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ORIGINAL ARTICLE

Improvement in cognitive impairment following a 12-week aerobic exercise intervention in individuals with non-cirrhotic chronic hepatitis C

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Abstract

Cognitive impairment occurs in 30%–50% of patients with non-cirrhotic chronic hepatitis C virus (HCV) infection. Exercise is beneficial in preventing and treating cognitive impairment and cardiometabolic abnormalities in many chronic inflammatory diseases, but there are few studies investigating the impact of exercise in HCV infection. The study aimed to assess the effect of a 12-week aerobic exercise intervention on cognition and extrahepatic manifestations in individuals with HCV. In this nonrandomized controlled pilot study, individuals with HCV participated in a 12-week aerobic exercise intervention. Outcome measures included cognition (Montreal Cognitive Assessment [MOCA], Trail Making Test A & B [TMT-A; TMT-B], Digit Symbol Test [DST]), cardiorespiratory fitness (estimated $\dot{V}O_{2max}$), physical activity (accelerometry),

Abbreviations: ACE-R, Addenbrooke's cognitive examination—revised; BDI, Beck's depression inventory; BDNF, brain-derived neurotrophic factor; BMI, body mass index; BNCS, brief neurocognitive screening; CNS, central nervous system; CRP, C-reactive protein; CVD, cardiovascular disease; DAA, direct-acting antiviral; DST, digit symbol test; ESR, erythrocyte sedimentation rate; FAB, frontal assessment battery; FSS, fatigue severity scale; GLUF, fasting plasma glucose; HbA1c, glycated haemoglobin; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IL-1β, interleukin 1β; IL-6, interleukin 6; LFTs, liver function tests; LNS, letter number sequencing; MD, mean difference; MOCA, Montreal cognitive assessment; NAFLD, non-alcoholic fatty liver disease; PSQI, Pittsburgh sleep quality index; RBANS, repeat battery assessment of neuropsychological status; T0, baseline assessment; T1, week 13 assessment; T2, 12-week follow-up reassessment; T2DM, type 2 diabetes mellitus; TMT-A, trail making test A; TMT-B, trail making test B; TNF-α, tumour necrosis factor α; $\dot{V}O_{2max}$, maximal oxygen consumption.

anthropometry, quality of life (depression; fatigue; sleep quality) and biochemical markers. Outcomes were assessed at baseline (T0), intervention completion (T1) and 12 weeks after intervention completion (T2). Thirty-one patients completed the study (exercise group n = 13, control group n = 18). In the exercise group, cognition improved at T1 in the TMT-A (31% mean improvement, $p = 0.019$), TMT-B (15% mean improvement, $p = 0.012$) time and MOCA (14% mean improvement, $p \leq 0.001$). These improvements were not maintained at T2. Depression ($p = 0.038$), sleep quality ($p = 0.002$), fatigue ($p = 0.037$) and estimated $\dot{V}O_{2max}$ (7.8 mL kg^{-1} min^{-1} [22%] mean increase, $p = 0.004$) also improved at T1. In conclusion, this study demonstrates the benefits of a 12-week aerobic exercise intervention in improving cognition, quality of life and cardiorespiratory fitness in individuals with HCV. Larger studies are needed to confirm these findings and strategies for continued exercise engagement in individuals with HCV are warranted for sustained benefits.

KEYWORDS
aerobic exercise, cardiorespiratory fitness, cognitive impairment, exercise intervention, hepatitis C

1 | INTRODUCTION

The hepatitis C virus (HCV) is one of the most common causes of chronic liver disease worldwide,[1] with approximately 70%–75% of patient cases progressing to chronicity.[2] Individuals with HCV infection may develop hepatic fibrosis, cirrhosis and hepatocellular carcinoma.[2] Individuals with HCV may also develop extrahepatic manifestations including metabolic syndrome,[3] cardiovascular disease (CVD),[4] insulin resistance[4] and poor self-reported quality of life.[5–7] Furthermore, approximately 30%–50% of individuals with non-cirrhotic chronic HCV may develop cognitive impairment.[8] This is unrelated to genotype, viral load or substance abuse history.[8] The precise pathophysiological mechanisms underpinning cognitive impairment in HCV infection are unclear, but are postulated to include: (i) direct viral infiltration of the central nervous system (CNS) via a 'trojan horse' mechanism in infected monocytes[8]; and/or (ii) a viral-induced inflammatory cascade.[8]

The beneficial effects of exercise and physical activity for the treatment and management of many chronic inflammatory diseases such as CVD, type 2 diabetes mellitus (T2DM), metabolic syndrome, and cancer are well established.[9–12] Exercise and physical activity may also improve cognition in older adults,[13] individuals with mild cognitive impairment,[13] and in many chronic disease cohorts[14] presenting with cognitive impairment including cancer[15] and human immunodeficiency virus (HIV).[16] Additionally, exercise improves disease-related symptoms of depression, fatigue and sleep quality.[17–19] The precise type of exercise (aerobic, resistance or combination) and prescription (frequency, duration, intensity) needed to improve cognition is unclear, but cross-sectional studies have highlighted the cognitive benefits of improving cardiorespiratory fitness.[20–22] Increasing cardiorespiratory fitness, the physiological manifestation of aerobic exercise participation, is reported to have CNS benefits in HIV[22] and multiple sclerosis[23] cohorts, and has been associated with greater hippocampal volume,[24] and executive function.[25] The proposed physiological mechanisms resulting in improved cognition as a consequence of increased aerobic exercise participation and improved cardiorespiratory fitness are unknown. However, exercise-induced neuromodulation,[26,27] increased neurotrophic factor concentration such as brain-derived neurotrophic factor (BDNF),[28] increased brain volumes,[29] reduced inflammation[30] and reduced cardiovascular and cerebrovascular risk factors[26] have been described.

Although exercise is feasible and safe for individuals with HCV to undertake, the direct benefits of exercise in HCV remain unclear. Additionally, despite evidence that aerobic exercise may improve cognition in other chronic disease populations, no study to date has reported the effects of an aerobic exercise intervention on cognition in individuals with HCV.

The primary objective of this study was to determine the effects of a 12-week moderate-to-vigorous intensity aerobic exercise intervention on cognition in direct-acting antiviral (DAA)-naïve patients with non-cirrhotic chronic HCV. Secondary objectives were as follows: (i) to determine the impact of the exercise intervention on depression, fatigue and sleep quality; (ii) to determine the impact of the exercise intervention on cardiorespiratory fitness, anthropometry, vascular health, glucose and lipid metabolism, and BDNF and inflammatory cytokine concentrations; and (iii) to determine the sustainability of the exercise intervention on outcomes 12 weeks post-exercise intervention completion.

2 | MATERIALS AND METHODS

2.1 | Ethics declaration

The study was approved by the St. James's and Tallaght University Hospital Joint Research Ethics Committee. Written informed consent was obtained from all patients and the study was conducted in accordance with the guidelines outlined in the Declaration of Helsinki, 2013.[31] Recruitment and follow-up occurred between January 2017 and June 2019.

