High-intensity interval training in patients with intermittent claudication

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ABSTRACT

Objective: Provision, uptake, adherence, and completion rates for supervised exercise programs (SEP) for intermittent claudication (IC) are low. A shorter, more time-efficient, 6-week, high-intensity interval training (HIIT) program may be an effective alternative that is more acceptable to patients and easier to deliver. The aim of this study was to determine the feasibility of HIIT for patients with IC.

Methods: A single arm proof-of-concept study, performed in secondary care, recruiting patients with IC referred to usual-care SEPs. Supervised HIIT was performed three times per week for 6 weeks. The primary outcome was feasibility and tolerability. Potential efficacy and potential safety were considered, and an integrated qualitative study was undertaken to consider acceptability.

Results: A total of 280 patients were screened: 165 (59%) were eligible, and 40 (25%) were recruited. The majority (n = 31; 78%) of participants completed the HIIT program. The remaining nine patients were withdrawn or chose to withdraw. Completers attended 99% of training sessions, completed 85% of sessions in full, and performed 84% of completed intervals at the required intensity. There were no related serious adverse events. Maximum walking distance (+94 m; 95% confidence interval, 66.6-120.8 m) and the SF-36 physical component summary (+2.2; 95% confidence interval, 0.3-4.1) were improved following completion of the program.

Conclusions: Uptake to HIIT was comparable to SEPs in patients with IC, but completion rates were higher. HIIT appears feasible, tolerable, and potentially safe and beneficial for patients with IC. It may provide a more readily deliverable, acceptable form of SEP. Research comparing HIIT with usual-care SEPs appears warranted. (J Vasc Surg 2023;78:1048-56.)

Keywords: High-intensity interval training; Intermittent claudication; Supervised exercise program

Peripheral arterial disease (PAD) is caused by atherosclerosis of the arteries supplying the lower limbs, reducing blood supply.[1] Current estimates suggest that PAD affects 237 million people globally.[2] The classical symptom of PAD is intermittent claudication (IC), a reproducible ischemic lower limb muscle pain, precipitated by exertion, usually walking, and relieved by rest.[3-6] IC has deleterious effects on patients' walking ability,

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functional capacity, and quality of life (QoL), while also carrying a markedly increased mortality risk.[3,4,7-9] First-line management of IC includes cardiovascular risk reduction, achieved via statin and antiplatelet therapy, smoking cessation, diet, weight loss, and exercise. For symptomatic benefit, the recommended first-line treatment is a supervised exercise program (SEP).[10,11] Guidelines recommend that SEPs involve 2 hours of exercise per week for a 12-week period, encouraging patients to exercise to the point of maximal claudication pain.[10,12] Strong evidence supports the role of SEPs and shows that they are superior to home-based programs and are equivalent to angioplasty for symptomatic improvement.[13-15]

However, the effectiveness of SEPs is limited by low provision (48%),[16] uptake (25%), and completion (50%-75%).[17,18] Barriers to provision include a lack of funding and facilities, whereas patients often describe SEPs as too time-intensive.[16,19] Alternative exercise programs are required that are deliverable for providers and more acceptable to patients. Low-volume (ie, low amount of total exercise), short-duration (ie, program is performed over a short period of time), high-intensity interval training (HIIT) is more time-efficient,[20] and often performed using the single exercise modality of cycling. This means that it may be more attractive to patients, while being easier to implement in centers without a SEP, as it may require less staff time and facilities to deliver.

HIIT has demonstrated similar or superior physiological benefits compared with lower intensity programs across both healthy and clinical populations.[21-27] It may also be preferred by patients with IC.[19] Our 2019 systematic review identified that there was initial, limited evidence that HIIT may be beneficial for patients with IC.[28] However, due to the scant evidence, we recommended initial feasibility studies of low-volume, short-duration HIIT, as this appeared to be the most time-efficient version considered. Findings from our original cohort study led to a change in the inclusion/exclusion criteria but not the HIIT intervention protocol, thus informing the design of the current two-center, proof-of-concept study, which aimed to assess the feasibility, tolerability, and potential safety and efficacy of a short duration, low-volume HIIT program in people with IC.[29] This study also aimed to consider patient acceptability of the program.

