Research Article
NAFLD and Alcohol-Related Liver Diseases

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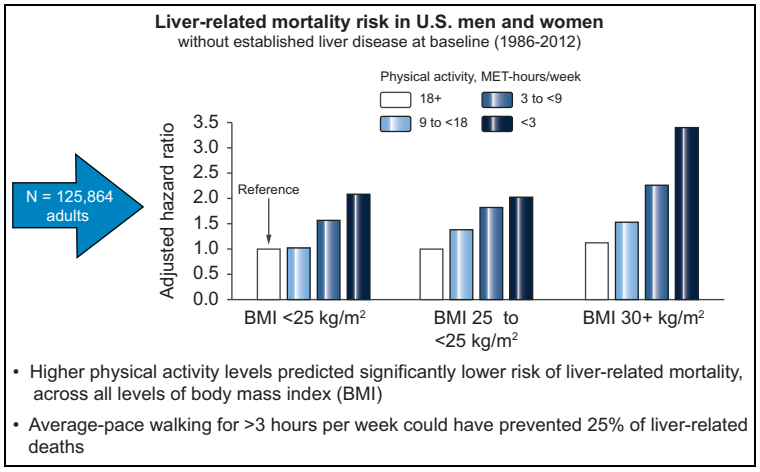
Physical activity compared to adiposity and risk of liver-related mortality: Results from two prospective, nationwide cohorts

Graphical abstract



Highlights

- Low physical activity and obesity predicted an excess risk of liver-related death.
- The excess risk conferred by obesity was markedly attenuated by physical activity.
- Overall, walking for >3 hours/week could have prevented 25% of liver-related deaths.

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Lay summary

This is the first large, prospective cohort study to simultaneously evaluate the impact of obesity and physical activity on the long-term risk of liver-related mortality in 2 nationwide populations of American men and women. The study demonstrated that obesity predicted significantly increased risk of liver-related mortality, while physical activity predicted significantly lower risk of liver-related mortality. Importantly, the excess risk of liver-related mortality observed with obesity was no longer statistically significant among adults who engaged in the equivalent of average-pace walking for 3 hours or more, per week.

https://doi.org/10.1016/j.jhep.2019.12.022
 J. Hepatol. 2020, 72, 1062–1069

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Physical activity compared to adiposity and risk of liver-related mortality: Results from two prospective, nationwide cohorts

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Background & Aims: Obesity in adulthood has been associated with increased risk of liver-related mortality. Whether higher levels of physical activity counteract the excess risk conferred by obesity remains unknown. We simultaneously evaluated the long-term impact of physical activity and adiposity on liver-related mortality, within 2 nationwide populations.

Methods: We conducted a prospective cohort study of 77,238 women and 48,026 men, with detailed, validated assessments of weekly physical activity (metabolic equivalent task [MET]-hours]), adiposity (body mass index [BMI], waist circumference), and diet, alcohol use and clinical comorbidities, biennially from 1986 through 2012. Using Cox proportional hazards regression models, we calculated multivariable-adjusted hazard ratios (aHRs) and 95% CIs for liver-related mortality, including death from hepatocellular carcinoma (HCC) and other complications of cirrhosis.

Results: Over 1,856,226 person-years, we recorded 295 liver-related deaths (108 HCC; 187 cirrhosis). Risk of liver-related mortality increased monotonically with higher BMI during adulthood (p_{trend}<0.0001) and with weight gain during early adulthood (p_{trend} <0.0001). The risk of liver-related mortality also declined progressively, with increasing physical activity (p_{trend} = 0.0003); the aHRs across increasing physical activity quintiles were: 1.0, 0.70 (95% CI 0.51–0.96), 0.59 (95% CI 0.42–0.84), 0.52 (95% CI 0.36–0.74) and 0.46 (95% CI 0.31–0.66). Compared to lean-active adults (BMI <25; ≥18 MET-hours/week), the aHRs for obese-active, lean-sedentary, and obese-sedentary adults were: 1.04 (95% CI 0.73–1.37), 2.08 (95% CI 1.21–3.33) and 3.40 (95% CI 2.06–5.56), respectively. Findings were similar for HCC-specific and cirrhosis-specific mortality. Overall, engaging in average-pace walking for >3 hours/week could have prevented 25% of liver-related deaths (95% CI 0.12–0.38).

Conclusions: In 2 prospective, nationwide cohorts, both excess adiposity and reduced physical activity were significant predictors of liver-related mortality. Achieving higher physical activity levels counteracted the excess liver-related risks associated with obesity.

Lay summary: This is the first large, prospective cohort study to simultaneously evaluate the impact of obesity and physical activity on the long-term risk of liver-related mortality in 2 nationwide populations of American men and women. The study demonstrated that obesity predicted significantly increased risk of liver-related mortality, while physical activity predicted significantly lower risk of liver-related mortality. Importantly, the excess risk of liver-related mortality observed with obesity was no longer statistically significant among adults who engaged in the equivalent of average-pace walking for 3 hours or more, per week.

Introduction

In 2016, more than 34,000 Americans died from chronic liver disease, which includes death from hepatocellular carcinoma (HCC) and from other complications of cirrhosis.[1,2] Over the past 20 years, the prevalence of cirrhosis in the US has doubled, and rates of liver-related mortality have increased by more than 65%,[2] due in part to the growing epidemics of obesity and non-alcoholic fatty liver disease (NAFLD). Despite this, knowledge of modifiable lifestyle factors remains incomplete, and effective strategies to prevent liver-related mortality are lacking.

