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Survival effects of physical activity on mortality among persons with liver disease☆

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ABSTRACT

Physical activity is protective of premature mortality and those with liver disease are at an increased risk of early mortality. It is thus plausible to suggest that physical activity may have survival benefits among those with liver disease, but this has yet to be investigated. In a national sample, we examine the prospective association of objectively-measured physical activity on all-cause mortality among those with liver disease. Data from the 2003–2006 National Health and Nutrition Examination Survey (with follow-up through 2011) were evaluated (analyzed in 2015). Physical activity was assessed via accelerometry over 7 days. Liver disease was assessed via self-report of physician diagnosis. Covariates included age, gender, race-ethnicity, serum cotinine, income-to-poverty ratio, C-reactive protein, cholesterol medication use, blood pressure medication use, alcohol behavior, self-reported liver disease status, serum alanine aminotransferase (ALT), serum gamma-glutamyltransferase (GGT) and comorbid illness. The sample included 162 adults who self-reported a physician-diagnosis of liver disease. The unweighted median follow-up period was 80.0 months (IQR = 68–91; SD = 18.0). In the sample, 12,815 person-months occurred with a mortality incidence rate of 1.09 deaths per 1000 person-months. After adjustments, for every 10 min/day increase in moderate-to-vigorous physical activity (MVPA), participants had an 89% reduced risk of all-cause mortality ($HR_{adjusted}$ = 0.11; 95% CI: 0.02–0.47; P = 0.004). There was no evidence of moderation by alcohol behavior, ALT, GGT or Hepatitis C virus status. These findings demonstrate that modest increases in MVPA may have survival benefits among those with a self-reported liver condition.

Introduction

Emerging research provides suggestive evidence that regular participation in physical activity (PA) may help to prevent against liver disease (Ryu et al., 2015; Berzigotti and Saran, 2015; Whitsett and VanWagner, 2015; Keating et al., 2015; Pinto et al., 2015; Hallsworth et al., 2015). The most common cause of liver disease in the United States is a spectrum of liver conditions known collectively as non-alcoholic fatty liver disease (NAFLD). NAFLD is an obesity-related condition with an increased prevalence of other chronic diseases (e.g., insulin resistance) (Chen et al., 2015; Vozarova et al., 2002) and premature all-cause mortality (Kunutsor et al., 2014). However, the extent to which PA may favor survival benefits among those with any liver disease is less understood. As a result, the purpose of this brief study was to examine the relationship between PA and all-cause mortality risk among persons with a history of liver disease.

Methods

Design

Data were extracted from the 2003–2006 National Health and Nutrition Examination Survey (NHANES; only available cycles with accelerometry data). Participant data was linked to death certificate data through December 31, 2011 from the National Death Index.

Liver disease

Participants were asked: "Has a doctor or other health professional ever told you that you had any kind of liver condition?" Participants who answered "yes" to this question were assessed herein. Among these participants, evidence of antibodies against the Hepatitis C virus was assessed with a Hepatitis C antibody test, with methodological details described elsewhere (Smith and Yartel, 2014).

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Free-living objectively-measured PA

Free-living PA was assessed during all waking hours using the ActiGraph 7164 accelerometer. SAS (version 9.2) was used to reduce accelerometry data to those with ≥4 days of ≥10 h/day of monitored data and integrate it into 1 minute time intervals. Non-wear time was identified as ≥ 60 consecutive minutes of zero activity counts, with allowance for 1–2 min of activity counts between 0 and 100. Activity counts/min ≥ 2020 was used as the threshold to determine time spent at moderate-to-vigorous PA (MVPA) across the valid days (Loprinzi, 2015a).

Covariates

As described elsewhere (http://www.cdc.gov/nchs/nhanes.htm), covariates included self-reported age (continuous; years), self-reported gender, self-reported race-ethnicity (Mexican American, non-Hispanic white, non-Hispanic black, and other), laboratory-determined serum cotinine (marker of active/passive smoking status; continuous; ng/mL), income-to-poverty ratio (continuous), laboratory-determined C-reactive protein (CRP; continuous, mg/dL), self-reported cholesterol medication use (yes/no), self-reported blood pressure medication use (yes/no), self-reported alcohol behavior (average # of alcoholic drinks/day in past 12 months; continuous), self-reported liver disease status (yes/no), laboratory-determined serum alanine aminotransferase (ALT; continuous, U/L), laboratory-determined serum gamma-glutamyltransferase (GGT; continuous, U/L) and self-reported comorbid illness (ordinal variable).

