

Perceptions of Exercise and Its Challenges in Patients With Nonalcoholic Fatty Liver Disease: A Survey-Based Study

Oliver Glass,¹ Daniel Liu,² Elizabeth Bechara,³ Cynthia D. Guy,⁴ Jane Pendergast,⁵ Anna Mae Diehl,⁶ and Manal F. Abdelmalek⁶

Exercise is a foundational treatment for nonalcoholic fatty liver disease (NAFLD); however, the majority of patients are unable to initiate and maintain effective exercise habits and remain at increased risk for progressive liver disease. Barriers and limitations to exercise in patients with NAFLD have not been fully identified. We performed a single survey of 94 patients with biopsy-proven NAFLD to understand baseline physical activity and sedentary behavior, self-perceived fitness, limitations to exercise, potential solutions to increase physical activity behavior, and perception of exercise as a foundational treatment for NAFLD. For exploratory analyses, we evaluated differences in responses to the survey by grouping severity of hepatic fibrosis as follows: nonalcoholic fatty liver (NAFL); early stage (nonalcoholic steatohepatitis [NASH] F0, NASH F1, NASH F2); and late stage (NASH F3, NASH F4). Zero weekly total physical activity was reported by 29% of patients with NAFLD. Late-stage NASH had significantly lower vigorous ($P = 0.024$), walking ($P = 0.029$), total weekly activity ($P = 0.043$), and current fitness level ($P = 0.022$) compared to early stage NASH. Overall, 72% of patients with NAFLD reported limitations to exercise, with the greatest proportion citing lack of energy (62%), fatigue (61%), prior/current Injury (50%), and shortness of breath (49%). A preference for personal training to increase their physical activity was indicated by 66% of patients with NAFLD, and 63% preferred exercise over medication to treat NAFLD. **Conclusion:** The majority of patients with NAFLD have limitations to exercise but prefer exercise as a treatment option for NAFLD in the form of personal training. Patients with NAFLD may have unique physiologic limitations to exercise that worsen with fibrosis severity. Exercise interventions or services that are personalized and scalable may improve sustainability of exercise habits in the long term. (*Hepatology Communications* 2022;6:334-344).

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide, affecting 25%-30% of the adult general population. Of those with NAFLD, 25% will progress from simple steatosis or nonalcoholic fatty liver (NAFL) to nonalcoholic steatohepatitis (NASH), increasing the risk for progressive fibrosis and cirrhosis. NASH is diagnosed following histopathologic assessment of a liver biopsy and is characterized

as accumulation of fat in the liver, with necroinflammation, ballooned hepatocytes, and/or fibrosis. In the absence of US Food and Drug Administration-approved therapies for NAFLD, diet and exercise are considered the foundational treatments. Exercise, i.e., planned and purposeful physical activity, has been demonstrated to improve liver fat as well as the histopathologic features of NASH, independent of weight loss.⁽¹⁻³⁾ Patients with NAFLD are encouraged to

Abbreviations: HU, Hounsfield unit; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; IPAQ-SF, International Physical Activity Questionnaire short form; MET, metabolic equivalent task; NAFL, nonalcoholic fatty liver; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

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meet 150–200 minutes of moderate-intensity exercise per week by the European Association for the Study of the Liver and American Association for the Study of Liver Diseases.⁽⁴⁾ However, patients with NAFLD have difficulty exercising and performing daily activities.⁽⁵⁾ It has been reported that more than half of patients with NAFLD are not physically active and only a fraction are able to meet the minimal recommendations of exercise.⁽⁶⁾

The limitations and challenges to exercise in patients with NAFLD are not completely understood but may be influenced by both physiologic and behavioral factors.⁽⁷⁾ As NAFLD progresses, mitochondrial dysfunction increases in the liver, altering energy metabolism and homeostasis.⁽⁸⁾ These perturbations in energy metabolism and homeostasis not only impact liver but also impact the energy that is required by skeletal muscles for complex motor functions, like exercise.^(8,9) Cross-sectional studies indicate that patients with NAFLD experience high levels of fatigue, impaired physical function, and poorer cardiorespiratory fitness, which can lead to difficulty initiating and maintaining effective exercise habits.^(10,11) While cardiorespiratory fitness and physical function have been associated with NAFLD severity, fatigue appears to be independent of body mass index (BMI) and disease severity, suggesting that additional factors may also contribute to challenges with exercise.⁽¹⁰⁾ Barriers and limitations to physical activity and exercise in patients with NAFLD beyond fatigue have not been formally acknowledged or identified, hindering the development of comprehensive strategies that successfully facilitate increasing physical activity and reducing sedentary behavior. In order to leverage the benefits of exercise as a foundational treatment for NAFLD, we must first understand

its limitations and challenges in patients with NAFLD. Furthermore, we must identify appropriate opportunities whereby tools and solutions can be effectively incorporated into the treatment timeline. Without accounting for barriers and limitations, even the most effective exercise prescriptions or recommendations will likely fail in the long term.

