activity.

LPA, -0.08 ms [-0.12 to -0.03]; MPA, -0.14 ms [-0.22 to -0.05]; VPA, -1.56 ms [-2.22 to -0.89]; MVPA, -0.15 ms [-0.23 to -0.07]) and after further adjustment for lifestyle factors (Model 2: mean acceleration -0.61 ms [-0.99 to -0.22]; LPA, -0.06 ms [-0.11 to -0.02]; MPA, -0.11 ms [-0.20 to -0.03]; VPA, -1.34 ms [-2.00 to -0.68]; MVPA, -0.12 ms [-0.20, 0.04]). Fig. 2 provides a graphical illustration of the associations between hepatic cT1 and PA exposure variables (fully adjusted models), with exposure variables expressed in SD units.

Table S2 details the baseline characteristics of the sample split into upper and lower median groups for body fat and liver fat. Liver fat and body fat were positively related in this sample (r = 0.308, p <0.01). Tables 2 and 3 present generalised linear model analysis between cT1 and PA exposure variables with the sample median split by high and low body fat and liver fat, respectively. Overall, associations were stronger in the higher body fat and liver fat groups, particularly for VPA. The dispersion of PA exposure variables *vs.* hepatic cT1 in the upper median categories for liver fat and body fat is shown in Figs S2A-E and S3A-E.

Discussion

Using the UK Biobank population-based cohort, this study examined associations between habitual levels of device-measured PA and MRI-determined hepatic fibro-inflammation. Our primary finding is that PA is inversely associated with hepatic fibro-inflammation, particularly at greater intensities of PA. Moreover, the association between VPA and hepatic fibro-inflammation is stronger in people with higher levels of body and liver fat.

When looking at the whole sample, we observed that mean acceleration (a marker of total PA volume) and all intensities of PA (LPA, MPA, VPA) were inversely associated with hepatic cT1. The strongest association with hepatic cT1 was seen with VPA. These findings suggest that an active lifestyle is linked with lower hepatic fibro-inflammation, and greater protection may be gained by performing activities requiring more intense levels of exertion. It is notable that these associations are independent of key sociodemographic and lifestyle factors, including markers of dietary quality. However, in this analysis, adjustments were not made for body fat or liver fat as they are deemed to be potential mediators of the association between PA and hepatic cT1, rather than covariates.

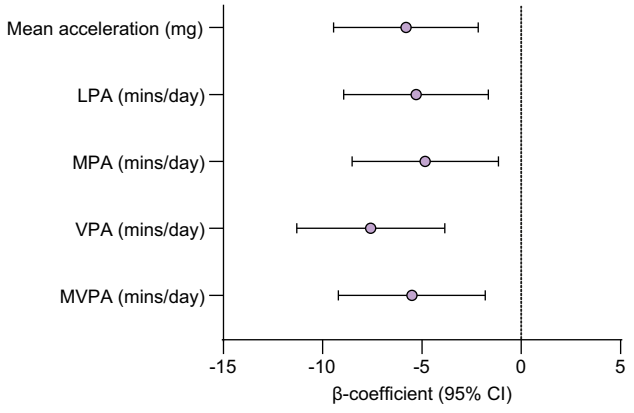

Fig. 2. Forest plot of associations between hepatic cT1 score and physical activity exposure variables. Data are presented as per standard deviation of the exposure variables. cT1, iron-corrected T1; LPA, light physical activity; MPA, moderate physical activity; VPA, vigorous physical activity; MVPA, moderate-to-vigorous physical activity.

Given the pathophysiological relevance of liver fat and body fat to hepatic inflammation and fibrogenesis,[40] we split our sample by median liver fat and body fat to determine whether the strength of associations varied between groups. We hypothesised that stronger associations would be seen in the upper median groups in which participants exhibit a poorer cardiometabolic health profile. As expected, we found that the overall pattern of results across PA exposures in the upper median groups is similar to the aggregated model. Conversely, no associations were evident between PA exposure variables and hepatic cT1 in the lower median groups. This profile was similar when the sample was split by median liver fat or body fat, likely reflecting their tight pathophysiological underpinning and positive association. Crucially, in the upper median models, associations remained statistically significant in the fully adjusted model only when VPA was included as the exposure variable. Additionally, the strength of association between VPA and hepatic cT1 was around two-fold greater in the upper median models (body fat: -2.68 ms [-4.24 to -1.13]; liver fat: -2.33 ms [-3.73 to -0.93]), compared with the model in the full sample (-1.34 ms [-2.00 to -0.68]). These findings demonstrate that the relationship between PA and hepatic cT1 is stronger in people with higher levels of body fat and liver fat, which may relate to their sub-clinical pathology and greater potential for change. By extension, it is possible that stronger associations, and greater therapeutic benefit, may be gained by individuals with established NAFLD. Additionally, the stronger association apparent between VPA and hepatic cT1 may suggest that the greatest clinical benefit could be conferred by more formal PA interventions (*i.e.*, exercise training), rather than behaviour change interventions focusing on the enhancement of incidental PA.