2.2 | Participants

Thirty-one patients with non-cirrhotic chronic HCV (mean age: 40 ± 8 years, mean body mass index [BMI]: 26.5 ± 4.8 kg/m^2, male/female n: 18/13) who were DAA-naïve attending the hepatology outpatient clinic at St James's Hospital, Dublin, Ireland completed the intervention (exercise group, n = 13, control group, n = 18). Prior to enrolment in the study, participants were screened for suspected cognitive impairment using the brief neurocognitive screening (BNCS) battery consisting of the: (i) trail making tests part A and B (TMT-A; TMT-B); and (ii) the digit symbol test (DST).[32] Inclusion criteria were as follows: (i) aged ≥18 years; (ii) HCV mono-infection; (iii) non-cirrhotic (liver stiffness measurement ≤12.5 kPa); (iv) the ability to attend bi-weekly exercise classes in St James's Hospital, Dublin, Ireland for 12 weeks; and (v) a positive screen for suspected cognitive impairment via the BNCS (score ≥2 standard deviations below normative ranges in ≥one test or ≥1 standard deviation below normative ranges in ≥two tests). Normative values were taken from two sources[33,34] in accordance with the study by McNamara et al.,[32] and ranges are presented in Table S1. Exclusion criteria were as follows: (i) contraindications to exercise testing or prescription[9]; (ii) significant orthopaedic or neuromuscular limitations; (iii) unwillingness to participate; and (iv) a history of head injury or other neurological conditions. Participants that failed the BNCS underwent an in-depth neuropsychological assessment with a psychologist trained in neuropsychological testing (OS) and had a medical screen to exclude any uncontrolled cardiopulmonary disease or other contraindications to exercise testing or prescription as outlined in the American College of Sports Medicine guidelines.[9] Participant recruitment and attrition rates are presented in Figure 1.

2.3 | Study design

This study was a nonrandomized controlled pilot study which formed part of a larger study titled: Viral Hepatitis C Associated Neurocognitive Dysfunction in Ireland in the DAA era', funded by the Health Research Board, Ireland (HRA-POR-2015-1185), which aimed to (i) determine the prevalence of suspected cognitive impairment in Irish individuals with HCV; and (ii) determine if cognitive impairment is ameliorated following DAA-induced HCV eradication compared to a formal exercise intervention. A total of 709 eligible individuals were screened for suspected cognitive impairment. Of these 709 individuals, 334 had evidence of cognitive impairment, and 178 met the inclusion criteria and were eligible to participate. Of these 178 individuals, 135 completed the baseline in-depth neuropsychological assessment with a psychologist trained in neuropsychological testing (OS). Of these 135 individuals, 69 were allocated to the DAA group whose results are not included in this study. Of the remaining 66 individuals, 24 failed to engage in the baseline physical assessment. Following baseline physical assessments (T0), the remaining 42 individuals were allocated to an exercise group (n = 23) or control group (n = 19), based on participants' individual preference. Individual preference was chosen as this was a proof of concept study and consultation with patient representatives highlighted that group preference was important for individuals with HCV. Participants in the exercise group then embarked on the exercise intervention which comprised 3–5 aerobic exercise sessions per week (2 exercise specialist/physiotherapist-led supervised exercise sessions and 1–3 unsupervised exercise sessions), for 12 weeks in a dedicated hospital-based clinical research facility. The control group received standard care. Participants in the exercise and control group did not receive DAA therapy during the exercise study. The aerobic exercise intervention is further detailed in *Supplementary Methods*. Following completion of the intervention, all participants were reassessed at week 13 (T1). Participants in the exercise group were then encouraged to continue exercise, participation but no formal intervention was prescribed or monitored. All participants were then reassessed 12 weeks after intervention completion (T2), to determine if any changes in outcomes were sustained longitudinally. For each assessment timepoint (T0-T2), participants were requested to avoid strenuous physical activity, caffeine and alcohol intake for 24 hours prior to each assessment and fast for 12 hours prior to each assessment to ensure standardization of each assessment timepoint. All assessments and timepoints are detailed in Table 1.

2.4 | Neuropsychological assessment

Cognition was assessed using a combination of both brief and in-depth neuropsychological testing. The BNCS (TMT-A; TMT-B; DST)[32] and the Montreal cognitive assessment (MOCA)[35] were employed as brief cognitive screening tests. The TMT assesses visuomotor skill, processing speed, attention and mental flexibility.[32] Part A requires participants to connect a series of numbers in ascending order as quickly as possible, while part B involves connecting both 13 numbers and 12 letters in ascending and alphabetical order as quickly as possible. The DST assesses divided attention, tracking, motor speed and visuospatial scanning.[32] This test requires participants to match as many numbers with the corresponding symbols according to a provided key, in 90 seconds. The MOCA assesses visuospatial, executive function, immediate and delayed memory, attention, language, abstraction and orientation cognitive domains.[35] A randomized version of the MOCA was administered at each timepoint to minimize a practice effect. Brief neuropsychological testing was conducted at all timepoints (T0-T2).