To date, no studies have evaluated the potential limitations of physical activity or exercise in patients with NAFLD. In our study, we performed a single survey to assess baseline physical activity and sedentary behavior, self-perceived fitness, limitations to exercise, potential solutions to increase physical activity, and perception of exercise as a foundational treatment for NAFLD.

Patients and Methods

HUMAN SUBJECTS

We performed a prospective data collection of patients with biopsy-proven NAFLD. Patients received liver biopsies as part of their standard of care treatment for NAFLD and were recruited for participation after final histologic assessment. The presence of NAFLD was defined histologically according to the criteria established by the NASH Clinical Research Network.⁽¹²⁾ NAFLD was defined as the presence of >5% hepatic steatosis on liver biopsy and the absence of histologic and serologic evidence for other chronic liver disease. Demographics (i.e., height, weight, BMI, age, sex, race, ethnicity, smoking status, diabetes status, liver aminotransferases, and medical history) were extracted by a systematic chart review at the time of

ARTICLE INFORMATION:

From the ¹Division of General Internal Medicine, Duke University, Durham, NC, USA; ²Department of Ecology and Evolutionary Biology, Princeton University, Princeton, NJ, USA; ³Duke University Health System, Durham, NC, USA; ⁴Department of Pathology, Duke University, Durham, NC, USA; ⁵Department of Biostatistics and Bioinformatics, Duke University, Durham, NC, USA; ⁶Division of Gastroenterology and Hepatology, Duke University, Durham, NC, USA.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Manal F. Abdelmalek, M.D., M.P.H.
Division of Gastroenterology
Duke University Medical Center
P.O. Box 3913

Durham, NC 27710, USA
E-mail: manal.abdelmalek@duke.edu
Tel.: +919-684-6274

enrollment. Diabetes mellitus was defined as the presence of an existing medical diagnosis in the medical record, a glycosylated hemoglobin A1C >6.5%, and/or use of any medication (oral insulin sensitizing agents or insulin therapy) used to treat diabetes mellitus.

INCLUSION/EXCLUSION CRITERIA

Adults ≥ 18 years old with biopsy-proven NAFLD were offered participation in the survey. No exclusion criteria were defined.

SURVEY

Our four-page survey was delivered in paper format and consisted of the following four sections: (1) weekly physical activity and sedentary behavior; (2) barriers and limitations and potential solutions to exercise; (3) perception of fitness; and (4) perception of exercise as a foundational treatment for NAFLD. Response options for the survey were either oriented (multiple selection), quantitative (1-10), open-ended, or single selection (yes/no/maybe, exercise/medication/both). No compensation was provided for participation in the study.

Survey section (1) is derived from the International Physical Activity Questionnaire short form (IPAQ-SF)⁽¹³⁾ but differs by including examples of physical activity types as well as the addition of questions pertaining to whether participants “ever” performed the specified physical activity intensities. The IPAQ-SF is a validated instrument that evaluates frequency and duration of walking, moderate, and vigorous activity during the last 7 days for physical activities related to leisure, work, household, and transportation.⁽¹³⁾ Additionally, the IPAQ evaluates self-reported sedentary behavior within the last 7 days. Survey section (2) asked participants about limitations to exercise, followed by a list of commonly described limitations to exercise to choose from. In order to identify potential solutions to circumvent their limitations, participants were asked to choose from a list of preselected options that would help increase desire or ability to be more physically active or engage in regular exercise. Survey section (3) asked participants about their perception of their current fitness level, their best fitness level, and their perception of the importance of fitness, using a Likert scale from 1 to 10. Survey section (4) asked participants about their

perception of exercise as a foundational treatment for NAFLD. Using a yes/no/neither response choice, participants were asked about preference in choosing exercise (the foundational treatment) or a medication in treating NAFLD with increasing medication-related side effects.

STATISTICAL ANALYSIS

Demographic and clinical data are expressed as means (SD). Group comparisons between fibrosis severity were assessed using analysis of variance and the Kruskal-Wallis test for continuous variables or chi-squared test for categorical variables, with $P < 0.05$ considered significant. Subgroups within NAFLD were defined as NAFL; those with early stage NASH (NASH F0, NASH F1, NASH F2); and those with late-stage NASH (NASH F3, NASH F4). All total weekly physical activity measures by intensity were converted to metabolic equivalent tasks (METs) to allow for comparisons.⁽¹⁴⁾ Total weekly vigorous activity time (number of vigorous activity days multiplied by mean vigorous activity daily minutes) was multiplied by a factor of 8, total weekly moderate activity was multiplied by 4, and total weekly walking was multiplied by 3.3 to obtain total MET minutes per week.⁽¹⁵⁾ Predictors of non-zero versus zero total METs were assessed individually and jointly using Spearman correlations, Kruskal-Wallis test, and logistic regression. Predictors considered were age, sex, stage, smoking status (yes/no), diabetes status (nondiabetic, prediabetic, diabetic), whether or not they had at least one limitation, their self-assessment of current physical fitness and importance of fitness, as well as whether medication use limited their activity level (yes vs. no, maybe). Race and ethnicity were not considered due to the small counts in several categories. A generalized linear model assuming a right-skewed (gamma) distribution with log link was fit to total METs among those with non-zero METs to look for predictors of greater levels of activity. Candidate predictors for that model were age, BMI, sex, stage, smoking status, diabetes status, alanine aminotransferase (ALT), current fitness self-assessment, and importance of fitness self-assessment; whether or not they had engaged in vigorous activity, moderate activity, number of walk days, amount of sit time; whether they had limitations due to medications (yes vs. no, maybe); and the specific limitations of pain, physical ability, fatigue, discomfort, lack of energy, and/or shortness of breath.