Obesity and physical inactivity represent major public health problems for patients with chronic liver disease. Approximately 80% of Americans with NAFLD are overweight,[3] and most do not engage in physical activity,[4] even when their liver disease is mild.[5,6] Obesity is a risk factor for cirrhosis,[7,8] HCC[9–12] and liver-related death.[7,13] Furthermore, physical activity is inversely

Keywords: Cirrhosis; Lifestyle; Modifiable risk factor; Prevention.
Received 8 October 2019; received in revised form 6 December 2019; accepted 16 December 2019; available online 15 January 2020
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https://doi.org/10.1016/j.jhep.2019.12.022

associated with HCC incidence,[9] and in short-term clinical studies, physical activity interventions improve liver fat, inflammation and fibrosis, even in the absence of weight loss.[14–17] However, whether this translates to long-term reductions in liver-related mortality is unknown. While it has been suggested that achieving higher levels of fitness might eliminate the adverse effects of obesity on long-term hepatic outcomes,[18,19] evidence to support this hypothesis is lacking. To date, no prospective epidemiologic study has simultaneously evaluated the long-term influence of physical activity and adiposity on liver-related mortality.

Numerous national subspecialty societies provide specific physical activity recommendations for the prevention of cancer,[20] heart disease,[21] and other chronic conditions.[22,23] In contrast, no recommendations currently exist for the prevention of major adverse hepatic events, including death from cirrhosis and from HCC. Given the growing burden of chronic liver disease, understanding the optimal level of activity to prevent liver-related mortality remains an important unmet need.

Thus, we prospectively evaluated the relationships between physical activity, adiposity and liver-related mortality, within 2 nationwide populations of men and women in the US. Specifically, we assessed whether achieving higher levels of activity might counteract the association between excess body weight and liver-related mortality.

Patients and methods

Participants

The Nurses' Health Study (NHS) prospectively enrolled 121,700 female registered nurses, aged 30–55 years, in 1976, and the Health Professionals Follow-up Study (HPFS) prospectively enrolled 51,529 male health professionals, aged 40–75 years, in 1986.[24,25] Since enrollment, participants have returned detailed biennial questionnaires, providing prospectively updated data on lifestyle, medical history, physical activity and disease outcomes, with follow-up that consistently exceeds 90%.[26] We included all individuals from both cohorts who completed the first comprehensive physical activity assessment in 1986.[27,28] We excluded anyone with missing information on baseline physical activity or body mass index (BMI), self-reported cirrhosis (n = 775), viral hepatitis (n = 305), or prior cancer, except non-melanoma skin cancer (n = 8,366), consistent with prior work.[29] This left 125,264 participants (77,238 women, 48,026 men), eligible for analysis.

The NHS and HPFS cohorts were approved by the Institutional Review Boards of the Brigham and Women's Hospital and the Harvard T.H. Chan School of Public Health (1999-P-011114), and those of participating registries as required. Return of questionnaires was considered as informed consent.

Assessments of adiposity

BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2) in 1986, and biennially thereafter. The validity and reliability of these measurements in these cohorts have previously been demonstrated (r = 0.97 for men and women).[30] The baseline questionnaire queried early adulthood weight (*i.e.* 21 years [men] and 18 years [women]), which has been validated (r = 0.87).[31] We constructed 3 BMI exposures: cumulative average updated BMI, calculated from all questionnaires up to the start of each 2-year interval, early adulthood BMI, and mid-life BMI (in 1986).

Abdominal adiposity was defined using validated waist circumference (WC) and waist-to-hip ratio (WHR) measurements, reported in HPFS in 1987 and 1996, and in NHS in 1986, 1996 and 2000.[30] The correlation coefficients between self-reported and technician-measured WC and hip circumferences were 0.95 and 0.88, respectively, among men, and 0.89 and 0.84, respectively, among women.[30]

Physical activity and covariate assessment

Detailed physical activity assessments were first obtained in 1986 and updated biennially thereafter.[32,33] Prior studies have demonstrated the validity and reproducibility of physical activity data in these cohorts.[25,34] With each questionnaire, participants report average weekly time engaged in leisure activities, including walking, jogging, running, bicycling, swimming, calisthenics, rowing, squash, racquet ball and tennis, heavy outdoor work (since 1988), and weight training (since 1990). This permits calculation of weekly energy expenditure in metabolic equivalent task–hours (MET-hours), using validated approaches (Supplementary Methods).[35]

Cumulative average updated activity was defined as average weekly time spent engaged in moderate or vigorous physical activity (*i.e.* requiring ≥3 MET-hours) from all questionnaires up to each 2-year interval, consistent with prior studies.[32,33] We also calculated baseline (1986) physical activity. Physical activity was not assessed in the 1990 NHS questionnaire, therefore we carried these data forward by 1 interval (*i.e.* we applied 1988 data to the 1990-92 interval). Otherwise, missing data were not carried forward. As in prior work,[29] covariates were selected *a priori* (Supplementary Methods). Incident cirrhosis or viral hepatitis diagnosed during the prior 2-year interval were ascertained from each questionnaire.[36]