When considering the association between PA and hepatic cT1, it is important to contextualise the strength of the relationship. Based on the β-coefficients relating to VPA as the exposure variable in our upper median split models, meeting the current UK guidelines for VPA[41] (11 min per day; 75 min per week), would be associated with a 25 to 30 ms reduction in hepatic cT1. This magnitude of influence may hold clinical relevance given that a difference in hepatic cT1 of 23 ms was recently found to separate individuals with NAFLD (836 ms) and NASH (859 ms).[28] It is speculated that a more potent influence of VPA may be apparent in populations with established NAFLD and/or NASH where the hepatic pathology is more severe. Indeed, within our sample, hepatic cT1 scores were relatively healthy, even for most individuals in the higher categories of body fat and liver fat.

Our findings are generally consistent with prior observational data showing that more intense PA is linked with protection from NASH.[21,42] In a cross-sectional analysis involving patients with biopsy-defined NASH, higher levels of cardiorespiratory fitness (a marker of habitual PA) were identified in people with lower (≤4) *vs.* higher (≥5) NAFLD activity scores.[42] Furthermore, in a retrospective analysis of individuals with biopsy-proven NAFLD, the probability of individuals having NASH was one-third lower in those meeting PA guidelines for VPA.[21] Moreover, the risk of having advanced fibrosis (bridging fibrosis or cirrhosis) was halved in those meeting VPA guidelines, whilst MPA was not associated with any histological benefit. In contrast, whilst we observed the strongest associations with VPA in the

Table 3. Associations between hepatic *c*T1 score and physical activity outcomes in median split low and high liver fat samples.

	β-coefficient	*p* value	Lower 95% CI	Upper 95% CI
Low liver fat (n = 420)				
Mean acceleration (mg)				
Unadjusted model	0.20	0.26	-0.15	0.54
Adjusted model 1	0.11	0.53	-0.24	0.46
Adjusted model 2	0.14	0.46	-0.21	0.48
LPA (mins/day)				
Unadjusted model	0.02	0.44	-0.03	0.07
Adjusted model 1	0.01	0.70	-0.04	0.06
Adjusted model 2	0.01	0.79	-0.04	0.06
MPA (mins/day)				
Unadjusted model	0.06	0.20	-0.03	0.14
Adjusted model 1	0.04	0.38	-0.05	0.13
Adjusted model 2	0.04	0.39	-0.05	0.12
VPA (mins/day)				
Unadjusted model	0.26	0.36	-0.30	0.82
Adjusted model 1	0.08	0.79	-0.51	0.67
Adjusted model 2	0.12	0.70	-0.47	0.70
MVPA (mins/day)				
Unadjusted model	0.06	0.18	-0.03	0.14
Adjusted model 1	0.04	0.39	-0.05	0.12
Adjusted model 2	0.04	0.39	-0.05	0.12
High liver fat (n = 420)				
Mean acceleration (mg)				
Unadjusted model	**-0.81**	**0.04**	**-1.59**	**-0.03**
Adjusted model 1	**-0.90**	**0.02**	**-1.67**	**-0.13**
Adjusted model 2	-0.72	0.10	-1.49	0.06
LPA (mins/day)				
Unadjusted model	-0.06	0.06	-0.13	0.00
Adjusted model 1	-0.06	0.09	-0.12	0.01
Adjusted model 2	-0.05	0.23	-0.11	0.02
MPA (mins/day)				
Unadjusted model	-0.08	0.22	-0.22	0.05
Adjusted model 1	-0.09	0.19	-0.22	0.04
Adjusted model 2	-0.06	0.52	-0.19	0.07
VPA (mins/day)				
Unadjusted model	**-1.96**	**0.01**	**-3.36**	**-0.56**
Adjusted model 1	**-2.63**	**<0.01**	**-4.04**	**-1.23**
Adjusted model 2	**-2.33**	**<0.01**	**-3.73**	**-0.93**
MVPA (mins/day)				
Unadjusted model	-0.09	0.16	-0.22	0.04
Adjusted model 1	-0.10	0.11	-0.23	0.02
Adjusted model 2	-0.08	0.36	-0.21	0.05