Results

PATIENT CHARACTERISTICS

Demographic and clinical data obtained from 94 study participants are summarized in Table 1. Overall, mean \pm SD age was 58 ± 11 years, 57% were men, 89% were Caucasian, 52% had diabetes mellitus, and 6% were smokers. Mean \pm SD BMI was 34.3 ± 5.2 kg/m², aspartate aminotransferase (AST) and ALT were 47 ± 24 U/L and 50.4 ± 34.2 U/L, respectively. The majority of participants (62%) had NASH with stage 3 and stage 4 fibrosis (late-stage NASH), 25% had NASH and stage 1 and stage 2

fibrosis (early stage NASH), and 13% had NAFL. Compared to late-stage NASH, age was significantly lower in NAFL ($P = 0.028$).

PHYSICAL ACTIVITY BEHAVIOR

We evaluated weekly physical activity measures among participants, using a modified IPAQ survey described above. A total of 29% of participants with NAFLD were inactive, recording zero total weekly physical activity for all intensity levels (vigorous, moderate, and walking). Mean \pm SD weekly physical activity levels for patients with NAFLD were $422 \pm 1,630$ METs for vigorous intensity, $646 \pm 1,548$

TABLE 1. PATIENT CHARACTERISTICS OF THE 94 SURVEY PARTICIPANTS

	NAFLD n = 94	NAFL n = 12	Early Stage (NASH F0, F1, F2) n = 23	Late Stage (NASH F3, F4) n = 59	P Value
Age, mean (SD)	58 (11)	51 (15)	58 (10)	60 (10)	0.028
Sex					0.150
Male, n (%)	54 (57)	2 (17)	11 (48)	27 (46)	
Race, n (%)					0.571
Caucasian	84 (89)	10 (83)	21 (91)	53 (90)	
African American	6 (6)	1 (8)	1 (4)	4 (7)	
American Indian/Alaskan Native	1 (1)	0	0	1 (2)	
Asian	1 (1)	0	1 (4)	0	
Other	2 (2)	1 (8)	0	1 (2)	
Ethnicity					0.118
Hispanic	5 (5)	2 (17)	0	3 (5)	
Non-Hispanic	87 (93)	10 (83)	23 (100)	54 (92)	
NA	2 (2)			2 (3)	
BMI (kg/m ²), mean (SD)	34.3 (5.2)	34.9 (6.3)	32.2 (4)	35 (5.3)	0.094
Smoking status, n (%)					0.811
Smoker	6 (6)	1 (8)	2 (9)	3 (5)	
Nonsmoker	87 (93)	11 (92)	21 (91)	55 (93)	
Unknown	1 (1)	0	0	1 (2)	
Diabetes status					
Diabetic, n (%)	49 (52)	5 (42)	7 (30)	37 (63)	
Prediabetic, n (%)	7 (7)	1 (8)	5 (22)	1 (2)	
Nondiabetic, n (%)	38 (40)	6 (50)	11 (48)	21 (36)	
AST (U/L), mean (SD)	47 (24)	46 (28.8)	40.7 (21.7)	49.7 (23.8)	0.346
ALT (U/L), mean (SD)	50.4 (34.2)	65.1 (45.5)	56.7 (40)	44.8 (27.6)	0.111
NAFLD diagnosis, n (%)					
NAFL	12 (13)	12	0	0	
NASH F0	4 (4)	0	4	0	
NASH F1	8 (9)	0	8	0	
NASH F2	11 (12)	0	11	0	
NASH F3	22 (23)	0	0	22	
NASH F4	37 (39)	0	0	37	

Abbreviation: NA, not answered.

for moderate intensity, and $769 \pm 1,530$ for walking (Fig. 1A). Mean \pm SD total weekly METs were $1,836 \pm 3,150$ (Fig. 1B). Because disease severity has been shown to be inversely associated with cardiorespiratory fitness,⁽¹⁶⁾ we assessed whether physical activity intensities or total weekly physical activity differed among the subgroups NAFL, early stage NASH, and late-stage NASH. Compared to early stage NASH, late-stage NASH had lower total weekly METs

($P = 0.043$), lower vigorous weekly METs ($P = 0.024$), similar moderate weekly METs ($P > 0.05$), and lower walking weekly METs ($P = 0.029$) (Fig. 1C-F).