ARTICLE HIGHLIGHTS

- **Type of Research:** Multicenter, prospective, nonrandomized cohort
- **Key Findings:** In 40 patients with intermittent claudication, high-intensity interval training is feasible and tolerable while also being potentially safe and efficacious for improving maximum walking distance (+94m; 95% confidence interval, 66.6-120.8 m).
- **Take Home Message:** High-intensity interval training is a promising intervention for patients with intermittent claudication and warrants further consideration.

METHODS

This single-arm, proof-of-concept study is reported in accordance with the applicable items of the pilot and feasibility trials extension of the Consolidated Standards of Reporting Trials checklist (Supplementary Table I, online only). It was also prospectively registered on clinicaltrials.gov (NCT04042311), and the protocol has been published in full.[20] Ethical approval was obtained via a local National Health Service research ethics committee (Bradford Leeds – 18/YH/0112).

Patients who were clinically assessed, appropriately diagnosed with IC, and deemed suitable for management with a usual-care SEP were referred to the study team for potential recruitment. Referral was made by vascular consultants, specialist registrars, specialist nurses, vascular scientists, or exercise physiologists. Inclusion criteria included an ankle-brachial pressure index of <0.9 at rest or a drop of ≥ 20 mmHg at the ankle after exercise testing. Patients with asymptomatic PAD or critical limb-threatening ischemia were excluded, as were those who exhibited significant comorbidities that precluded safe participation in exercise testing and/or training.[30] Finally, those able to walk ≥ 15 minutes during baseline treadmill testing were excluded.

Full details of the intervention are available elsewhere.[20] The details provided here and/or within the protocol are in accordance with the Template for Intervention Description and Replication (TIDieR) checklist (Supplementary Table II, online only).

Briefly, participants who were eligible and consented underwent 6 weeks of cycle-based HIIT performed for 20 minutes, three times per week. To allow for the completion of missed sessions, the intervention period could be extended by up to 2 weeks. Participants were considered to have satisfactorily completed the intervention if they completed ≥ 15 of 18 sessions ($>80\%$ adherence). Exercise prescription was based on the peak power output achieved during baseline cardiopulmonary exercise testing (CPET), with the aim of achieving 855 to 100% of peak heart rate by the end of the second HIIT interval. The HIIT work to rest ratio was 1:1, with participants completing 10 intervals for an overall exercise time of 20 minutes. If required, a titrated introduction to the HIIT program was used with fewer exercise intervals being completed in the first 2 weeks. Patients were also allowed to complete less than 10 intervals for longer than the first 2 weeks if required but were encouraged to complete 10 as soon as possible thereafter.

The intervention was delivered face-to-face either individually or as part of a group by exercise physiologists

who had undergone appropriate educational and vocational training. They also had experience of delivering HIIT interventions in clinical populations.

The only change made to the intervention during the study period was that, if required, the intensity was reduced to allow participants to achieve 10 intervals (by reducing the resistance and/or cycle cadence), before being increased again, if tolerated, once 10 intervals had been achieved.

Outcomes, sample size, and data analysis. The primary aim of this study was to assess the feasibility and tolerability of short-term, low-volume HIIT for patients with IC. Potential efficacy and safety were also investigated, and an integrated qualitative study was performed to assess patient acceptability.

Outcomes are detailed in full elsewhere.[20] Feasibility was based on eligibility, recruitment, and completion rates, whereas tolerability was based on reasons for withdrawal and ability to complete the intervention as intended, at the required intensity. Information on intervention fidelity (ie, tolerability) was based on information recorded by the exercise physiologists during exercise sessions.

Potential efficacy was based on changes from baseline for intermittent claudication distance, maximum walking distance, quality of life (QoL), and measures of cardiorespiratory fitness. Potential safety was based on the occurrence of related adverse events (AEs).

As a proof-of-concept study with no statistical testing, there was no formal sample size requirement. To obtain key feasibility and tolerability figures, we aimed to recruit 40 participants.