Outcomes

Deaths were reported by next-of-kin, the postal authorities or the National Death Index, with >98% follow-up for both cohorts.[37,38] For all deaths, we sought death certificates and, when appropriate, requested permission to review medical records, from which the cause of death was confirmed and classified according to ICD-8 codes. Major surgeries were ascertained and updated with each biennial questionnaire. The primary endpoint was liver-related mortality, defined as death from HCC or from a non-HCC complication of cirrhosis, consistent with recommendations[39] (Supplementary Methods). As previously described, all HCC cases were confirmed through blinded review of medical records.[29]

Statistical analysis

To best represent long-term patterns and minimize within-person variation, our primary analysis used cumulative average updated exposures.[32,33] To account for potential changes in physical activity after a diagnosis of cirrhosis, we suspended updating of exposures after incident cirrhosis was reported in follow-up. For the primary analysis, we applied an 8-year latency period, with follow-up beginning in 1994; this permits the assessment of updated exposures, while minimizing potential reverse causation.[40] The 8-year period was selected *a priori*, given the prolonged time that may elapse between the development of cirrhosis and decompensation or death.[41] In additional analyses, we used baseline and extended latency exposures (with a lag of 12 years). BMI was modeled in World

Health Organization categories (<19, 19-<25, 25-<30, 30-<35 and ≥35 kg/m^2). Physical activity was categorized in quintiles based upon its distribution, and further in clinically-informative categories (*e.g.* <3, 3-<9, 9-<18, 18 to <27 and ≥27 MET-hours/week), corresponding to the equivalent of average-pace walking for <1, 1 to <3, 3 to <6, 6 to <9 and ≥9 hours/week. These categories were selected because walking is readily adoptable and was the most commonly-reported form of exercise, as it is in the broader US population.[42] Early adulthood weight change was calculated as the difference between weight in mid-life (1986) and early adulthood weight, and grouped into 5 categories.[33] WC and WHR were modeled continuously and in quartiles. For all models, linear trend was assessed using continuous variables.

Person-time of follow-up accrued from return of the baseline questionnaire to the date of death or end of follow-up (January 31, 2012 [HPFS]; June 1, 2012 [NHS]), whichever came first. We used Cox proportional hazards regression conditioned on age (years), questionnaire cycle and sex to calculate age- and multivariable-adjusted hazard ratios (aHR) and 95% CI for liver-related mortality, accounting for *a priori*, time-varying covariates (Supplementary Methods).

In stratified models, we assessed the influence of BMI or physical activity according to pre-specified sub-groups, and we tested the significance of interactions using the log likelihood ratio test. We also compared HCC-specific and cirrhosis/decompensation-specific mortality. To understand whether physical activity might counteract the excess risk conferred by adiposity, we jointly evaluated physical activity and BMI, as well as physical activity and WC. Finally, we calculated the population attributable risk conferred by low (<9 MET-hours/week) and very low (<3 MET-hours/week) levels of activity, to estimate the percentage of liver-related deaths that might have been prevented if all participants had engaged in regular physical activity, assuming a causal relationship between factors.[43]

Sensitivity analyses

We tested the robustness of our results in numerous sensitivity analyses. First, we extended the latency period to 12 years (from 8 years). Second, because severe underlying disease or obesity may limit exercise, we excluded anyone reporting no baseline physical activity. Third, because incident viral hepatitis or cirrhosis may represent intermediates that impact both adiposity and exercise,[4,19] we constructed separate models further accounting for those factors. Fourth, we continued updating exposures after the date of diagnosis of cirrhosis. Fifth, to more completely address the influence of alcohol use on liver-related mortality, we repeated the analysis after excluding anyone with significant alcohol consumption (*i.e.* ≥1 drink per day among women, or ≥2 drinks/day among men). In exploratory analyses, we compared resistance training and aerobic activity, and we repeated our primary analysis with liver transplantation included as a competing event. Finally, in an exploratory analysis, we compared the relative influence of obesity and physical activity on liver-related mortality, among adults with known cirrhosis in 1986 (n = 775), who previously were excluded from the analysis.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC), with a 2-sided significance p value<0.05. For further details regarding the methods used, please refer to the CTAT table and supplementary information.

Results

Overall, we recorded 383 liver-related deaths among 77,238 women and 48,026 men. Table 1 shows the age-standardized characteristics according to BMI category, in 1986. Table S1 outlines the corresponding characteristics by physical activity quintile. After applying the 8-year latency, there were 105,894 individuals (70,810 women; 35,084 men), and 295 liver-related deaths (187 cirrhosis; 108 HCC) over 1,856,226 person-years of follow-up.

Total and central adiposity

After multivariable adjustment, each 1-unit increase in cumulative average updated BMI predicted a 5.1% higher risk of liver-related mortality (95% CI 1.03–1.07; p_{trend}<0.0001). Compared to normal BMI (19-<25), the aHRs for BMI 25-<30, 30-<35 and ≥35 kg/m^2 were 1.40 (95% CI 1.06–1.84), 2.22 (95% CI 1.56–3.16) and 2.97 (95% CI 1.84–4.79), respectively (Table 2). These findings were similar in men and women (Table S2), and they were consistent across all strata defined by pre-specified risk factors, including age, race/ethnicity, diabetes, alcohol use, smoking and diet (all $p_{interactions}$>0.05; Table S3). Moreover, this strong, positive gradient of risk was similar for HCC-specific and cirrhosis-specific mortality ($p_{heterogeneity}$= 0.34; Table S4).