SEDENTARY BEHAVIOR

Mean daily sitting time among all patients with NAFLD was 8.5 ± 4.4 hours and was not statistically significant ($P > 0.05$) among subgroups (mean \pm SD,

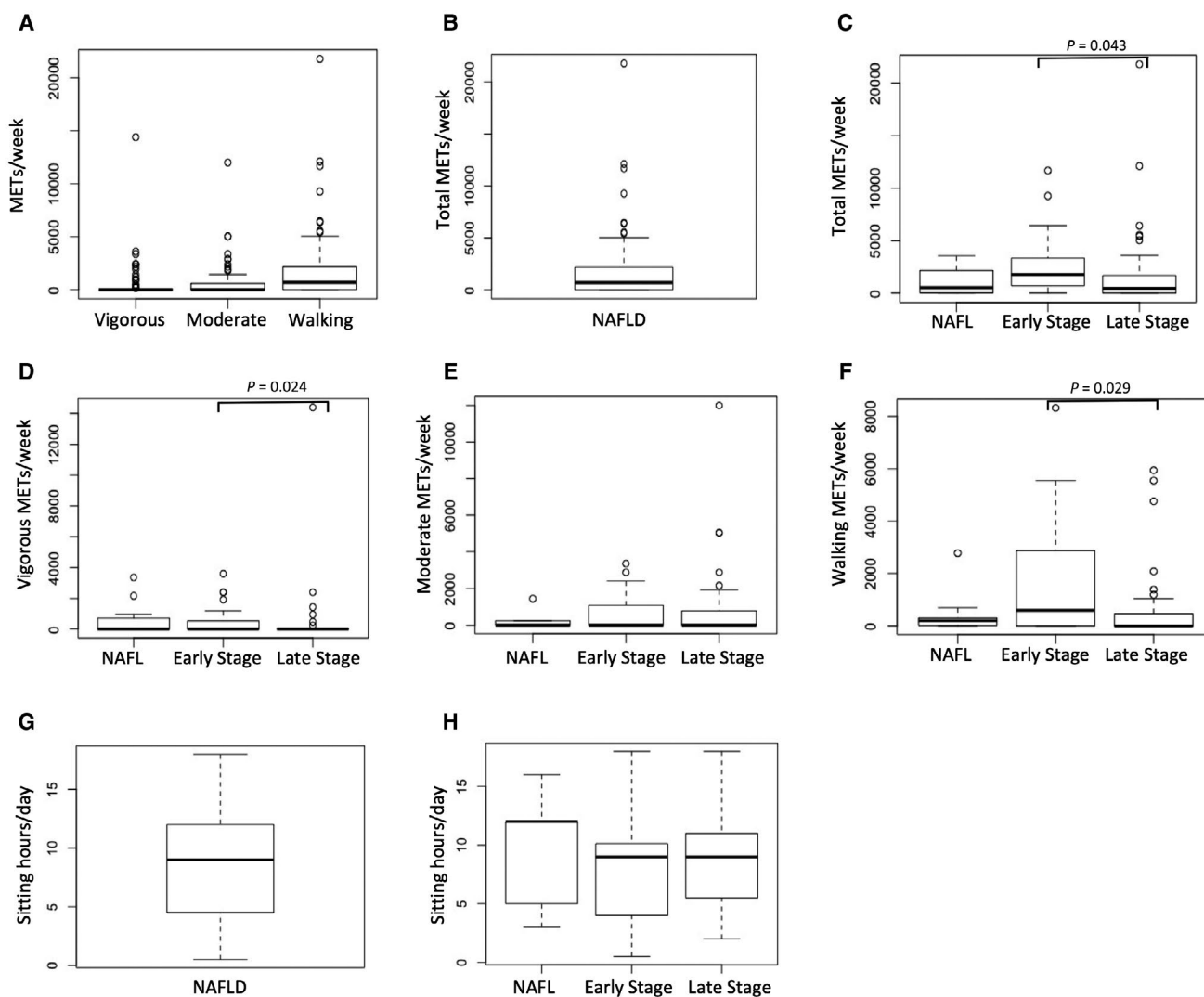


FIG. 1. Weekly physical activity by METs and sedentary behavior in patients with NAFLD. (A) Weekly vigorous, moderate, and walking METs in patients with NAFLD ($n = 94$). (B) Total weekly METs in patients with NAFLD. (C) Total weekly METs by NAFL, early stage NASH, and late-stage NASH. (D) Weekly vigorous METs by NAFL, early stage NASH, and late-stage NASH. (E) Weekly moderate METs by NAFL, early stage NASH, and late-stage NASH. (F) Weekly walking METs by NAFL, early stage NASH, and late-stage NASH. (G) Total daily hours spent sitting in patients with NAFLD. (H) Total daily hours spent sitting by NAFL, early stage NASH, and late-stage NASH. Box plots show median (bold horizontal line), interquartile range (box), third quartile (upper limit of box), and first quartile (lower limit of box). Dashed lines indicate data range; horizontal lines show minimum (bottom) and maximum (top) values.