Descriptive statistics are reported for our feasibility, tolerability, and safety outcomes. For potential efficacy measures, improvements from baseline are reported with 95% confidence intervals (CIs).

Acceptability was assessed using in-depth, semi-structured interviews with a sample of patients from three groups: (1) patients who completed the intervention (completers); (2) patients who started the intervention but chose to withdraw prematurely (withdrawers); and (3) patients who declined participation (decliners). The withdrawer group differs slightly from non-completers in that withdrawers includes only those who chose to withdraw, whereas non-completers also includes those who were excluded.

Interviews were conducted either face-to-face or via telephone, informed by a topic guide, recorded using a Dictaphone, transcribed verbatim, and anonymized. As between six and 12 interviews are considered sufficient to achieve saturation,[31] a target of 10 interviews per group was used. Data were analyzed in the Nvivo software using inductive thematic analysis, whereby themes were identified from within the data.[32]

Procedures. Ankle-brachial pressure index was recorded at rest and following a graded treadmill walking test, performed to establish intermittent claudication distance and maximum walking distance, as previously described.[20,33] QoL was measured using the Medical Outcomes Study Short-Form 36 v.2 (SF-36) and the King's College Hospitals Vascular QoL (VascuQoL) questionnaires.[34,35]

Cardiorespiratory fitness was also measured during CPET as previously described, for the purpose of exercise prescription and outcome measurement.[20] Peak oxygen uptake was defined as the highest value achieved during exercise or early in recovery, averaged over 30 seconds. The ventilatory anaerobic threshold was determined using the V-slope and ventilatory equivalents methods.[36,37]

These measures were taken at baseline (week 0), upon completion of the program (week 6), and 12 weeks later (week 18). An additional follow-up was performed 4 weeks after program completion (week 10) at the Hull site only, including 21 participants.

RESULTS

Baseline characteristics of all recruited participants (n = 40) are shown in Table I. Mean age was 69 ± 8 years, body mass index was 28 ± 4 kg/m^2, and 87.5% were male. The mean ankle-brachial pressure index of the worst leg was 0.63 ± 0.21 (range, 0.15-1.0). The proportion of participants with concomitant diabetes was 15%. Most participants (75%) were taking best medical therapy for PAD in the form of statin and antiplatelet therapy. Age and ankle-brachial pressure index of the worst leg were similar between completers and non-completers (69 ± 9 vs 70 ± 8 years and 0.62 ± 0.21 vs 0.65 ± 0.20, respectively).

Feasibility and tolerability. Between August 2019 and January 2022, 280 patients with IC were referred to the SEP of whom 165 were eligible (59%) and 40 consented to participate in supervised HIIT (24%) (Fig 1). No participants were recruited between March 2020 and March 2021 due to COVID-19 restrictions. Reasons for ineligibility and non-participation are shown in Fig 1.

Of the recruited participants, three were excluded from further participation or were withdrawn by the study team; one had abnormal electrocardiogram (ECG) changes and a hypertensive response to cardiopulmonary exercise test (CPET), another was recruited just before the COVID-19 lockdown and no longer met the inclusion criteria when the study resumed, and the final participant received a diagnosis of aortic stenosis. The latter participant had symptoms of increasing unexplained breathlessness during the HIIT program and was referred back to their GP. For this participant, there were no significant ECG changes apparent at baseline.

Table I. Baseline demographics of the overall cohort and completers and non-completers