The income-to-poverty ratio is calculated by dividing the family income by the poverty guidelines, which is specific to the family size, year assessed, and state of residence. High sensitivity CRP was used as a marker of systemic inflammation, using latex-enhanced nephelometry, with samples taken prior to PA assessment. The comorbid illness variable indicated the summed number of morbidities for each participant, based on physician diagnosis of: arthritis, chronic obstructive pulmonary disease, coronary artery disease, heart attack, stroke, overweight/obese (measured BMI ≥ 25 kg/m^2), diabetes and hypertension.

ALT was assessed using the LX20. In the reaction, ALT catalyzes the reversible transamination of L-alanine and α-ketoglutarate to pyruvate and L-glutamate. The pyruvate is then reduced to lactate in the presence of lactate dehydrogenase (LDH) with the concurrent oxidation of NADH to NAD. The LX20 uses an enzymatic rate method to determine the GGT activity in serum or plasma. In the reaction, the GGT catalyzes the transfer of a gamma-glutamyl group from the colorless substrate, gamma-glutamyl-p-nitroaniline, to the acceptor, glycylglycine with production of the colored product, p-nitroaniline.

Analysis

Statistical analyses were performed via procedures from survey data using Stata (v.12); analyzed in 2015. All analyses included the use of survey sample weights, clustering and primary sampling units to account for the complex NHANES design. Cox proportional hazard models were used to examine the association between PA and all-cause mortality. Schoenfeld's residuals were used to verify the proportional hazards assumption.

Results

In the 2003–2006 NHANES cycles, 248 adults self-reported a physician-diagnosis of liver disease and had data on the study covariates; among these 248 adults, 32 died during the follow-up period. After excluding those with insufficient (<4 days of 10+ h/day of monitoring data) accelerometry data (n = 86), 162 participants remained, with 14 deaths occurring during the follow-up period and constituted the primary analytic sample.

The unweighted median follow-up period was 80.0 months (IQR = 68–91; SD = 18.0). In the sample, 12,815 person-months occurred with a mortality incidence rate of 1.09 deaths per 1000 person-months. Among these 162 participants, 24 (14.8%) had a positive Hepatitis C antibody test, and among these 24, 1 died during the follow-up period. No confirmatory HCV polymerase chain reaction information is available. Table 1 displays the characteristics of the study variables.

As shown in Table 2, in an unadjusted Cox proportion model, for every 10 min/day increase in MVPA, participants had a 63% reduced risk of all-cause mortality (HR = 0.37; 95% CI: 0.18–0.74; P = 0.007). After adjustments, for every 10 min/day increase in MVPA, participants had an 89% reduced risk of all-cause mortality ($HR_{adjusted}$ = 0.11; 95% CI: 0.02–0.47; P = 0.004). The proportional hazards assumption was not violated (P = 0.24) and the Harrell's C concordance statistic was 0.86. Notably, there was no evidence of multiplicative interaction between MVPA and ALT/GGT, markers of liver inflammation, with all-cause mortality; multiplicative interaction term for MVPA and ALT (HR = 0.94; 95% CI: 0.87–1.02; P = 0.13) and MVPA and GGT (HR = 0.98; 95% CI: 0.97–1.01; P = 0.07). Also, there was no evidence of multiplicative interaction between MVPA and alcohol consumption with mortality (interaction term: HR = 0.55; 95% CI: 0.15–2.00; P = 0.35). Further, when we excluded the 24 individuals with a positive Hepatitis C antibody test, MVPA remained significantly associated with mortality (HR = 0.11; 95% CI: 0.02–0.58; P = 0.01).

As stated in the Methods section, prior to excluding those with insufficient accelerometry data, 248 participants (32 died during the follow-up period) comprised the sample. Among these 248 participants, 42 (16.9%) had a positive Hepatitis C antibody test, and among these 42, 2 died during the follow-up period. Among this slightly larger sample (248 vs. 162), additional analyses using self-reported MVPA (described elsewhere(Loprinzi, 2015b)) were computed. Unadjusted results (Table 2) showed that, for every 500 MET-min-week increase (equivalent to 30 min/day of MVPA), participants had a non-significant 43% reduced risk of all-cause mortality (HR = 0.57; 95% CI: 0.31–1.04; P = 0.06). After adjusting for age, gender and race-ethnicity, for every 500 MET-min-week increase, participants had a 44% reduced risk of all-cause mortality (HR = 0.56; 95% CI: 0.32–0.99; P = 0.04). After further adjustment (i.e., covariates noted in the footnote of Table 2), MVPA was just outside the statistical significance level (HR = 0.54; 95% CI: 0.28–1.06; P = 0.07). These attenuated results for self-

Table 1
Unweighted baseline characteristics, 2003–2006 NHANES (N = 162).