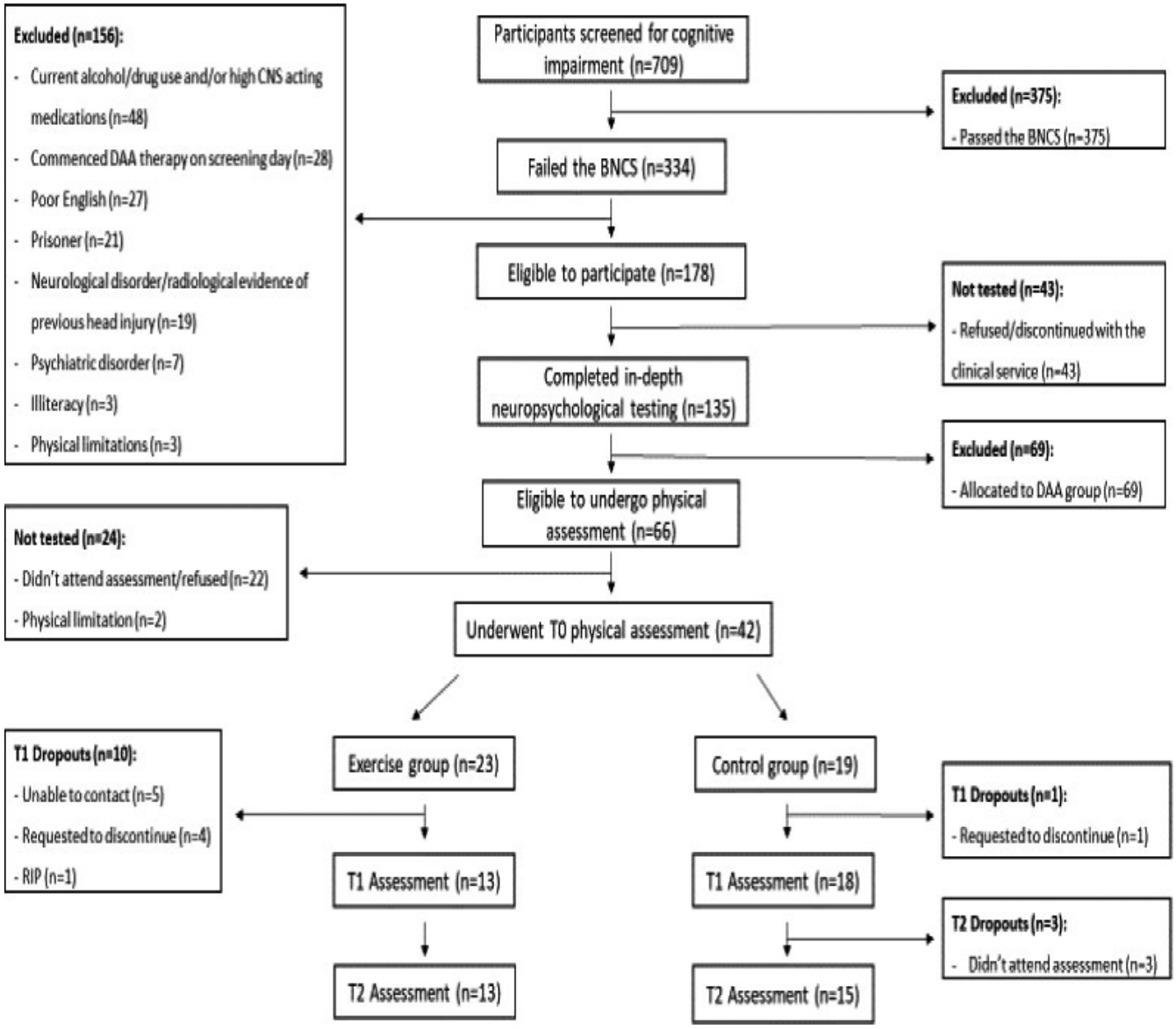

FIGURE 1 Participant recruitment and attrition flow-chart. BNCS, Brief Neurocognitive Screening; CNS, Central Nervous System; DAA, Direct-Acting Antiviral; RIP, Participant died during the study period; T0, Baseline assessment; T1, Week 13 (intervention completion) assessment; T2, 12-week follow-up assessment

The in-depth neuropsychological assessment was conducted at T0 and T2. Four tests were administered: (i) the Repeated Battery Assessment of Neuropsychological Status (RBANS)[36]; (ii) the Addenbrooke's Cognitive Examination – Revised (ACE-R)[37]; (iii) the Frontal Assessment Battery (FAB)[38]; and (iv) the Letter Number Sequencing (LNS).[39] The in-depth neuropsychological assessment protocol is detailed in *Supplementary Methods*.

2.5 | Sleep quality, fatigue and depression assessment

Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI).[40] The PSQI is a validated self-reported questionnaire that assesses sleep quality in the previous month. A score of 5/21 or more indicates poor sleep quality.[40] Fatigue was assessed using the Fatigue Severity Scale (FSS)[41]. The FSS is a validated, self-reported questionnaire that assesses fatigue experienced in the previous week. Depression was assessed using Beck's Depression Inventory (BDI)[42]. The BDI is a validated self-reported questionnaire that assesses the presence and severity of depressive symptoms in the previous four weeks. Sleep quality, fatigue and depression were assessed at T0 and T1.

2.6 | Cardiorespiratory fitness and physical activity assessment

Cardiorespiratory fitness was assessed using the Modified Bruce submaximal cardiopulmonary exercise test protocol on an electrically

TABLE 1 Study outcome timepoints

		T0 Assessment	T1 Assessment	T2 Assessment
Timepoints		**Week 0**	**Week 13**	**Week 24**
Study Assessments	Participant Demographics	X		
	BNCS	X	X	X
	MOCA	X	X	X
	Blood Sampling	X	X	X
	Physical activity	X	X	X
	Body mass and BMI	X	X	X
	Vascular health	X	X	
	Body composition	X	X	
	Cardiorespiratory exercise test	X	X	
	PSQI, FSS and BDI questionnaires	X	X	
	In-depth neuropsychological assessment	X		X

Abbreviations: BDI, Beck's Depression Inventory; BMI, Body Mass Index; FSS, Fatigue Severity Scale; MOCA, Montreal Cognitive Assessment; PSQI, Pittsburgh Sleep Quality Index; T0, Baseline assessment; T1, Week 13 (intervention completion) assessment; T2, 12-week follow-up assessment BNCS, Brief Neurocognitive Screening.

driven treadmill (COSMED T150, DE)[43] to give estimates of maximal oxygen consumption ($\dot{V}O_{2max}$). Physical activity was assessed using a tri-axial accelerometer (Actigraph GT3X+, Actigraph Corp, USA). The accelerometer recorded data at 30 Hz for seven consecutive days during participants' waking hours and was worn on the right hip and secured using an elasticated waistband. Cardiorespiratory fitness was assessed at T0 and T1, and physical activity was assessed at all timepoints (T0-T2). The cardiopulmonary exercise test, $\dot{V}O_{2max}$ estimation and physical activity assessment protocols are detailed in *Supplementary Methods*.

2.7 | Cardiometabolic health assessment

Standing height was assessed using a wall-mounted vertical stadiometer, and body mass was measured using a digital scale. Measures of fat mass and skeletal muscle mass were assessed using bioimpedance analysis (Seca mBCA 515, Seca, Germany). Participants were requested to void their bladder and bowels prior to bioimpedance analysis to ensure standardization of measurements. To determine the degree of central obesity, waist circumference and hip circumference were measured using a non-stretch measuring tape around the bare abdomen and widest part of the hips, respectively, and waist-to-hip ratio was subsequently calculated. Fasting venous blood samples were collected to measure liver function tests (LFTs), lipid profiles, fasting plasma glucose (GLUF), glycated haemoglobin ($HbA1_c$) and circulating inflammatory markers (C-reactive protein, CRP; erythrocyte sedimentation rate, ESR; BDNF; tumour necrosis factor-alpha, TNF-α; interleukin 6, IL-6 and interleukin 1-beta, IL-1β). BDNF, TNF-α, IL-6 and IL-1β concentrations were measured using DuoSet ELISA kits (R&D Systems, USA) and plates were read spectrophotometrically at 450 nm using a VersaMax plate reader. Bioimpedance and measures of central obesity were assessed at T0 and T1, and all remaining cardiometabolic assessments were assessed at all timepoints (T0-T2).

2.8 | Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences software version 25. Data were assessed for normality using the Shapiro-Wilk test. Baseline between-group differences were assessed using independent *t* tests or Mann-Whitney *U* tests for normal and non-normal data, respectively. Time by group interactions between T0 and T1 and T0 and T2 were assessed using a two-way repeated-measures analysis of variance. Paired *t* tests or Wilcoxon signed-rank tests were used to assess within-group differences for repeated measures for normal and non-normal continuous data, respectively. McNemar's test was used to assess within-group differences for repeated measures for categorical data. Measures of effect size were calculated using partial eta^2 (η^2) and defined as small (0.01), medium (0.06) or large (0.14)[44]. Where appropriate, missing data are noted on each respective table and figure. Continuous data are displayed as mean (standard deviation) or median (interquartile range) for normal and non-normal data, respectively. Categorical data are displayed as number (percentage). Statistical significance for all tests was set at $p \leq 0.05$.