Patient demographics	Overall cohort (N = 40)	Completers (n = 31)	Non-completers (n = 9)
Age, years	69 ± 8	69 ± 9	70 ± 8
Height, cm	168.5 ± 7.2	168.5 ± 7.1	168.3 ± 8.3
Weight, kg	79.9 ± 14.5	80.0 ± 14.2	79.4 ± 16.6
BMI, kg/m^2	28.0 ± 3.9	28.0 ± 3.7	27.9 ± 4.8
Systolic blood pressure, mmHg	146 ± 20	144 ± 20	154 ± 19
Diastolic blood pressure, mmHg	81 ± 13	82 ± 12	76 ± 14
ABPI (worst leg)	0.63 ± 0.21 (range, 0.15-1.0)	0.62 ± 0.21 (range, 0.15-1.0)	0.65 ± 0.20 (range, 0.35-0.89)
Rutherford category			
1	12 (31)	10 (32)	2 (25)
2	16 (41)	14 (45)	2 (25)
3	11 (28)	7 (23)	4 (50)
ICD, meters	130.2 ± 88.8	140.9 ± 94.6	88.6 ± 43.6
MWD, meters	327.5 ± 206.8 (range, 38.5-701.9)	356.2 ± 205.3 (range, 50.1-701.9)	219.7 ± 186.0 (range, 38.5-611.6)
Gender			
Male	35 (87.5)	27 (87.1)	8 (88.9)
Female	5 (12.5)	4 (12.9)	1 (11.1)
Smoking status			
Non-smoker	5 (12.5)	4 (12.9)	1 (11.1)
Ex-smoker	22 (55)	17 (54.8)	5 (55.6)
Current smoker	13 (32.5)	10 (32.3)	3 (33.3)
Respiratory disease	12 (30)	8 (25.8)	4 (44.4)
Coronary artery disease	6 (15)	5 (16.1)	1 (11.1)
Cerebrovascular disease	3 (7.5)	3 (9.7)	0 (0)
Diabetes	6 (15)	6 (19.4)	0
Statin	37 (92.5)	30 (96.8)	7 (77.8)
Antiplatelet	32 (80)	24 (77.4)	8 (88.9)
Optimal medical therapy	30 (75)	24 (77.4)	6 (66.7)
Antihypertensive therapy	24 (60)	19 (61.3)	5 (55.6)
Vasoactive treatment	15 (37.5)	12 (38.7)	3 (33.4)
Beta-blockade	7 (17.5)	7 (22.6)	0 (0)

ABPI, Ankle-brachial pressure index; *BMI*, body mass index; *ICD*, intermittent claudication distance; *MWD*, maximum walking distance.
Data are presented as number (%) or mean ± standard deviation.

Of the remaining 37 participants, six withdrew; two due to an inability to tolerate CPET, one due to an inability to tolerate HIIT, and two for unrelated personal reasons. The final participant did not give a reason for withdrawal. The reasons for intolerability were: (1) severe chronic obstructive pulmonary disease; (2) thigh pain secondary to a previous femur fracture; and (3) general exercise intolerance. The third participant reported a feeling of severe aching and discomfort the day after his baseline CPET and chose to withdraw.

Thirty-one participants (78%) completed the HIIT program; 28 participants completed all 18 sessions, two completed 17 sessions, and one completed 13 sessions, over an average of 6.7 ± 1.6 weeks. This represents a 99% session adherence rate and a 75% successful intervention completion rate. More than 85% peak heart rate was achieved by the second interval, as intended, in 70% of sessions. When this was not achieved by the end of the second interval, it was achieved by the end of the fifth interval in 90% of sessions (Fig 2). In total, 84% of completed intervals were at the required intensity (Fig 2). All 10 intervals were completed in 85% of sessions, with 94% of participants able to complete 10 intervals by session six. The remaining 6% of participants completed 10 intervals by session seven.

Logistical issues at one study site meant follow-up testing was not always possible immediately after the 6-week HIIT program. In such cases, participants chose to continue the program beyond 6 weeks, until testing was available. The average number of sessions