9.8 ± 4.5 hours for NAFL; 8 ± 4.9 hours for early stage NASH; and 8.5 ± 4.3 hours for late-stage NASH) (Fig. 1G,H).

PERCEPTION OF FITNESS

The definition of fitness includes “a set of attributes that people have or achieve that relates to the ability to perform physical activity” and the ability

to carry out daily tasks with vigor.⁽¹⁷⁾ Using a Likert scale of 1 (extremely unfit) to 10 (extremely fit), we asked participants about their self-perceived level of fitness in order to understand the state or manifestation of NAFLD health-related physical activity behaviors.^(18,19) Compared to early stage NASH (mean ± SD, 5 ± 2), mean current fitness levels were significantly lower in late-stage NASH (mean ± SD, 4 ± 2; *P* = 0.022) (Fig. 2A).

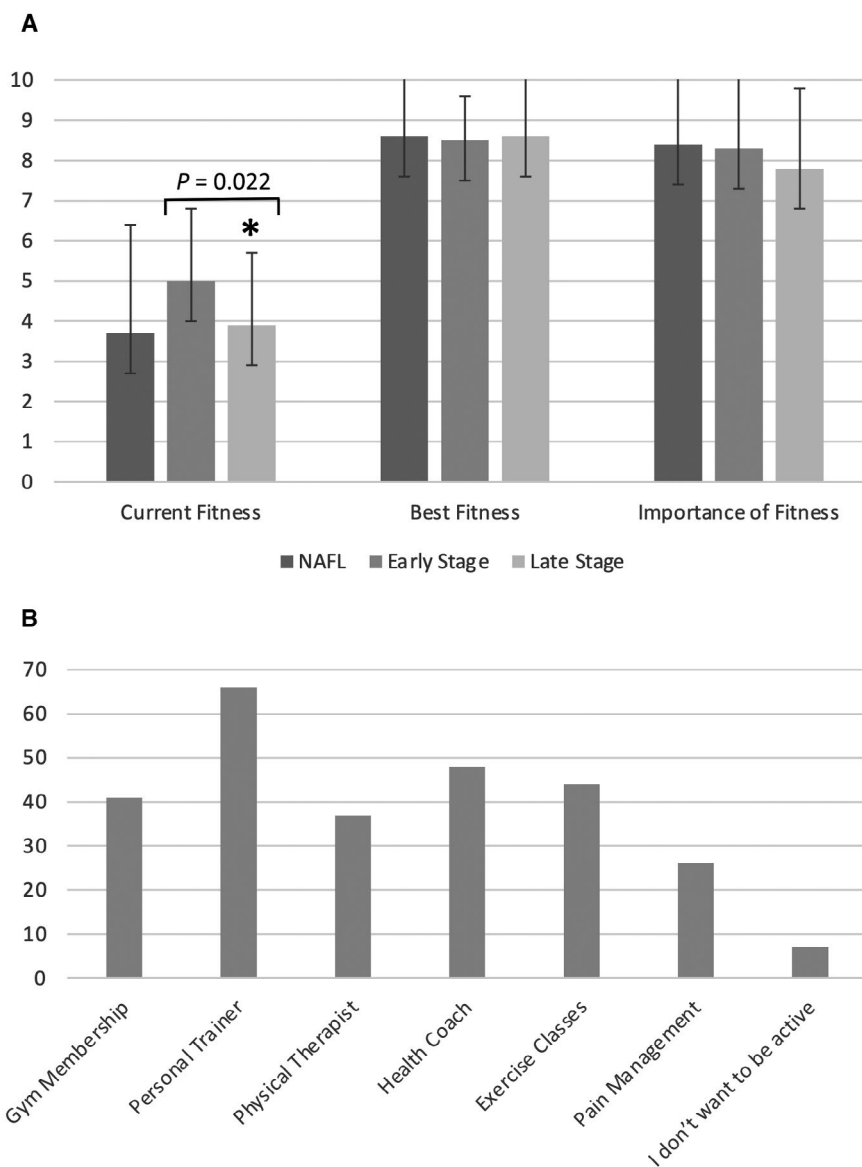


FIG. 2. Fitness levels and fitness-related services that would increase the desire and/or ability for patients with NAFLD to be more physically active. (A) Current, best, and importance of fitness in NAFL, early stage NASH, and late-stage NASH, using a 1-10 scale. Means are presented with SD; **P* < 0.05. (B) Proportion of responses to fitness-related services from patients with NAFLD.