3 | RESULTS

3.1 | Baseline characteristics

Of the 42 participants who completed the T0 assessment, 31 completed the intervention (exercise group n = 13; control group n = 18, Figure 1). There were no significant differences in

TABLE 2 Baseline participant characteristics

Variable	Exercise group (n = 13)	Control group (n = 18)	Between-group *p* value
Age, years‡	42 (9)	38 (8)	0.293[a]
Sex, n (%n)			0.483[c]
Male	9 (69)	9 (50)	
Female	4 (31)	9 (50)	
Education, years†	12 (4)	13 (5)	0.115[b]
Smoking status, n (%n)			1.000[d]
Current smoker	7 (54)	8 (44)	
Former smoker	3 (23)	5 (28)	
Non smoker	3 (23)	5 (28)	
Years since HCV diagnosis‡	9.4 (6.9)	11.8 (8.6)	0.405[a]
Mode of infection, n (%n)			1.000[c]
IVDA	8 (62)	10 (56)	
No identifiable risk factors	5 (38)	8 (44)	
Substance misuse history, n (%n)			0.333[d]
None	5 (39)	7 (39)	
Past	8 (61)	8 (44)	
Current	0 (0)	3 (17)	
Methadone maintenance, n (%n)			0.701[d]
Yes	5 (39)	5 (28)	
No	8 (61)	13 (72)	
Viral load (copies/mL)†	966,337 (1,714,096)	468,745 (1,610,947)	0.708[b]
Genotype, n (%n)			0.840[d]
1 (a/b)	8 (62)	13 (72)	
3	4 (31)	4 (22)	
4	1 (8)	1 (6)	
Hepatic stiffness (kPa)†	5.5 (2.0)	5.3 (1.2)	0.258[b]
Body mass index (kg/m2)†	25.1 (6.8)	25.9 (5.8)	0.594[b]
Cardiorespiratory fitness level, n (%n)$			0.714[d]
Below average	5 (38)	9 (52)	
Average	4 (31)	4 (24)	
Above average	4 (31)	4 (24)	
Self-reported fatigue			
FSS global score†	41 (23)[1]	44 (24)	0.950[b]
None, n (%n)	1 (9)	0 (0)	0.626[d]
Mild, n (%n)	0 (0)	1 (6)	
Moderate, n (%n)	4 (33)	4 (22)	
Severe, n (%n)	7 (58)	13 (72)	
Self-reported sleep quality			
PSQI global score†	6 (9)	8 (6)	0.594[b]
Poor sleep quality, n (%n)	8 (62)	14 (78)	0.433[d]
Good sleep quality, n (%n)	5 (38)	4 (22)	
Self-reported depression			

(Continues)

TABLE 2 (Continued)

Variable	Exercise group (n = 13)	Control group (n = 18)	Between-group *p* value
BDI global score†	15 (11)	11 (22)[2]	0.680[b]
None, n (%n)	3 (23)	10 (58)	0.109[d]
Mild, n (%n)	4 (31)	2 (12)	
Moderate, n (%n)	4 (31)	1 (6)	
Severe, n (%n)	2 (15)	4 (24)	

Abbreviations: BDI, Beck's Depression Inventory; FSS, Fatigue Severity Scale; IVDA, Intravenous Drug Abuse; PSQI, Pittsburgh Sleep Quality Index.

[1]n = 12.

[2]n = 17.

[a]Independent *t* test.

[b]Mann-Whitney *U* test.

[c]χ^2 test.

[d]Fisher's exact test.

†Median (interquartile range).

‡Mean (standard deviation).

$Defined according to age and gender-adjusted norms by the Cooper Institute for Aerobic Research.[43]

baseline characteristics between the exercise group and control group (Table 2). Participants were diagnosed with multiple coexisting comorbidities including obesity (BMI ≥ 30 kg/m^2, 19%) and metabolic syndrome (26%), and below-average, age and gender-adjusted cardiorespiratory fitness[43] (47%).

3.2 | Intervention adherence

Adherence to the exercise intervention was 76% (supervised sessions = 80% [total sessions = 24], unsupervised sessions = 72% [total sessions = 26]). During the supervised exercise sessions, all participants sustained their prescribed heart rate intensity and fully completed each exercise session duration. During the unsupervised sessions, all participants self-reported as meeting the required intensity, type and duration prescribed each week.

3.3 | Cognition

Between T0 and T1, there was significant time by group interactions in the exercise group compared with the control group, with large effect sizes, for the TMT-A time to completion (31 ± 12% mean improvement, $p = 0.019$, partial $\eta^2 = 0.181$), TMT-B time to completion (15 ± 24% mean improvement, $p = 0.012$, partial $\eta^2 = 0.206$) and the MOCA score (14 ± 10% mean improvement, $p \leq 0.001$, partial $\eta^2 = 0.379$). There were significant within-group improvements in the exercise group at T1 for the TMT-A ($p = 0.002$) and TMT-B ($p = 0.013$) time to completion, the DST score (18 ± 18% mean improvement, $p = 0.004$) and the MOCA score ($p \leq 0.001$) compared to T0. All neuropsychological performance results between T0 and T1 are detailed in Table 3. Between T0 and T2, there were no significant time by group interactions in the exercise group compared with the control group for the TMT-A ($p = 0.538$, partial $\eta^2 = 0.015$) and TMT-B ($p = 0.590$, partial $\eta^2 = 0.012$) time to completion, the DST score ($p = 0.130$, partial $\eta^2 = 0.086$) or the MOCA score ($p = 0.319$, partial $\eta^2 = 0.040$). There was a significant within-group improvement in the DST (mean difference [MD] =7.4 ± 4.4, $p \leq 0.001$) at T2 in the exercise group compared to T0 but there were no significant within-group improvements for the TMT-A (Z = −1.883, $p = 0.060$) and TMT-B (MD = −15.1 ± 27.9 s, $p = 0.087$) time to completion or the MOCA score (MD = −0.2 ± 2.0, $p = 0.790$). Between T0 and T2, there were no significant time by group interactions in the exercise group compared with the control group for any in-depth neuropsychological assessments (Table S3).

3.4 | Quality of life

Between T0 and T1, there were significant time by group interactions in the exercise group, with large effects sizes, compared with the control group for the BDI ($p = 0.038$, partial $\eta^2 = 0.144$), PSQI ($p = 0.002$, partial $\eta^2 = 0.277$) and FSS ($p = 0.037$, partial $\eta^2 = 0.147$). There were also significant within-group improvements in the exercise group at T1 for the BDI ($p = 0.010$), PSQI ($p = 0.001$) and the FSS ($p = 0.041$) scores compared to T0. All quality of life scores between T0 and T1 are detailed in Table 3.

3.5 | Cardiorespiratory fitness and physical activity

In the control group, one participant was contraindicated to undertake the exercise test and was excluded from this analysis. Between T0 and T1, there was a significant time by group interaction in the exercise group compared with the control group, with a large effect size, for estimated$\dot{V}O_{2max}$ (7.8 ± 6.6 mL kg^{-1} min^{-1} [22 ± 19%] mean improvement, $p = 0.004$, partial $\eta^2 = 0.263$). There was a significant within-group improvement in the exercise group for estimated

TABLE 3 Changes in cognition and quality of life outcomes between pre-intervention (T0) and post-intervention (T1) timepoints.