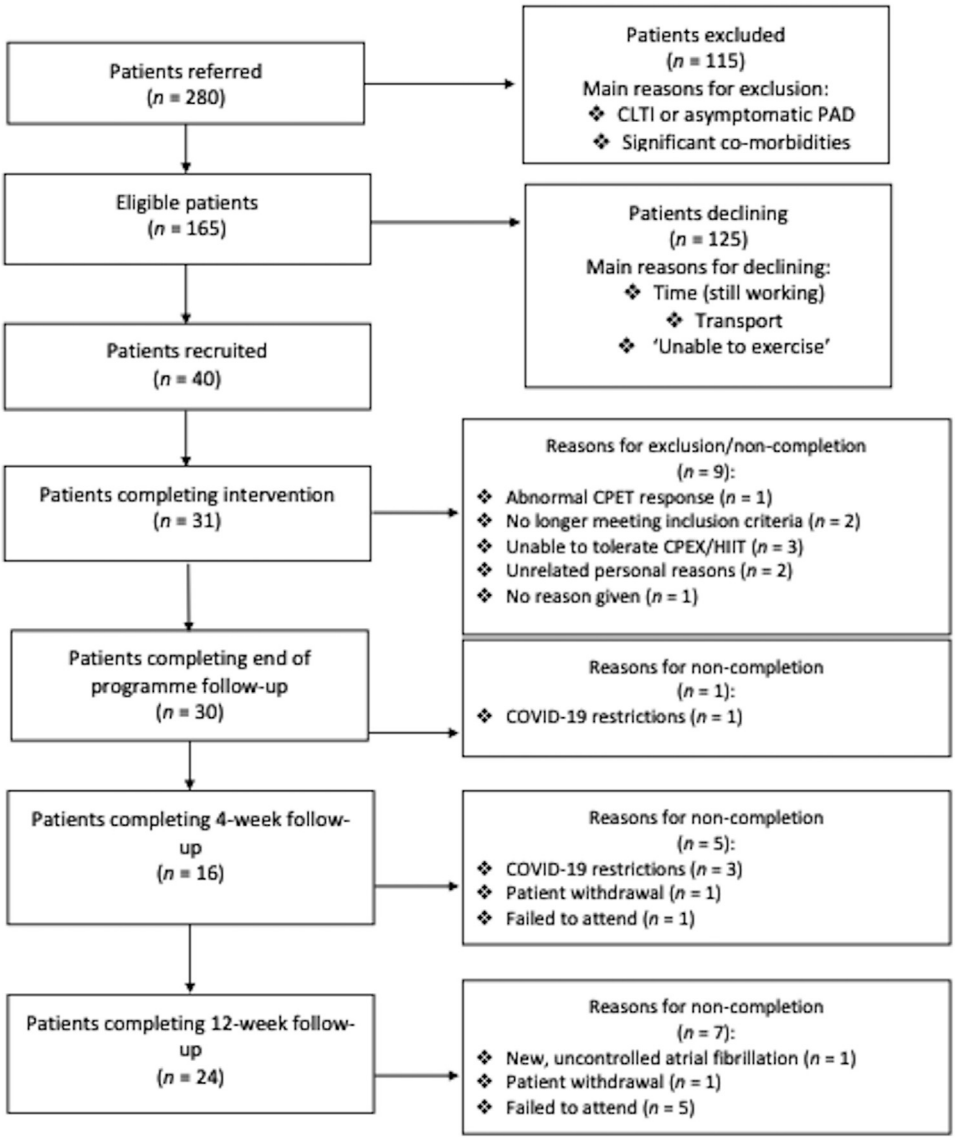

Fig 1. Participant flow chart. *CLTI*, Chronic limb-threatening ischemia; *CPET*, cardiopulmonary exercise testing; *HIIT*, high-intensity interval training; *PAD*, peripheral arterial disease.

completed at this site was 20, over 9.0 ± 1.9 weeks. This finding also provides support for the tolerability of the intervention but may slightly exaggerate physiological outcomes.