Data were analysed using generalised linear models with a normal distribution and identity link function, and are presented as β-coefficients and 95% CIs. *P* values <0.05 indicate statistical significance.
Model 1 adjusted for sex, age, ethnicity, education, employment status, household income, Townsend deprivation.
Model 2 adjusted for model 1 + number of medications, smoking status, alcohol intake, fruit and vegetable intake, processed meat intake.
β-coefficients derived from general linear regression models.
LPA, light physical activity; MPA, moderate physical activity; MVPA, moderate-to-vigorous physical activity; VPA, vigorous physical activity.

present study, significant inverse associations were also evident for all other PA exposure variables. Unfortunately, the assessment of PA via self-report is a limitation of the study by Kistler *et al.*,[21] particularly as PA assessments were limited to leisure-time activities. Therefore, activity undertaken in the occupational, transport and household domains were omitted; and measures of total activity volume are imprecise. Moreover, it is recognised that more intense forms of PA are more accurately captured in self-reported PA questionnaires, questioning whether the reported lack of association between MPA and NASH probability was related to misclassification in the study by Kistler *et al.*.[21] The present study therefore extends these preliminary findings by using direct and precise assessments of habitual PA. Our study also confirms the relevance of PA in non-clinical populations, which is important given that participants were clinically indicated for liver biopsy in previous studies. Additional intervention trials are now required to directly test whether PA, of various intensities, can reduce hepatic fibro-inflammation in people with clinically elevated hepatic inflammation and fibrosis.

The biological feasibility of our findings is supported by pre-clinical studies using rodent models of NASH. In the context of NASH-promoting diets, exercise training has been shown to attenuate markers of hepatic inflammatory signalling and fibrogenesis (*e.g.*, hepatic stellate cell activity, collagen deposition, extracellular matrix deposition).[16–18,20,43] Furthermore, one study directly contrasted the protective effect of exercise training with volume-matched protocols of moderate-intensity continuous exercise *vs.* vigorous-intensity intervals.[16] In this study, vigorous-intensity interval exercise more potently suppressed hepatic inflammatory signalling and oxidative stress.

Important strengths of the present study include the utilisation of a deeply phenotyped cohort, possessing precise measurements of outcome and exposure variables. This

specifically includes device-worn measurements of PA, as opposed to self-reported data used previously.[21] Moreover, the short (5-second) epochs from the accelerometer data provided the sensitivity to detect very brief periods of movement at different intensities. This was particularly crucial for the VPA exposure variable; most participants accumulated less than 5 min/day of vigorous activity, yet this outcome held the strongest association with hepatic cT1. Relevant limitations include the unrepresentative sample demographic, which compared to the UK population, is older, more highly educated and less ethnically diverse. Additionally, the MRI technique used to assess hepatic fibro-inflammatory activity is unable to distinguish between hepatic inflammation and fibrosis *per se*, and therefore only provides a global indication of advanced hepatic pathology. Finally, it should be noted that measurement of exposure, outcome and confounding variables were assessed at different phases of the UK Biobank cohort; with demographic information (2006 to 2014) collected several years before PA (2013 to 2015), MRI (2014 to 2015) and anthropometric (2014+) data. These time discrepancies may have weakened associations between exposure and outcome variables.

In conclusion, this cross-sectional analysis demonstrates that device-measured PA is inversely associated with hepatic cT1, as measured by MRI, and this association is strongest with VPA. Furthermore, the relationship between VPA and hepatic cT1 is more evident in people with higher levels of body fat and liver fat, potentially implying that the most potent therapeutic effects of VPA would be conferred to those with established NAFLD. These findings support the on-going refinement and personalisation of PA guidelines for the management of NAFLD; with recognition that more intense levels of PA may protect against advanced features of chronic liver disease.

Abbreviations

cT1, iron-corrected T1; DXA, dual-energy X-ray absorptiometry; LPA, light physical activity; ms, milliseconds; MPA, moderate physical activity; MVPA, moderate-to-vigorous physical activity; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PA, physical activity; PDFF, proton density fat fraction; VPA, vigorous physical activity.

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Conflict of interest

None of the authors have any conflicts of interest to declare.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

GA, AS, SW, SM, DS, JS, TY and JK conceived the study. AS, WJ, TY, SW, GA and JK led the data analysis. GA, AS, SW, SM, DS, and JK developed the original draft of the manuscript. All authors reviewed and approved the final version of the manuscript.

Data availability statement

We are not permitted to share UK Biobank data. All *bona fide* researchers can apply to use UK Biobank data for health-related research that is in the public interest.

Disclaimer

The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

Supplementary data

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Author names in bold designate shared co-first authorship

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