To minimize potential reverse causation, we conducted additional analyses using BMI exposures from early adulthood (*i.e.* age 18 years [women], or 21 years [men]) and from mid-life (in 1986). Consistent with the primary analysis, higher mid-life BMI predicted significantly increased risk of liver-related mortality in later life (p_{trend} <0.0001); specifically, compared to mid-life BMI 19-<25, the highest risk was observed with mid-life BMI ≥35 kg/m^2 (aHR 2.04, 95% CI 1.34–3.11; Table 2). These findings remained similar after further accounting for early adulthood BMI (p_{trend} <0.0001). Additionally, we observed that a higher early adulthood BMI also was independently associated with increased risk of liver-related mortality (p_{trend} = 0.0002), even after further adjusting for mid-life BMI (p_{trend} = 0.0003).

In analyses focused on central adiposity, each 1 cm increase in WC predicted a significantly (5.6%) higher risk of liver-related mortality (95% CI 1.02–1.09; p_{trend} = 0.003). Compared to the lowest WC quartile, the aHR in the highest quartile was 2.09 (95% CI 1.16–3.77). These patterns of association were similar when WHR was used in place of WC (p_{trend} <0.0001).

Physical activity

Overall, every 3 MET-hours/week of exercise – the equivalent of walking at an average pace for 1 hour/week – conferred a 3.5% reduction in risk of liver-related mortality (95% CI 0.95–0.98). The multivariable aHRs across increasing physical activity quintiles were: 1.0, 0.70 (95% CI 0.51–0.96), 0.59 (95% CI 0.42–0.84), 0.52 (95% CI 0.36–0.74) and 0.46 (95% CI 0.31–0.66), respectively (p_{trend} <0.0001; Table 2). This inverse gradient was not materially altered after further accounting for BMI (p_{trend} = 0.0003), and it was similar when we considered only baseline exposures (p_{trend} = 0.009). We observed consistent, inverse associations among both women and men (Table S2), and in analyses comparing HCC-specific and cirrhosis-specific mortality ($p_{heterogeneity}$=0.42; Table S4). Our findings also remained similar when physical activity was modeled in clinically relevant categories (*i.e.* <3, 3-<9, 9-<18, 18-<27 and ≥27 MET-hours/week),

Table 1. Age-standardized characteristics of NHS (n = 77,238) and HPFS (n = 48,026) participants according to BMI category, in 1986.

	BMI category, kg/m^2				
Cohort	**<19**	**19 to <25**	**25 to <30**	**30 to <35**	**≥35**
Women (NHS)	3,533	40,275	21,976	6,897	4,557
Median BMI, kg/m^2 [IQR]	18.3 [17.5–18.9]	23.4 [22.2–24.1]	26.6 [25.8–27.9]	31.2 [30.5–32.3]	36.0 [35.1–38.5]
Age, years, SD	52.8 (7.3)	52.1 (7.1)	53.3 (7.0)	53.2 (6.9)	52.1 (6.9)
White race, %	96.2	96.3	95.8	95.8	95.2
Waist-to-hip ratio, SD	0.78 (0.09)	0.80 (0.14)	0.84 (0.11)	0.86 (0.11)	0.86 (0.11)
Physical activity, MET-hours/week [IQR]	7.9 [2.7–20.5]	8.6 [3.1–20.4]	7.1 [2.5–16.8]	5.2 [2.1–13.7]	3.9 [1.5–10.9]
Hypertension, %	15.2	25.1	37.9	47.1	51.8
Dyslipidemia, %	17.1	30.3	38.3	39.8	36.0
Type 2 diabetes, %	2.8	3.6	9.7	18.1	26.1
Smoking status, %					
Current	23.3	13.4	9.7	8.2	6.4
Former	36.3	42.4	44.9	45.3	44.7
Never	40.4	44.2	45.4	46.5	48.9
Alcohol intake, g/day [IQR]	1.8 [0–7.3]	1.8 [0–8.5]	1.1 [0–4.7]	0 [0–2.5]	0 [0–1.8]
Regular aspirin use,[1] %	34.0	39.7	43.2	43.8	43.6
Adherence to a healthy diet,[2] %	22.8	26.6	24.6	21.7	18.2
Men (HPFS)	1,744	13,550	20,166	8,794	3,772
Median BMI, kg/m^2 [IQR]	17.9 [16.9–18.5]	22.3 [21.1–23.8]	26.9 [25.8–28.2]	31.5 [30.7–32.5]	36.7 [35.2–39.8]
Age, years, SD	54.0 (9.9)	52.5 (9.6)	53.4 (9.3)	52.9 (8.6)	52.1 (8.9)
White race, %	94.9	95.1	95.9	96.2	96.6
Waist-to-hip ratio, SD	0.91 (0.06)	0.93 (0.06)	0.96 (0.06)	0.98 (0.07)	1.00 (0.08)
Physical activity, MET-hours/week [IQR]	10.9 [3.1–25.9]	15.1 [5.0–32.3]	10.8 [3.6–25.9]	7.6 [2.3–19.4]	5.0 [1.6–15.4]
Hypertension, %	25.9	30.6	42.6	57.1	65.0
Dyslipidemia, %	28.9	40.2	46.2	49.4	48.0
Type 2 diabetes, %	5.3	4.8	8.2	17.2	25.5
Smoking status, %					
Current	11.9	6.5	6.4	6.1	6.1
Former	37.5	39.5	45.3	47.9	46.5
Never	50.6	54.0	48.3	46.0	47.4
Alcohol intake, g/day [IQR]	1.8 [0–8.3]	2.6 [1.8–13.1]	2.0 [1.8–12.7]	1.8 [1.3–9.6]	1.8 [0.9–5.1]
Regular aspirin use,[1] %	34.3	43.9	47.4	49.0	49.0
Adherence to a healthy diet,[2] %	32.3	29.5	22.2	18.6	17.1