Of the 31 participants finishing the program, 30 completed the end of program follow-up assessment. One participant was unable to attend due to COVID-19 restrictions coming into effect immediately after their final HIIT session. CPET data was also not available for an additional participant at the end of program follow-up due to premature test termination by the participant. At 4-week follow-up, 16 of 21 participants attended. Three were not performed due to COVID-19 restrictions, one participant withdrew, and another failed to attend. For

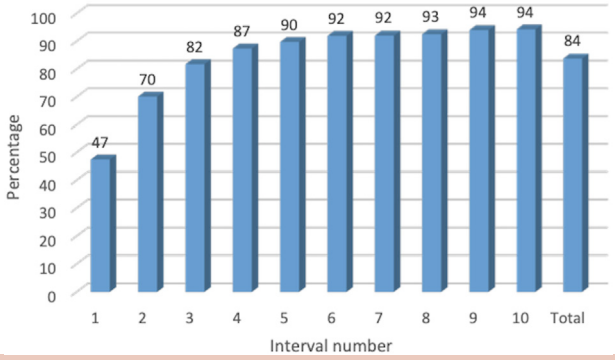

Fig 2. Percentage of high-intensity interval training (HIIT) intervals completed at the required intensity.

Table II. Pre- and post-intervention clinical outcomes, with mean difference for those that completed the program

Variable	Pre (n = 30)	Post (n = 30)	Mean difference (95% CI)
ICD, m	142.5 ± 95.5	218.6 ± 166.6	76.1 (30.2-122.2)
MWD, m	366.5 ± 201.0	455.0 ± 220.8	88.5 (62.0-114.9)
Resting ABPI (worst leg)	0.64 ± 0.20	0.65 ± 0.17	0.01 (−0.03 to 0.05)
$\dot{V}O_{2peak}$, $mL \cdot kg^{-1} \cdot min^{-1}$	16.4 ± 3.9	17.1 ± 4.3	0.7 (−0.02 to 1.39)
VAT, $mL \cdot kg^{-1} \cdot min^{-1}$	10.0 ± 1.9	10.4 ± 2.2	0.4 (−0.08 to 0.88)
Peak power output, W	101.6 ± 39.4	106.0 ± 43.0	4.3 (0.3-8.4)

ABPI, Ankle-brachial pressure index; *CI*, confidence interval; *ICD*, intermittent claudication distance; *MWD*, maximum walking distance; *VAT*, ventilatory anaerobic threshold; $\dot{V}O_{2peak}$, peak oxygen consumption; *W*, watt.
Data are presented as mean ± standard deviation with mean difference given with 95% CIs.

12-week follow-up, 24 of 31 participants attended. Five participants failed to attend, one participant withdrew, and one participant had new, uncontrolled atrial fibrillation. CPET data were not available for a further four participants at this time point. One participant refused, one test was prematurely terminated by the participant, and two participants were no longer suitable for CPET due to pacemaker insertion and new onset of left bundle branch block. Three of the 12-week follow-ups were performed significantly late due to COVID-19 restrictions. Full participant flow is shown in Fig 1.

Safety. There were 16 AEs, with nine being related to the intervention or study procedures. There were six episodes of dizziness after exercise, one episode of back spasm after exercise, one episode of a headache after exercise, and one participant had a hypertensive response to CPET, which was asymptomatic. Although related, none of these events were deemed to be serious; they all resolved quickly and were not unexpected.

There were no serious AEs related to the intervention or study procedures.

Potential efficacy. Improvements were noted in a number of efficacy measures, including intermittent claudication distance (+76 m; 95% CI, 30-122 m), maximum walking distance (+88.5 m; 95% CI, 62-115 m), the VascuQoL pain (+0.8; 95% CI, 0.5-1.1), symptom (+0.5; 95% CI, 0.2-0.9) and total (+0.4; 95% CI, 0.1-0.7) scores as well as the physical component summary of the SF-36 (+2.2; 95% CI, 0.3-4.1) (Tables II and III). These improvements remained at 4- and 12-week follow-up, with the physical functioning (+7.7%; 95% CI, 1.3-14.1) and bodily pain (+9.9%; 95% CI, 0.9-18.9) domains of the SF-36 also demonstrating an improvement at 12-week follow-up (Supplementary Table III, online only).

There were no improvements in cardiorespiratory fitness measures derived from CPET at any timepoint (Table II and Supplementary Table III [online only]). There was an improvement in peak power output immediately following the program (Table II), but this was not maintained (Supplementary Table III, online only).