Variable	Exercise Group (n = 13)			Control Group (n = 18)			Time X Group Interaction
	T0	T1	*p* value	T0	T1	*p* value	*p* value (partial η2)
TMT-A (s)†	43 (11)[1]	27 (10)[1]	**0.002**[a,**]	38 (23)	36 (14)	0.349[a]	**0.019 (0.181)**[§]
TMT-B (s)‡	103 (33)[1]	82 (16)[1]	**0.013**[b,*]	109 (32)	121 (50)	0.194[b]	**0.012 (0.206)**[§]
DST‡	40 (13)	46 (15)	**0.004**[b,**]	44 (13)	48 (14)	**0.002**[b,**]	0.148 (0.071)
MOCA‡	23.4 (2.3)	26.4 (1.3)	**≤0.001**[b,***]	23.2 (3.6)	22.7 (3.9)	0.359[b]	**≤0.001 (0.379)**[§§§]
Visuospatial†	3.0 (1.5)	5.0 (1.0)	**0.011**[a,*]	4.0 (2.0)	3.0 (2.3)	**0.034**[a,*]	**≤0.001 (0.381)**[§§§]
Naming†	3.0 (0.0)	3.0 (0.0)	1.000[a]	3.0 (0.0)	3.0 (1.0)	0.480[a]	0.603 (0.009)
Attention†	5.0 (1.0)	5.0 (1.0)	0.317[a]	5.0 (2.3)	5.0 (2.3)	1.000[a]	0.679 (0.006)
Language†	1.0 (1.5)	2.0 (2.0)	0.429[a]	1.0 (1.3)	1.5 (3.0)	0.967[a]	0.471 (0.018)
Abstraction†	2.0 (0.5)	2.0 (0.0)	0.083[a]	2.0 (0.0)	1.5 (1.3)	**0.026**[a,*]	**0.007 (0.231)**[§§]
Delayed Memory†	3.0 (2.0)	4.0 (1.0)	0.058[a]	2.5 (2.5)	3.0 (3.3)	**0.023**[a,*]	0.871 (0.001)
Orientation†	6.0 (0.5)	6.0 (0.0)	0.157[a]	6.0 (0.0)	6.0 (0.3)	1.000[a]	0.471 (0.018)
Pass MOCA, n (%n)	3 (23)	11 (85)	**0.021**[c,*]	4 (22)	5 (28)	1.000[c]	N/A
BDI†	15 (11)	4 (13)	**0.010**[a,**]	11 (22)[2]	11 (17)[2]	0.244[a]	**0.038 (0.144)**[§]
PSQI†	6 (9)	3 (5)	**0.001**[a,***]	8 (6)	7 (6)	0.548[a]	**0.002 (0.277)**[§§]
FSS†	41 (23)[1]	18 (34)[1]	**0.041**[a,*]	44 (24)	42 (29)	0.286[a]	**0.037 (0.147)**[§]

BDI, Beck's Depression Inventory; DST, Digit Symbol Test; FSS, Fatigue Severity Scale; MOCA, Montreal Cognitive Assessment; PSQI, Pittsburgh Sleep Quality Index; T0, Baseline assessment; T1, Week 13 (intervention completion) assessment; TMT-A, Trail Making Test A; TMT-B, Trail Making Test B.

[1]n = 12.

[2]n = 17.

[a]Wilcoxon signed-rank test.

[b]Paired *t* test.

[c]McNemar's test.

†Median (interquartile range).

‡Mean (standard deviation).

§Significant time x group interaction ($p \leq 0.05$).

§§Significant time x group interaction ($p \leq 0.01$).

§§§Significant time x group interaction ($p \leq 0.001$).

*Significant Within-Group Difference ($p \leq 0.05$).

**Significant within-group difference ($p \leq 0.01$).

***Significant within-group difference ($p \leq 0.001$).

$\dot{V}O_{2max}$ ($p = 0.001$) at T1 compared to T0. The time spent in sedentary activity, light physical activity and moderate-to-vigorous physical activity was unchanged in both groups at T1 compared with T0. All cardiorespiratory fitness and physical activity data between T0 and T1 are detailed in Table 4. Between T0 and T2, there were no significant time by group interactions observed in the exercise group compared with the control group for any measures of physical activity.

3.6 | Cardiometabolic markers and liver function tests

Between T0 and T1 and T0 and T2, there were no significant time by group interactions observed in the exercise group compared to the control group for circulating inflammatory markers and BDNF, glucose and lipid regulation, measures of anthropometry and vascular health, and LFTs (Table 4).

4 | DISCUSSION

This study is the first to investigate the effects of a 12-week moderate-to-vigorous intensity aerobic exercise intervention on cognitive and cardiometabolic endpoints in DAA-naïve individuals with non-cirrhotic chronic HCV with suspected cognitive impairment. The main findings were that 12 weeks of aerobic exercise resulted in: (i) significantly improved measures of cognition; (ii) significantly improved self-reported depression, fatigue and sleep quality; (iii) significantly improved estimated $\dot{V}O_{2max}$; (iv) no significant changes

TABLE 4 Changes in cardiorespiratory fitness, physical activity and cardiometabolic outcomes between pre-intervention (T0) and post-intervention (T1) timepoints.