BMI, body mass index; HPFS, Health Professionals Follow-up Study; MET, metabolic equivalent task; NHS, Nurses' Health Study; NSAID, non-steroidal anti-inflammatory drug. All data reported as percentage (%) or mean ± SD unless noted otherwise. Except for mean of age, all data were age-standardized to the age distribution of participants. Physical activity was defined according to expended MET-hours/week (see methods).

[1]Regular use of aspirin was defined as consumption of at least 2 or more standard-dose (325 mg) tablets per week (*vs.* non-regular or non-use).

[2]A healthy dietary pattern was defined using the Alternative Healthy Eating Index 2010 (AHEI-2010), modeled in quartiles. Adherence was defined as the highest quartile of the continuous alternative healthy eating index score.

corresponding to walking at an average pace for <1, 1 to <3, 3 to <6, 6 to <9 and ≥9 hours per week (p_{trend} <0.0001; Table S5).

At baseline, 32% of participants had low physical activity (<9 MET-hours/week), and 11% had very low physical activity (<3 MET-hours/week). Accordingly, we estimated that exercising for at least 3 MET-hours/week or more could have prevented 16% of liver-related deaths (95% CI 0.07–0.26), and exercising for >9 MET-hours/week could have prevented 25% of liver-related deaths (95% CI 0.12–0.38).

Joint associations

At all levels of BMI, increasing level of physical activity predicted significantly reduced risk of liver-related mortality (all p_{trend}<0.0001; Fig. 1). When examined jointly, the risk was lowest among lean-active adults (BMI <25, physical activity ≥18 MET-hours/week). Compared to this lean-active group, the highest risk was found among obese-sedentary adults (BMI ≥30; <3 MET-hours/week), who had an aHR of 3.40 (95% CI 2.06–5.56). Importantly, physical activity appeared to attenuate the excess risk associated with obesity: specifically, the aHRs were 1.04 (95% CI 0.73–1.37) for obese-active adults (BMI ≥30; ≥18 MET-hours/week), and 1.13 (95% CI 0.83–1.52) for obese-moderately active adults (BMI≥30; 9-<18 MET-hours/week). In contrast, being lean did not fully attenuate the excess risk associated with sedentary behavior: compared to lean-active adults, the aHR among lean-sedentary adults was 2.08 (95% CI 1.21–3.33). These findings were similar when we used WC in place of BMI (Fig. S1).

Early adulthood weight gain

Weight gain between early adulthood and mid-life contributed to significantly higher risk of liver-related mortality in later life (p_{trend} <0.0001), even after accounting for early adulthood weight (p_{trend} <0.0001) (Table 3). Compared to participants with stable weight (+/− 5kg), the highest risk was observed with weight gain ≥15 kg (aHR 1.82; 95% CI 1.32–2.51). This association was significantly modified by physical activity level: compared to persons with stable weight between early adulthood and mid-life, the aHRs for weight gain ≥15 kg were 1.41 (95% CI 0.79–2.51) for active adults, and 2.19 (95% CI 1.30–3.69) for sedentary adults ($p_{interaction}$ = 0.014). These associations were similar for both HCC- and cirrhosis-specific mortality (Table S6).

Sensitivity analyses

Our findings were robust across all sensitivity analyses, including: i) after applying a 12-year latency period (Table S7);

Table 2. Liver-related mortality according to BMI and physical activity, in the pooled NHS and HPFS cohorts.