LIMITATIONS TO PHYSICAL ACTIVITY OR EXERCISE

Limitations to physical activity or exercise was indicated by 72% of patients with NAFLD (Table 2), and 27% responded that their limitations to physical activity or exercise were due to medications. In order to further understand the types of limitations to physical activity or exercise, we asked participants to choose from a prespecified list of 12 physical, behavioral, psychosocial, and environmental-based options. The greatest proportion of patients with NAFLD reported limitations as lack of energy (62%) and fatigue (61%) followed by prior/current Injury (50%), shortness of breath (49%), discomfort (47%), physical ability (46%), and pain (44%) (Table 2). The lowest proportion of limitations included lack of access (7%) and cost (17%). As an exploratory analysis, we evaluated differences in limitations due to disease severity in NAFL, early stage NASH, and late-stage NASH. There were significant differences between early stage and late-stage NASH for lack of energy ($P = 0.036$) and shortness of breath ($P = 0.004$). Compared to early stage NASH, NAFL also indicated greater reporting of shortness of breath ($P = 0.004$).

SOLUTIONS TO INCREASE PHYSICAL ACTIVITY AND/OR EXERCISE

Initiating and maintaining physical activity behaviors in those with NAFLD can be supported by gym memberships and access to fitness instructors or personal trainers.⁽²⁰⁾ In order to identify fitness-related services that would increase the desire and/or ability for patients with NAFLD to be more physically active, we asked survey participants to choose from a prespecified list of fitness-related services with brief descriptions of each. The majority of responders (66%) chose a personal trainer, followed by a health coach (48%); exercise classes offered at work, church, or community groups (44%); gym membership (41%); and physical therapist (37%). Pain management had the least proportion of responses at 26%. Only 7% indicated that they did not want to be more physically active (Fig. 2B).

PERCEPTION OF EXERCISE AS A FOUNDATIONAL TREATMENT OF NAFLD

Attitudes and acceptance of exercise as a bona fide treatment option for NAFLD have not been assessed.

TABLE 2. LIMITATIONS TO PHYSICAL ACTIVITY AND EXERCISE IN PATIENTS WITH NAFLD

	NAFLD (n = 94)	NAFL (n = 12)	Early Stage (n = 23)	Late Stage (n = 59)	PValue*
Limitations to physical activity/exercise, % yes	72	86	57	77	0.170
Limitations of physical activity/exercise due to medications, % yes	27	50	22	24	0.215
Limitations, % yes					
Pain	44	58	48	39	0.420
Physical ability	46	50	44	51	0.228
Fatigue	61	67	52	63	0.613
Discomfort	47	67	43	44	0.333
Lack of energy	62	67	39	69	0.036
Cost	17	17	4	22	0.160
Time	31	25	39	27	0.524
Lack of access	7	8	4	8	0.809
Lack of interest	32	8	35	36	0.172
Lack of enjoyment	31	17	44	32	0.809
Prior/current injury	50	50	57	47	0.762
Shortness of breath	49	58	17	59	0.002
No limitations to exercise	7	8	13	6	0.464

* P value significant at <0.05 .

TABLE 3. PREFERENCE FOR EXERCISE, MEDICATION, OR NEITHER AS TREATMENT FOR NAFLD

Response Choice	Proportion Yes, %
Exercise	
No medication side effects	63
Mild medication side effects	68
Moderate medication side effects	88
Severe medication side effects	94
Medication	
No medication side effects	36
Mild medication side effects	27
Moderate medication side effects	7
Severe medication side effects	1
Neither	
No medication side effects	1
Mild medication side effects	5
Moderate medication side effects	4
Severe medication side effects	5

We asked participants whether they would choose exercise, medication, or neither to treat their NAFLD. Overall, 63% of patients with NAFLD preferred exercise over medication, with only 1% choosing neither (Table 3). We then asked whether medication side effects would influence the proportion of patients that choose exercise. The preference to exercise increased for the additional questions that qualified medication side effects as follows: mild (68%), moderate (88%), or severe (94%) side effects.

FACTORS INFLUENCING PHYSICAL ACTIVITY BEHAVIOR

As an exploratory analysis, we evaluated factors influencing physical activity behavior (total METs per week) in patients with NAFLD. In univariate analysis, positive correlations of total METs per week were found with ALT ($r = 0.30$, $P = 0.005$), current fitness level ($r = 0.36$, $P = 0.0004$), and importance of fitness ($r = 0.18$, $P = 0.084$) (Table 4). Negative correlations were found with age ($r = -0.38$, $P = 0.0002$), sit time ($r = -0.30$, $P = 0.003$), and the total number of limitations to physical activity or exercise ($r = -0.26$, $P = 0.010$). Having participated in some vigorous activity ($P = 0.009$), being a male participant ($P = 0.060$), and early or late-stage NASH ($P = 0.054$) were associated with higher total METs per week. Limitations to physical activity or exercise ($P = 0.0029$), including