Variable	Exercise Group (n = 13)			Control Group (n = 18)			Time X Group Interaction
	T0	T1	*p* value	T0	T1	*p* value	*p* value (partial η^2)
Estimated $\dot{V}O_{2max}$ (mL kg^2 min^2)†	38.2 (10.1)	46.1 (11.0)	**0.001**[a,***]	35.1 (12.6)[1]	35.6 (11.4)[1]	0.721[a]	**0.004 (0.263)**[§§]
Physical Activity (min/week)							
Sedentary‡	3645 (1685)	2998 (1239)	0.753[b]	3456 (1057)	2911 (1681)	0.248[b]	0.673 (0.006)
Light‡	1799 (1041)	1875 (732)	0.753[b]	1713 (881)	1941 (1105)	0.948[b]	0.745 (0.004)
MVPA‡	203 (255)	149 (441)	0.861[b]	215 (333)	221 (196)	0.862[b]	0.439 (0.021)
MVPA (10-min bouts)‡	78 (272)[2]	57 (333)[2]	0.722[b]	86 (154)	66 (198)	0.501[b]	0.610 (0.009)
Physical Activity (%)							
Sedentary†	61 (12)	59 (9)	0.598[a]	61 (15)	58 (17)	0.368[a]	0.794 (0.002)
Light†	34 (10)	35 (8)	0.628[a]	34 (14)	37 (13)	0.353[a]	0.733 (0.004)
MVPA‡	3.6 (4.6)	3.0 (8.0)	0.382[b]	4.3 (5.8)	4.2 (3.8)	0.647[b]	0.907 (0.000)
MVPA (10-min bouts)‡	1.4 (4.2)[2]	1.1 (5.4)[2]	0.477[b]	1.4 (2.5)	1.3 (4.8)	0.501[b]	0.848 (0.001)
Meeting WHO PA Guidelines, n (%n)	9 (69)	6 (46)	0.375[c]	11 (61)	14 (78)	0.250[c]	N/A
Meeting WHO PA Guidelines (10-Min bouts), n (%n)	3 (25)[2]	4 (33)[2]	1.000[c]	5 (28)	6 (33)	1.000[c]	N/A
Anthropometry							
Body Mass (kg)†	77.9 (18.0)	76.4 (16.6)	0.178[a]	74.8 (12.5)	73.8 (12.5)	0.120[a]	0.684 (0.006)
BMI (kg/m2)‡	25.1 (6.8)	26.1 (5.8)	0.172[b]	25.9 (5.8)	25.5 (5.1)	**0.016**[b,*]	0.773 (0.003)
WC (cm)‡	88 (22)	87 (19)	0.055[b]	87 (13)	85 (11)	0.931[b]	0.196 (0.057)
WHR†	0.89 (0.06)	0.89 (0.09)	0.880[a]	0.85 (0.07)	0.86 (0.08)	0.572[a]	0.652 (0.007)
FM (%)†	32.1 (10.4)	30.3 (9.8)	0.097[a]	29.6 (11.5)	28.2 (10.4)	0.063[a]	0.707 (0.005)
SMM (kg)†	25.6 (6.4)	26.4 (4.3)	0.389[a]	25.5 (5.7)	25.3 (5.4)	0.455[a]	0.233 (0.049)
Vascular Health							
SBP (mm/Hg)†	125 (16)	125 (16)	0.926[a]	120 (10)[1]	120 (13)[1]	0.817[a]	0.945 (0.000)
DBP (mm/Hg)†	88 (17)	83 (11)	0.291[a]	82 (8)[1]	79 (7)[1]	0.103[a]	0.743 (0.004)
TVR (s*mmHg/mL)†	1.29 (0.18)	1.22 (0.17)	0.151[a]	1.21 (0.13)[1]	1.23 (0.19)[1]	0.785[a]	0.307 (0.037)
AI (%)‡	20 (13)	13 (18)	0.100[b]	12 (22)[1]	10 (12)[1]	0.776[b]	0.167 (0.067)
PWV (m/s)†	6.4 (1.1)	6.4 (1.1)	0.779[a]	6.0 (0.7)[1]	6.0 (0.7)[1]	0.736[a]	0.664 (0.007)
Lipid Metabolism							
TC (mmol/L)†	3.58 (0.55)	3.66 (0.54)	0.430[a]	3.80 (0.97	3.92 (0.92)	0.228[a]	0.820 (0.002)
HDL-C (mmol/L)†	1.46 (0.48)	1.48 (0.55)	0.831[a]	1.49 (0.46)	1.49 (0.52)	1.000[a]	0.846 (0.001)
LDL-C (mmol/L)†	1.59 (0.56)	1.61 (0.69)	0.875[a]	1.88 (0.81)	1.93 (0.76)	0.593[a]	0.819 (0.002)
TGs (mmol/L)‡	0.98 (0.60)	1.28 (0.42)	0.249[b]	0.89 (0.94)	0.72 (0.98)	0.744[b]	0.554 (0.012)
Glucose Metabolism							
GLUF (mmol/L)‡	5.1 (0.7)	5.1 (1.6)	0.814[b]	4.9 (0.7)	4.8 (0.7)	0.678[b]	0.489 (0.017)
$HbA1_c$ (mmol/mol)†	36 (5)[3]	35 (6)[3]	0.774[a]	34 (2)[4]	35 (3)[4]	**0.016**0[a,*]	0.146 (0.086)
Inflammatory Markers							
CRP (mg/L)‡	1.5 (4.9)	1.1 (3.0)	0.161[b]	1.0 (0.2)	1.0 (0.9)	0.866[b]	0.217 (0.052)
ESR (mm/hr)‡	2.0 (2.0)[5]	2.0 (3.5)[5]	0.715[b]	2.0 (3.0)[6]	2.0 (1.0)[6]	0.752[b]	0.927 (0.000)

(Continues)

TABLE 2 (Continued)

Variable	Exercise Group (n = 13)			Control Group (n = 18)			Time X Group Interaction
	T0	T1	*p* value	T0	T1	*p* value	*p* value (partial η^2)
BDNF (pg/mL)‡	6637 (11,015)[5]	6552 (11,588)[5]	0.214[b]	15,864 (11,452)[3]	14,722 (10,947)[3]	0.398[b]	0.318 (0.055)
TNF-α (pg/mL)†	377 (321)[5]	416 (381)[5]	0.531[a]	220 (166)[3]	185 (117)[3]	0.428[a]	0.278 (0.368)
IL-1β (pg/mL)†	70 (62)[5]	55 (77)[5]	0.865[a]	137 (22)[3]	158 (66)[3]	0.515[a]	0.390 (0.125)
IL-6 (pg/mL)‡	314 (0)[5]	163 (0)[5]	0.593[b]	49 (260)[3]	59 (215)[3]	0.612[b]	0.437 (0.077)
IL-10 (pg/mL)†	1059 (1057)[5]	1041 (1048)[5]	0.237[a]	964 (1341)[3]	1603 (2473)[3]	0.432[a]	0.494 (0.167)
Liver Function Tests							
AST (IU/L)‡	40 (18)[2]	41 (22)[2]	0.422[b]	37 (27)	36 (21)	0.586[b]	0.617 (0.009)
ALT (IU/L)‡	45 (33)	45 (46)	0.972[b]	42 (36)	44 (30)	0.384[b]	0.319 (0.034)
ALP (IU/L)†	72 (30)	69 (29)	0.164[a]	60 (23)	64 (26)	0.179[a]	0.073 (0.107)
GGT (IU/L)‡	57 (74)	58 (74)	0.294[b]	24 (24)	35 (32)	0.948[b]	0.439 (0.021)

Abbreviations: AI, Augmentation Index; ALP, Alkaline Phosphatase; ALT, Alanine Transaminase; AST, Aspartate Aminotransferase; BDNF, Brain-Derived Neurotrophic Factor; BMI, Body Mass Index; CRP, C-Reactive Protein; DBP, Diastolic Blood Pressure; ESR, Erythrocyte Sedimentation Rate; FM, Fat Mass; GGT, Gamma-Glutamyl Transferase; GLUF, Fasting Plasma Glucose; $HbA1_c$, Glycated Haemoglobin; HDL-C, High-Density Lipoprotein Cholesterol; IL-10, Interleukin 10; IL-1β, Interleukin 1 Beta; IL-6, Interleukin 6; LDL-C, Low-Density Lipoprotein Cholesterol; MVPA, Moderate-to-Vigorous Physical Activity; PA, Physical Activity; PWV, Pulse Wave Velocity; SBP, Systolic Blood Pressure; SMM, Skeletal Muscle Mass; T0, Baseline assessment; T1, Week 13 (intervention completion) assessment; TC, Total Cholesterol; TGs, Triglycerides; TNF-α, Tumour Necrosis Factor-Alpha; TVR, Total Vascular Resistance; $\dot{V}O_{2max}$ Maximal Oxygen Consumption; WC, Waist Circumference; WHO, World Health Organisation; WHR, Waist-to-Hip Ratio.

[1]n = 17.

[2]n = 12.

[3]n =11.

[4]n = 15.

[5]n = 9.

[6]n = 16.

[a]Paired *t* test.