	BMI or PA Category					*p* for trend
Updated 8-year latency[1]						
BMI, kg/m²	**<19**	**19 to <25**	**25 to <30**	**30 to <35**	**≥35**	–
Liver-related deaths/person-years	23/222,779	50/543,500	92/566,877	58/305,736	72/217,334	–
Crude Incidence/100,000 person-years	10	9	16	19	33	–
Age-adjusted HR (95% CI)	1.24 (0.57–2.67)	1 (ref.)	1.55 (1.18–2.03)	2.92 (1.08–4.10)	4.37 (2.77–6.91)	<0.0001
Multivariable-adjusted HR;‡ (95% CI)	1.19 (0.55–2.58)	1 (ref.)	1.40 (1.06–1.84)	2.22 (1.56–3.16)	2.97 (1.84–4.79)	<0.0001
Physical activity (MET-hour/week)	**Lowest quintile**	**Second quintile**	**Third quintile**	**Fourth quintile**	**Highest quintile**	
Median [IQR]	1.2 [0.4 to 2.3]	5.1 [3.6 to 7.7]	11.0 [8.6 to 15.6]	21.3 [17.2 to 28.3]	46.9 [34.6 to 65.5]	–
Liver-related deaths/person-years	93/341,257	66/370,359	55/388,307	44/384,463	37/371,840	–
Crude incidence/100,000 person-years	27	18	14	11	10	–
Age-adjusted HR (95% CI)	1 (ref.)	0.70 (0.51–0.96)	0.59 (0.42–0.84)	0.52 (0.36–0.74)	0.46 (0.31–0.66)	<0.0001
Multivariable-adjusted HR;‡ (95%CI)						
Without BMI	1 (ref.)	0.73 (0.53–1.01)	0.64 (0.45–0.90)	0.58 (0.40–0.84)	0.50 (0.34–0.73)	<0.0001
With BMI	1 (ref.)	0.75 (0.54–1.03)	0.67 (0.47–0.95)	0.63 (0.44–0.91)	0.54 (0.37–0.78)	0.0003
Baseline[1]						
BMI, kg/m²	**<19**	**19 to <25**	**25 to <30**	**30 to <35**	**≥35**	
Liver-related deaths/person-years	10/64,737	131/1,489,374	148/1,032,255	64/257,102	30/95,528	–
Crude incidence/100,000 person-years	15	9	14	25	31	
Age-adjusted HR (95% CI)	1.93 (1.01–3.69)	1 (ref.)	1.56 (1.23–1.98)	2.89 (2.15–3.90)	3.83 (2.57–5.71)	<0.0001
Multivariable-adjusted HR;[1] (95% CI)	1.66 (0.87–3.17)	1 (ref.)	1.35 (1.06–1.72)	1.90 (1.38–2.60)	2.04 (1.34–3.11)	<0.0001
Physical activity (MET-hour/week)	**Lowest quintile**	**Second quintile**	**Third quintile**	**Fourth quintile**	**Highest quintile**	
Median [IQR]	0.9 [0.4 to 1.5]	3.6 [2.9 to 4.4]	8.4 [6.7 to 10.2]	17.9 [14.3 to 21.1]	39.4 [31.5 to 55.4]	–
Liver-related deaths/person-years	108/560,489	81/579,411	65/592,292	62/604,128	67/602,677	–
Crude incidence/100,000 person-years	19	14	11	10	11	–
Age-adjusted HR (95% CI)	1 (ref.)	0.73 (0.54–0.97)	0.58 (0.42–0.78)	0.57 (0.42–0.77)	0.53 (0.39–0.73)	<0.0001
Multivariable-adjusted HR;[1] (95% CI)						
Without BMI	1 (ref.)	0.79 (0.59–1.05)	0.72 (0.53–0.98)	0.65 (0.48–0.89)	0.64 (0.47–0.87)	0.009
With BMI	1 (ref.)	0.80 (0.60–1.07)	0.77 (0.56–1.05)	0.68 (0.50–0.92)	0.68 (0.49–0.93)	0.009

BMI, body mass index; NHS, Nurses' Health Study; HPFS, Health Professionals Follow-up Study; HR, hazard ratio; MET-hour, metabolic equivalent task hour; PA, physical activity.

‡Multivariable Cox proportional hazards regression model conditioned on age (years), sex and year of questionnaire return, with further adjustment for race (white, black, hispanic, asian or other), alcohol intake (0–4.9 g/day, 5-14.9 g/day, ≥15 g/day), smoking status (current *vs.* prior *vs.* never), type 2 diabetes (yes *vs.* no), hypertension (yes *vs.* no), dyslipidemia (yes *vs.* no), statin medication use (yes *vs.* no), regular aspirin use (≥2 tablets per week *vs.* no), coffee consumption (continuous), adherence to a healthy diet, defined by the continuous alternative healthy eating index. P for linear trend was assessed using the exposure of interest (BMI or PA) as a continuous variable (see Methods).

[1]For the baseline analyses, BMI and PA were ascertained in 1986, with follow-up from 1986–2012 (n = 125,264). For the latency analyses, an 8-year period was used, with a follow-up beginning in 1994 (n = 105,894). For details see methods.

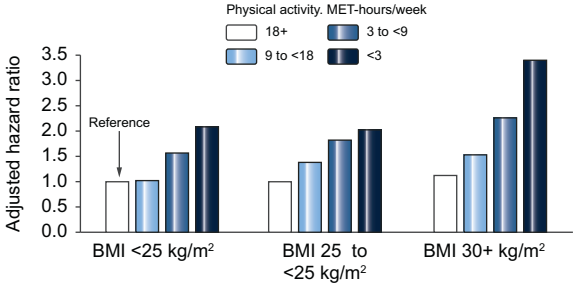

Fig. 1. Multivariate risk of liver-related mortality according to body mass index and physical activity level.

ii) after excluding any participant who reported no exercise (n = 14,364 excluded; Table S8); iii) after further adjusting for incident viral hepatitis or cirrhosis (Table S9); iv) after continuing to update exposures, after a diagnosis of incident cirrhosis or viral hepatitis (Table S10); and v) after excluding any participant with significant alcohol consumption (*i.e.* ≥1 drink per day among women, or ≥2 drinks/day among men) (Table S11). In an exploratory analysis comparing resistance training and aerobic activity, the observed magnitude of benefit appeared similar (Table S12). Additionally, including liver transplantation as a competing event did not materially impact our results (not shown). Finally, in an exploratory analysis of adults with underlying cirrhosis in 1986 (n = 775), we observed a similar, significant, inverse association between increasing physical activity level and reduced liver-related mortality risk (p_{trend} = 0.002).