TABLE 4. UNIVARIATE ANALYSIS OF FACTORS ASSOCIATED WITH TOTAL WEEKLY METs IN PATIENTS WITH NAFLD

Continuous Predictors	<i>r</i>	<i>P</i> Value*
Age	-0.38	0.0002
BMI	-0.11	0.318
AST	0.09	0.407
ALT	0.30	0.005
Sit time	-0.30	0.003
Number of limitations to physical activity/exercise	-0.26	0.010
Current overall fitness	0.36	0.0004
Importance of fitness	0.18	0.084
Best fitness level	0.07	0.491
Categorical Predictors	Test Statistic	<i>P</i> Value*
Sex (M/F)	3.54	0.060
Race	1.92	0.750
Ethnicity	0.23	0.631
Smoking status	0.07	0.788
Diabetes status	1.9	0.386
NAFLD stage (NAFL, early stage, late stage)	5.82	0.054
Limitation to physical activity/exercise	11.67	0.003
Specific limitation		
• Pain	2.75	0.097
• Physical ability	4.05	0.044
• Fatigue	4.77	0.029
• Discomfort	5.00	0.025
• Lack of energy	8.60	0.003
• Cost	0.05	0.815
• Lack of time	2.50	0.114
• Lack of access	1.63	0.202
• Lack of interest	2.20	0.138
• Lack of enjoyment	0.26	0.607
• Prior/current injury	-2.37	0.124
• Shortness of breath	4.64	0.031

**P* value significant at <0.05 .

Abbreviations: F, female; M, male.

physical ability ($P = 0.044$), fatigue ($P = 0.029$), discomfort ($P = 0.025$), lack of energy ($P = 0.003$), and shortness of breath ($P = 0.031$) were associated with lower total METs per week.

Because 27% of survey participants reported no physical activity behavior, we used candidate predictors in a generalized linear model to determine factors associated with higher METs per week among those reporting some level of physical activity or exercise. Age ($P = 0.0002$) was negatively associated with total METs per week, while early stage NASH ($P = 0.001$) and late-stage ($P = 0.007$) NASH were positively associated with total METs per week (Table 5).

TABLE 5. MULTIVARIATE ANALYSIS OF FACTORS ASSOCIATED WITH TOTAL WEEKLY MET'S IN PATIENTS WITH NAFLD

	Estimate	SE	95% CI	Chi-Square	PValue*
Age	-0.05	0.01	-0.07 to 0.02	13.69	0.0002
BMI	-0.05	0.03	-0.11 to 0.01	2.51	0.113
Early stage (vs. NAFL)	1.30	0.41	0.50-2.10	10.23	0.001
Late stage (vs. NAFL)	1.00	0.37	0.27-1.72	7.16	0.007
Diabetes (vs. prediabetes)	0.50	0.51	-0.49 to 1.49	0.97	0.325
No diabetes (vs. prediabetes)	0.45	0.48	-0.48 to 1.39	0.91	0.341
Sit time	0.01	0.001	-0.001 to 0.001	0.02	0.886
Current fitness	0.16	0.08	-0.002-0.31	3.72	0.054
Importance of fitness	-0.05	0.07	-0.18 to 0.09	0.45	0.502
Vigorous activity (yes)	0.74	0.65	-0.53 to 2.00	1.31	0.253
Moderate activity (yes)	0.27	0.59	-0.88 to 1.41	0.21	0.651
Medication limitation	0.36	0.34	-0.31 to 1.03	1.1	0.294
Total number of limitations	-0.06	0.05	-0.16 to 0.04	1.27	0.261
Intercept	9.87	1.74	6.46-13.27	32.29	<0.001
Scale parameter	1.35	0.22	0.99-1.84		

*P value significant at <0.05.

Abbreviations: CI, confidence interval; SE, standard error.

Discussion

There has been increasing interest to leverage the independent effects of exercise in order to improve liver-related outcomes in NAFLD.⁽²¹⁾ However, the majority of patients with NAFLD are unable to initiate and maintain effective exercise habits, creating significant barriers to implementation of exercise as a standard of care treatment. As NAFLD progresses, it may become more difficult for patients to exercise due to metabolic changes in skeletal muscle and liver/muscle energy homeostasis, which can become exacerbated by behavioral factors.⁽²²⁾ Compared to individuals with obesity and those with type II diabetes, patients with NASH have poorer liver adenosine triphosphate (ATP) recovery as well as heart rate recovery from exercise.^(23,24) The difficulty for patients with NAFLD to exercise does not appear to come from a lack of desire to be physically active. The majority of patients with NAFLD in our study prefer exercise as a treatment option for NAFLD over pharmacotherapy.