[b]Wilcoxon signed-rank test.

[c]McNemar's test.

†Mean (standard deviation).

‡Median (interquartile range).

§§Significant time x group interaction ($p \leq 0.01$).

*Significant Within-Group Difference ($p \leq 0.05$).

***Significant within-group difference ($p \leq 0.001$).

in cardiometabolic health including anthropometry, vascular health or lipid and glucose regulation; and (v) in the absence of continuous prescribed and monitored exercise, the benefits were not sustained by T2.

There is strong evidence that exercise significantly benefits cognition in chronic inflammatory diseases,[14] ageing cohorts[29] and in HIV-associated cognitive impairment.[16] Despite reports that approximately 30%–50% of individuals with non-cirrhotic chronic HCV may experience cognitive impairment,[8] this is the first study to assess the impact of exercise on cognition in HCV. Our study demonstrated significant improvements in measures of cognition following a 12-week moderate-to-vigorous aerobic exercise intervention. There was a 31% and 15% mean improvement in the TMT-A and TMT-B time to completion, respectively, indicating improvements in attention, processing speed and executive function. There was also a 14% improvement in the MOCA score, indicating an improvement in overall cognitive ability. In the only published aerobic exercise intervention in individuals with HIV assessing cognition, where the pathophysiology of cognitive impairment is similar to HCV,[8,45] McDermott et al. reported no significant improvements in cognition following 16 weeks of aerobic exercise.[22] The disparity in results compared to our study may be partially explained by many factors: (i) sample size: McDermott et al. had a smaller sample size (exercise group n = 5; control group n = 6); and (ii) lower overall adherence rate to the exercise intervention compared to our study (60%).[22] Although higher adherence rates generally produce greater cognitive benefits,[14,15] previous studies in individuals with mild cognitive impairment have reported improvements in cognition with similar adherence rates to McDermott and colleagues, but with longer durations (≥6 months).[29] McDermott et al also reported no significant

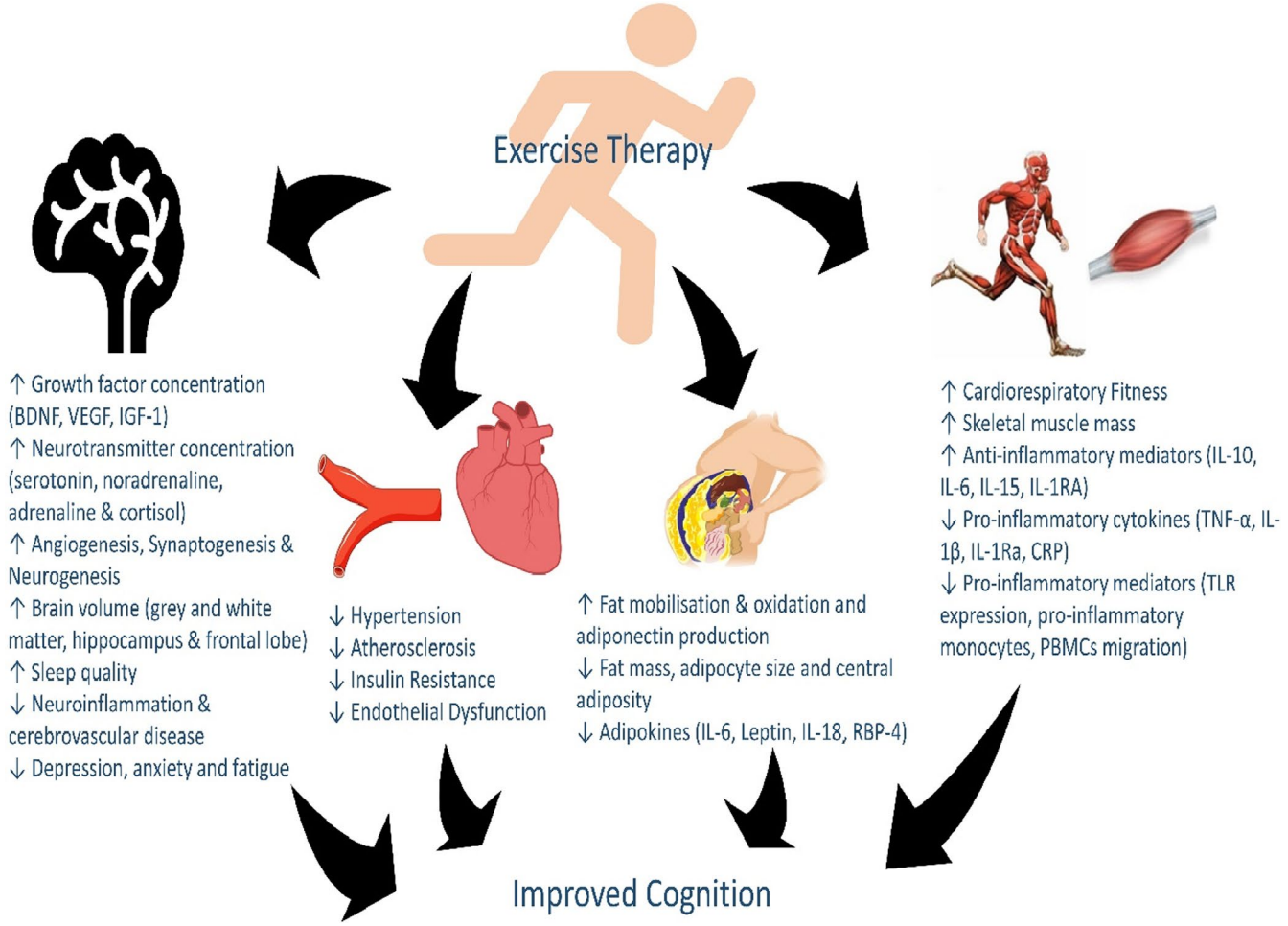

FIGURE 2 Potential physiological mechanisms for improved cognition. BDNF, Brain-derived neurotrophic factor; CRP, C-reactive protein; IGF-1, Insulin-like growth factor 1; IL-10, Interleukin 10; IL-15, Interleukin 15; IL-18, Interleukin 18; IL-1Ra, Interleukin 1 receptor agonist; IL-1RA, Interleukin 1 receptor antagonist; IL-1β, Interleukin 1 β; IL-6, Interleukin 6; IL-6, Interleukin 6; PBMC, Peripheral blood mononuclear cells; RBP-4, Retinol binding protein 4; TLR, Toll-like receptor; TNF-α, Tumour necrosis factor α; VEGF, Vascular-endothelial growth factor

improvements in cardiorespiratory fitness, initially low exercise load of the exercise intervention, and the enrolment of participants without suspected cognitive impairment as potential reasons for no significant cognitive changes.[22] The larger sample size and adherence rates in our study, combined with significant improvements in cardiorespiratory fitness and the inclusion criteria of suspected cognitive impairment, may explain the different results between the studies.