	Point estimates (95% CI)
MVPA, min/day	21.6 (18.5–24.6)
Age, mean yrs	53.9 (51.6–56.3)
Male, %	59.8 (52.2–67.5)
Non-Hispanic white, %	62.3 (54.8–69.8)
Income-to-poverty ratio	2.72 (2.47–2.96)
Cotinine, mean ng/mL	1.41 (0.96–1.85)
CRP, mean mg/dL	0.46 (0.33–0.59)
BMI, kg/m^2	28.9 (27.8–29.9)
% Obese (BMI ≥ 30 kg/m^2)	35.1 (29.0–41.0)
Comorbidities [a], mean	1.91 (1.72–2.10)
ALT (U/L)	37.82 (33.3–42.3)
GGT (U/L)	60.0 (40.4–79.6)
Current liver condition, %	46.2 (38.5–54.0)
Alcohol drinks, mean/day	1.81 (1.40–2.22)
Cholesterol medication, %	17.9 (11.9–23.8)
Hypertensive medication, %	27.7 (20.8–34.7)

ALT, Alanine aminotransferase.
BMI, Body mass index.
CRP, C-reactive protein.
GGT, Gamma-glutamyltransferase.
MVPA, moderate-to-vigorous physical activity.
[a] The comorbid illness variable indicated the summed number of morbidities for each participant, based on physician diagnosis of: arthritis, chronic obstructive pulmonary-disease, coronary artery disease, heart attack, stroke, overweight/obese (measured BMI ≥ 25 kg/m^2), diabetes and hypertension.

Table 2
Weighted unadjusted and adjusted Cox proportional hazard model results examining the association between self-reported and accelerometer-assessed moderate-to-vigorous physical activity (MVPA) with all-cause mortality among adults with a history of self-reported liver disease.

	Unadjusted			Adjusted[a]		
	HR	95% CI	P-value	HR	95% CI	P-value
Accelerometer-determined MVPA, 10-min/day increase	0.37	0.18–0.74	0.007	0.11	0.02–0.47	0.004
Self-reported MVPA, 500 MET-min/week increase	0.57	0.31–1.04	0.06	0.55	.028–1.06	0.07

Results for 4 different Cox proportional hazard models are shown; an unadjusted and adjusted model when using self-reported physical activity data (N = 248), and an unadjusted and adjusted model when using accelerometer-assessed physical activity data (N = 162).
MVPA, Moderate-to-vigorous physical activity.
MET, Metabolic equivalent of task.
HR, Hazard ratio.
[a] Covariates included age, gender, race-ethnicity, serum cotinine, income-to-poverty ratio, C-reactive protein, cholesterol medication use, blood pressure medication use, alcohol behavior, self-reported liver disease status, serum alanine aminotransferase, serum gamma-glutamyltransferase and comorbid illness.

reported MVPA are not surprising as previous research demonstrates weaker associations of self-reported MVPA with health outcomes when compared to objectively-measured MVPA (Atienza et al., 2011). Similar to the accelerometer-derived MVPA analyses, there was no evidence of multiplicative interaction between self-reported MVPA and ALT/GGT with all-cause mortality; multiplicative interaction term for self-reported MVPA and ALT (HR = 1.00; 95% CI: 0.99–1.01; P = 0.73) and self-reported MVPA and GGT (HR = 0.999; 95% CI: 0.997–1.00; P = 0.76).

Discussion

These findings demonstrate that modest increases in MVPA may have survival benefits among those with a self-reported liver condition. We have demonstrated that MVPA is inversely associated with all-cause mortality among those with a history of self-reported liver condition, and alcohol use and Hepatitis C status do not appear moderate this relationship. The potential protective effects of MVPA on mortality among those with a history of liver disease may be a result of the favorable cardiometabolic effects of MVPA engagement (Loprinzi, 2015a). Further, MVPA itself may help to positively influence liver functioning as a result of the simulation of lipid oxidation and inhibition of lipid synthesis in the liver through the activation of the AMP-activated protein kinase pathway (Lavoie and Gauthier, 2006).

These preliminary findings underscore the importance of promotion of safe forms of MVPA among patients with liver disease. Despite the notable strengths of this study, which include the novel investigation, objective measure of PA and a national sample, future research should aim to overcome the limitations of this study. For example, future studies should employ a large sample size to increase the mortality incidence rate and examine the influence of PA on mortality among those with specific liver diseases, particularly NAFLD.

Transparency document

The Transparency document associated with this article can be found in the online version.

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