Discussion

In 2 prospective cohorts of men and women in the US, low physical activity levels and elevated BMI were each independently associated with increased risk of liver-related mortality, including death from HCC and cirrhosis. Risk of liver-related mortality was consistently and significantly elevated with obesity in early adulthood, in mid-life, and even with modest weight gain during early adulthood. However, increased physical activity during adulthood predicted significantly lower risk of liver-related mortality, regardless of BMI. Importantly, we found that the excess risk conferred by obesity was substantially attenuated among adults who engaged in >9 MET-hours per week of physical activity, the equivalent of walking at an average pace for 3 hours per week or more.

Short-term clinical studies have demonstrated that physical activity is associated with reductions in liver fat, inflammation and insulin resistance;[14,15,19,36,44] further, among patients with HCC, therapeutic exercise may increase muscle mass,[45] while exercise capacity may predict post-hepatectomy survival.[46]

Table 3. Weight change in early adulthood, physical activity and risk of liver-related mortality in later life.[1]

	Weight loss		Weight gain			
Variable	**≥ −5kg**	**−5 to < 5kg**	**5 to <10 kg**	**10 to <15 kg**	**≥15 kg**	***p* for trend**
Liver-related deaths, n	116	71	42	69	83	–
Person-years	605,371	726,687	510,191	629,496	464,630	–
Multivariable-adjusted HR;[‡,1] (95% CI)	1.87 (1.38–2.52)	1 (ref.)	0.98 (0.74–1.21)	1.26 (0.83–1.91)	1.82 (1.32–2.51)	<0.0001
Multivariable-adjusted HR[‡] by PA strata (95% CI)						
Sedentary: <3 MET-hours/week	2.16 (1.31–3.58)	1 (ref.)	1.12 (0.66–1.89)	1.28 (0.63–2.56)	2.19 (1.30–3.69)	0.002
Moderate: 3 to <9 MET-hours/week	1.91 (1.12–3.27)	1 (ref.)	1.06 (0.48–2.31)	1.08 (0.62–1.88)	1.91 (1.09–3.36)	0.02
Active: ≥9 MET-hours/week	1.43 (0.89–2.31)	1 (ref.)	0.76 (0.46–1.27)	1.01 (0.49–1.87)	1.41 (0.79–2.41)	0.15

HR, hazard ratio; MET, metabolic equivalent task; PA, physical activity.
[‡]Multivariable Cox proportional hazards regression model conditioned on age (years), sex and year of questionnaire return, with further adjustment for weight in early adulthood (continuous kilograms), race (white, black, hispanic, asian or other), alcohol intake (0–4.9 g/day, 5–14.9 g/day, ≥15 g/day), smoking status (current *vs.* prior *vs.* never), type 2 diabetes (yes *vs.* no), hypertension (yes *vs.* no), dyslipidemia (yes *vs.* no), statin medication use (yes *vs.* no), regular aspirin use (≥2 tablets per week *vs.* no), and adherence to a healthy diet, defined by the alternative healthy eating index 2010 (AHEI), with all relevant covariates ascertained in 1986.
[1]This analysis included the baseline study population (n = 125,264) and excluded any participant with missing data regarding weight in early adulthood (defined as age 18 years [women] or 21 years [men]). Weight change was the difference in weight in kilograms between early adulthood and study baseline (in 1986). Physical activity (MET-hours/week) was defined using baseline data from 1986.

However, to date, no large-scale, prospective study has evaluated whether this might translate into improved long-term hepatic outcomes.[19] Published epidemiological evidence regarding physical activity and long-term hepatic events derive from just 3 prior studies, that linked higher physical activity levels to reduced incidence of hepatobiliary cancer.[9–11] However, those prior studies did not assess liver-related mortality, nor did they include prospectively updated exposures, or account for key clinical and lifestyle factors, including underlying cirrhosis, alcohol use, diet and smoking, which are essential to accurately estimate the long-term effects of physical activity and adiposity on hepatic outcomes. Specifically, failing to address underlying cirrhosis can lead to reverse causation, because cirrhosis contributes to weight loss and to increased mortality. In contrast, by excluding individuals with cirrhosis at baseline, and including detailed and updated clinical and lifestyle data over 26 years of follow-up, the current study is able to more precisely characterize the relationships between physical activity, adiposity and liver-related mortality.

We observed strong, inverse associations between increasing physical activity and reduced risk of liver-related mortality, that were consistent regardless of BMI or WC. Importantly, the excess risk associated with obesity was substantially attenuated in persons who exercised for at least 9 MET-hours/week, the equivalent of average-pace walking for just 3 hours/week. Given the lack of published data or clinical guidelines regarding the optimal weight or physical activity level required to improve major hepatic outcomes, these findings are both timely and important. Our data demonstrate for the first time that exercise is an independent, modifiable determinant of long-term hepatic outcomes. As such, our findings support additional research to identify the optimal type, intensity and duration of physical activity, for incorporation into prevention guidelines.