Our study is the first exercise intervention to assess cardiorespiratory fitness and physical activity levels in individuals with HCV using objective, validated measures. At baseline, 47% of participants had below-average cardiorespiratory fitness and only 27% were achieving the World Health Organisation physical activity guidelines.[10] Low cardiorespiratory fitness and physical activity levels have important health implications and contribute to all-cause mortality in adults.[10,46] The improvement in estimated $\dot{V}O_{2max}$ observed in the exercise group at T1 demonstrates that our exercise intervention's intensity and duration were sufficient to induce significant improvements in cardiorespiratory fitness. Changes in cardiorespiratory fitness following an exercise intervention in individuals with HCV were also reported by McKenna et al, although direct $\dot{V}O_{2max}$ assessments were not undertaken.[47] The mean improvement in estimated $\dot{V}O_{2max}$ observed in our study (7.8 mL kg^{-1} min^{-1}) is larger than that reported by McKenna et al. (1.6 mL kg^{-1} min^{-1})[47], possibly attributable to the shorter exercise duration and assessment criteria for $\dot{V}O_{2max}$ in Mckenna et al.[47] The large increase in cardiorespiratory fitness in our study may have contributed to improved cognition, as described in other cohorts.[21] In addition to the cognitive benefits, a 3.5 mL kg^{-1} min^{-1} increase in $\dot{V}O_{2max}$ is associated with a 10%–25% reduction in all-cause mortality,[48] which represents an important clinical modifier for CVD risk, the leading cause of mortality in HCV populations.[49]

Improvements in measures of cognition were accompanied by significant improvements in self-reported depression, sleep quality and fatigue in the exercise group. Exercise-induced improvements in depression are well-established. A 2016 meta-analysis reported a strong evidence base for using exercise therapy as a prevention and treatment of depression.[18] Our study results confirm previous studies in HCV cohorts reporting improvements in depression following exercise.[47,50] Exercise is also reported to have important benefits for

treating fatigue in other chronic disease cohorts, but our study is the first to report significant improvements in fatigue following an exercise-only intervention in individuals with HCV. Although this contradicts two previous exercise-only HCV studies,[47,50] a 2017 Cochrane review concluded that exercise reduces fatigue due to the positive effects on sleep quality, physical function and self-perceived general health.[51] Our study is also the first to report positive benefits of exercise on sleep quality in individuals with HCV. Sleep and exercise have a complex interplay but there is evidence that increasing exercise improves sleep quality by promoting increased sleep efficiency and duration, regardless of exercise mode or intensity.[19]

The physiological mechanisms underlying changes in cognition following exercise are not fully understood and may vary between chronic diseases. However, increased neuroplasticity, brain volumes and growth factor concentrations, and reductions in inflammation and cardiovascular/cerebrovascular risk factors are among the proposed mechanisms.[27] Increased cerebral blood flow induced by exercise increases cerebral growth factor concentrations, which may facilitate central mechanisms of cognitive improvement including increased angiogenesis, neurogenesis and synaptogenesis.[27] Increased growth factor concentration can also lead to brain volume expansion in the hippocampus, white and grey matter and the dentate gyrus.[24] The most commonly cited growth factor involved in exercise-induced neuroplasticity is BDNF.[28] We observed no changes in BDNF concentration in the exercise group at T1 or T2 compared to T0. Possible explanatory factors include that BDNF concentration is subject to diurnal or circadian variation alterations,[52] and has lower sensitivity to change when measured peripherally compared to centrally.[28] Exercise is also known to have anti-inflammatory effects,[30] but whether these anti-inflammatory effects directly lead to improvements in neuroinflammatory pathways in HCV-associated cognitive impairment is unknown. Exercise may exert anti-inflammatory effects by changing adipose tissue-derived inflammatory cytokines (adipokines) and muscular-derived inflammatory cytokines (myokines) concentrations in addition to reducing the expression of toll-like receptors on circulating immune cells.[30] Although our study did not detect significant changes in inflammatory cytokines, reductions in inflammatory mediators may have also been centrally localized and not detected in circulation.[53]

The physiological mechanisms underlying changes in quality of life measures following exercise are similar to that described for cognition.[51,54] In addition to the aforementioned mechanisms, exercise can increase serotonin, adrenaline and noradrenaline concentrations, which may have anti-inflammatory action.[55] Along with the inherent cognitive benefits, these neurotransmitters may also be involved in key pathways regulating depression, anxiety, sleep quality and fatigue.[55] Improvements in cognition and psychological well-being with exercise are intrinsically linked.[27] It is possible that the observed improvements in the quality of life measures in the exercise group in our study may have also contributed to secondary improvements in cognition. A schematic summary of the potential mechanisms for improving cognition and quality of life outcomes is detailed in Figure 2.

The failure to sustain the benefits of the exercise intervention at T2 is in keeping with previous exercise interventions in HCV,[47] non-alcoholic fatty liver disease (NAFLD)[56] and T2DM[57] cohorts, and emphasizes the unmet need for exercise maintenance in the unsupervised setting in these cohorts. Following a six-week exercise intervention, McKenna et al reported that improvements in cardiometabolic outcomes were not maintained upon a one-year follow-up,[47] stressing that effective strategies to promote long-term exercise are needed. Additionally, of the 66 participants that were eligible to take part in the intervention in our study, only 47% of participants (n = 31) completed the intervention, further highlighting the difficulty in engaging this cohort with exercise. Our findings have important implications for the sustainability of exercise in HCV cohorts and strongly suggest that continued engagement in exercise is needed for cognitive benefits to be maintained. The use of digital technology has shown potential to promote sustained exercise benefits in NAFLD patients,[58] but no studies have investigated the use of digital technology in a HCV cohort. The identification and elimination of exercise barriers may also improve the sustainability of exercise in this cohort. Although there are no published data on exercise barriers in individuals with HCV, in individuals with HIV, those with higher levels of social support and community engagement had higher levels of exercise engagement,[59] which may applicable to HCV cohorts.

This study has limitations: (i) the small sample size (n = 31), high dropout rate, low engagement with the exercise intervention, and lack of in-depth neuropsychological assessment at T1 makes it difficult to draw definitive conclusions on the effects of aerobic exercise on cognition in HCV; (ii) due to time constraints, cardiorespiratory fitness, quality of life outcomes and most cardiometabolic outcomes were not reassessed at the T2 assessment. These assessments may have provided further insights into the sustainability of the exercise intervention on these outcome measures; (iii) no sample size calculation was conducted at the study design and therefore may not be adequately powered to detect significant cognitive changes; and (iv) the study was not randomized; patients were allocated to the exercise group or control group based on individual preference, which may have introduced potential confounders leading to a degree of bias.

In conclusion, the results of this study demonstrate that 12 weeks of moderate-to-vigorous intensity aerobic exercise significantly improved measures of cognition in individuals with HCV with suspected cognitive impairment. These improvements were paralleled with improvements in self-reported depression, sleep quality and fatigue, and cardiorespiratory fitness. In the absence of continuous prescribed exercise, the benefits of the exercise intervention were not sustained at 12-week follow-up, highlighting that continued participation in exercise is needed in order to sustain these benefits. This pilot study paves the way for larger randomized controlled trials to investigate the effects of aerobic exercise on cognition, with a strong focus on using more in-depth neuropsychological batteries and investigating strategies to transition exercise into the community setting to promote lifelong participation.

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DATA AVAILABILITY STATEMENT

Data availability statement: All data are available upon reasonable request from the authors.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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