We observed that despite similar sedentary behavior, patients with NAFL, early stage NASH, or late-stage NASH have considerable variability in both intensity and duration of weekly physical activity. Cross-sectional studies suggest that vigorous and moderate intensity exercise is associated with less severe NASH.^(6,25) Thus, we expected that later stage

patients with NASH would report less vigorous, moderate, walking, and total exercise than NAFL or those with early stage NASH.⁽¹⁶⁾ In our study, patients with late-stage NASH reported lower vigorous, walking, and total weekly physical activity compared to patients with early stage NASH. Surprisingly, our NAFL group was more similar in exercise habits to patients with later stage NASH than early stage NASH. One reason is that our sample size in NAFL was potentially too small and captured the lowest proportion of the variability seen in physical activity habits of patients with NAFLD. A larger sample size would provide a better representation of actual physical activity levels of the NAFL group. The variability in the self-reported exercise habits across the spectrum of patients with NAFLD in our study mirrors much of the variability of standard of care responses in NAFLD clinical trials.⁽²⁶⁾ Efforts to standardize recommendations of exercise in clinical trials of NAFLD will need to consider variance in baseline physical activity of patients with NAFLD and evaluate limitations and challenges to exercise in those reporting no physical activity.⁽²⁷⁾ Further studies will need to determine key drivers to variability in physical activity habits among patients with NAFLD.

While self-reported physical activity and exercise provide a window into physical activity habits, of equal importance is the culmination of physical activity

behavior into a state of being or fitness.⁽¹⁷⁾ Health-related fitness is suboptimal across the spectrum of NAFLD, despite not being associated with severity of steatosis or fibrosis groups.⁽²⁵⁾ Current fitness level in our patients with NAFLD was approximately half of mean “best” fitness level and similar to total weekly physical activity levels. Reductions in fitness levels are typical as one ages, and progression of NASH may worsen this effect.⁽²⁸⁾ Our exploratory univariate and multivariate analyses support the negative association between age and weekly physical activity behavior. Further studies may provide greater insight to the relationship between fitness and physical activity in patients with NAFLD. Additionally, self-reported fitness level may provide a simpler method for clinicians to assess the impact of physical activity behavior on overall physical function and feeling rather than measuring individual weekly exercise intensities to ascertain health-related fitness or performing a cardiopulmonary exercise test.

In our study, an overwhelming majority of patients with NAFLD indicated that they have limitations to exercise, with the greatest proportion of limitations in physiologic factors, including lack of energy, fatigue, and shortness of breath. Limitations in these physiologic factors implicate potential deficiencies in cardiorespiratory fitness and mitochondrial function, resulting in lower resting fatty acid oxidation and depletion of ATP.^(29,30) Additionally, our exploratory analyses indicate that lack of energy, fatigue, and shortness of breath are negatively associated with weekly physical activity, and a higher proportion of patients with late-stage NASH have limitations in lack of energy and shortness of breath. Cardiorespiratory fitness is inversely associated with NAFLD severity; however, the contribution of mitochondrial dysfunction is not clear.⁽¹⁶⁾ It is possible that patients with late-stage NASH have greater mitochondrial dysfunction attributing to lack of energy and shortness of breath. The key limitations in our study are in contrast to prior work in type II diabetes that indicates “lack of time, obligations to others, inability to link exercise with [underlying disease], lack of perception of obesity as a health issue, inadequate emphasis by physicians, social/cultural issues, lack of infrastructure, and physical restriction” as limitations and challenges to physical activity or exercise.⁽³¹⁾ Considering the lowest proportion of limitations and challenges in our study were lack of access and cost, addressing underlying physiologic limitations may need to be prioritized among patients with NAFLD.

It is essential to consider appropriate supportive fitness-related services when seeking to increase the desire and/or ability for patients with NAFLD to be more physically active. Our cohort of patients with NAFLD indicated a preference toward personal training. Personal training provides a one-to-one opportunity for a fitness instructor to address concerns with exercise and tailor appropriate scaling options; however, personal training can be expensive and not always available to patients. The advent of in-home training options with interactive fitness equipment has dramatically changed the landscape of personal training by providing an economical and convenient option to exercise. Future studies evaluating the feasibility of virtual and at-home fitness instruction may allow for increased physical activity and exercise behaviors in NAFLD.

Our study has several limitations. First, the majority of our survey participants had later stage NASH compared to early stage NASH and NAFL, and thus our results may not be reflective of patients with NAFLD with earlier stage disease. Second, self-reported physical activity and exercise behaviors tend to be over reported by individuals with obesity, and the actual exercise behavior of patients with NAFLD may be less than what is reported in this study.⁽³²⁾ Third, only 29% of our survey participants self-reported no physical activity, which is much less than what has been previously identified.⁽⁶⁾ Thus, our results may be reflective of a more active NAFLD population.

Patients with NAFLD have physiologic and behavioral limitations to physical activity and exercise that impact their ability to initiate and sustain exercise. These limitations may worsen with disease progression. Given the significant variability in self-reported NAFLD physical activity behavior and unique limitations, tailored approaches to increase physical activity and decrease sedentary behavior will need to be considered. Personal training exercise that can be delivered in the home while also providing group interaction may be one of the most effective strategies to maintain healthy exercise behaviors in the long term.

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Author names in bold designate shared co-first authorship.

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