Several mechanisms might explain the shared effects of exercise and adiposity on liver disease progression and mortality. Obesity is marked by disproportionately increased visceral adipose tissue (VAT) volume, which promotes fibrosis progression,[47,48] while exercise preferentially reduces VAT, even when weight loss is not achieved.[36,49,50] Further, exercise interventions can attenuate liver fat and inflammation,[14,15,19,36,44] normalize pro-inflammatory biomarkers[50,51] and modulate bile acids,[52] which may impact the natural history of liver disease. Finally, because physical activity and obesity may operate on similar inflammatory and carcinogenic pathways, it is possible that a key benefit of physical activity is the minimization of long-term weight gain, over the lifespan.[53] Accordingly, it has been recommended that studies examining adiposity and physical activity leverage prospectively updated longitudinal data, to best elucidate these relationships.[53]

This study is strengthened by the prospective design, large sample size, and by the inclusion of 2 independent cohorts with high rates of follow-up and updated information regarding numerous risk factors for liver-related mortality. The prospective design minimizes potential recall bias, and any errors in recall would most likely have attenuated rather than exaggerated a true association. The use of repeated assessments reduces measurement error, while simultaneously addressing real-life changes in adiposity and physical activity patterns over time. Further, accounting for a range of times between exposure assessment and death minimizes the possibility of reverse causation.

We acknowledge several limitations. First, we cannot exclude the possibility of residual confounding, and we lacked detailed data regarding histological fibrosis stage, non-invasive estimates of fibrosis or adherence to HCC screening guidelines. However, the observed benefits of physical activity were robust across all sensitivity analyses, after carefully accounting for viral hepatitis and alcohol use, and they were similar in persons with and without underlying cirrhosis. Second, although reverse causation is possible, we conducted baseline and extended latency analyses in which exposures were assessed many years prior to study outcomes, rendering it highly unlikely that symptoms of undiagnosed liver disease could have biased our results. Third, we acknowledge that our participants are predominantly white, highlighting the need for future research in more diverse, prospective populations; however, our age- and sex-specific rates of HCC and cirrhosis-specific mortality,[39] and our well-validated covariate data,[24,25] closely approximate other epidemiological cohorts, supporting the generalizability of our findings. Fourth, specific types of physical activity may be more beneficial than others, underscoring the need for future studies with detailed, prospectively updated physical activity data and long-term outcomes, to define the optimal type and intensity of physical activity to maximize risk reduction. Finally, active participants may be more likely to adhere to other healthy behaviors; while our results were similar after carefully accounting for health-promoting factors like diet, alcohol and smoking, future studies are needed that focus on lifestyle overall.

In conclusion, within 2 prospective cohorts of American adults without established liver disease at enrollment, both low physical activity and obesity were independent predictors of liver-related mortality, including death from cirrhosis and HCC. Significantly elevated risk was apparent with obesity in early adulthood, in mid-life, and with weight gain during early adulthood. However, the excess risk conferred by obesity was markedly attenuated by physical activity, and it was no longer statistically significant among adults who engaged in >9 MET-hours per week of physical activity. These findings demonstrate that physical activity is a major modifiable determinant of long-term hepatic outcomes. They also support further research to characterize the optimal type and intensity of activity for the prevention of liver-related mortality.

Abbreviations

BMI, body mass index; HCC, hepatocellular carcinoma; HPFS, Health Professionals Follow-up Study; MET, metabolic equivalent task; NAFLD, non-alcoholic fatty liver disease; NHS, Nurses' Health Study; PA, physical activity; VAT, visceral adipose tissue; WC, waist circumference; WHR, waist-to-hip ratio.

Financial support

UM1 CA186107 (Nurses' Health Study infrastructure grant). P01 CA87969 (Nurses' Health Study program grant for cancer research). UM1 CA167552 (Health Professionals Follow-up Study infrastructure grant). NIH K24 DK078772 (RTC). NIH K24 DK098311 (ATC). NIH K07 CA188126 (XZ). NIH K23 DK122104 (TGS). Dr. Simon is supported by the American Association of the Study of Liver Diseases Clinical and Translational Research Award (CTORA), and by the Boston Nutrition Obesity Research Council (BNORC; NIH P30DK046200-26). Dr. Chan is a Stuart and Suzanne Steele MGH Research Scholar.

Conflict of interest

Dr. Chan has previously served as a consultant for Bayer Pharma AG for work unrelated to this manuscript. Dr. Meyerhardt has received institutional research funding from Boston Biomedical; JAM has served as an advisor/consultant to Ignyta, Array Pharmaceutical and Cota. The remaining authors have no disclosures and no conflicts of interest to disclose.

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

Authors' contributions

TGS: study design, data analysis and interpretation, drafting of the manuscript. MNK: data interpretation and review of the results. XL: data interpretation and review of the results. WY: data interpretation, review of the results and review of the manuscript. YM: source data collection, review of the results and review of the manuscript. DQC: source data collection and review of the manuscript. CSF: data interpretation and review of the manuscript. JAM: data interpretation and review of the manuscript. KEC: study design, data interpretation and review of the manuscript. RTC: data interpretation and review of the manuscript. MS: data interpretation, review of the results and review of the manuscript. XZ: data interpretation and review of the manuscript. ELC: study design, data interpretation, review of the results and review of the manuscript. ATC: study design, data interpretation, review of the results, review of the manuscript, overall study oversight and guarantor of the manuscript.

Role of the funding source

No sponsor had a role in the study design, data collection, analysis or interpretation of the data, or in the writing of the manuscript or the decision to submit the paper for publication. All authors had full access to the study data and had final responsibility for the decision to submit for publication.

Acknowledgements

We would like to thank the participants and staff of the Nurses' Health Study and the Health Professionals Follow-up Study for their valuable contributions as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WY. The authors assume full responsibility for analyses and interpretation of these data.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.12.022.

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