Acceptability. Qualitative interviews were conducted with 11 patients who successfully completed the HIIT program and 12 patients who declined participation. None of the patients who withdrew agreed to interview, meaning this group is not represented. Data indicated that the program and its structure was largely acceptable to patients, even those who chose to decline participation. A lack of time was still cited as a barrier by some patients, though others noted that the time-efficiency of a 6-week, rather than 12-week, program was attractive. Other barriers, identified by both completers and decliners, included mental (eg, a lack of motivation) and physical (eg, comorbidities) elements. However, suggestions for how to overcome some of these barriers were also made (eg, peer feedback within study materials from patients who had already completed an exercise program may increase motivation to participate).

Facilitators were also identified, and patients chose to participate to improve their own symptoms and/or contribute to research to improve future care for others.

For completers, the program was often described as challenging but enjoyable, and these patients would be willing to undertake it again. Improvements in both IC symptoms and general health were also reported.

Impact of COVID-19. The actual recruitment period for the INITIATE study was 30 months, compared to an anticipated period of 15 months. However, from March 2020 to April 1, 2021, all study-related activities were paused in response to the COVID-19 pandemic. In addition, the delay in restarting clinical activities meant that no participants were recruited in May 2021. Therefore, a total of 14 months of recruitment were lost, and the actual active recruitment period was slightly longer than anticipated at 16 months. Additionally, two patients who had already started the HIIT program were required to prematurely discontinue due to COVID-19 restrictions. One of these patients later completed the program after restrictions were lifted (following a new baseline assessment), whereas the other no longer met the inclusion criteria and was excluded.

Table III. Pre- and post-intervention quality of life (QoL) outcomes, with mean difference for those that completed the program

Variable	Pre (n = 30)	Post (n = 30)	Mean difference
VascuQoL pain score	3.7 ± 1.2	4.5 ± 1.1	0.8 (0.5 to 1.1)
VascuQoL social score	5.2 ± 1.7	5.4 ± 1.8	0.2 (−0.2 to 0.6)
VascuQoL activities score	4.3 ± 1.2	4.7 ± 1.2	0.3 (−0.2 to 0.7)
VascuQoL symptom score	4.9 ± 1.3	5.4 ± 1.0	0.5 (0.2 to 0.9)
VascuQoL emotional score	5.2 ± 1.3	5.5 ± 1.4	0.3 (−0.1 to 0.6)
VascuQoL total score	4.6 ± 1.1	5.0 ± 1.1	0.4 (0.1 to 0.7)
SF-36 physical functioning	53.3 ± 19.2	56.2 ± 19.1	2.9 (−2.8 to 8.5)
SF-36 role physical	52.9 ± 23.9	60.8 ± 24.7	7.9 (−0.9 to 16.7)
SF-36 pain	47.3 ± 19.9	54.1 ± 22.6	6.8 (−1.1 to 14.8)
SF-36 general health	54.4 ± 21.2	54.8 ± 21.7	4.3 (−4.3 to 5.1)
SF-36 vitality	53.2 ± 17.8	55.8 ± 19.3	2.6 (−3.2 to 8.5)
SF-36 social functioning	77.5 ± 24.7	75.4 ± 27.9	−2.1 (−11.8 to 7.7)
SF-36 role emotional	73.1 ± 25.2	75.6 ± 25.3	2.5 (−5.3 to 10.3)
SF-36 mental health	76.7 ± 14.5	76.7 ± 19.8	0.0 (−5.9 to 5.9)
SF-36 physical component summary	38.5 ± 7.0	40.7 ± 7.3	2.2 (0.3 to 4.1)
SF-36 mental component summary	52.3 ± 8.8	52.0 ± 10.4	−0.3 (−3.5 to 2.9)

SF-36, Short-Form 36; *VascuQoL*, vascular quality of life questionnaire.
Data are presented as mean ± standard deviation.

DISCUSSION

The primary aim of this study was to assess the feasibility and tolerability of short-term, low-volume HIIT for patients with IC. First, the participant eligibility rate (59%) for this study was similar to that for the routine SEP provided within one of our centers.[18] The recruitment rate (24%) was also similar, and the same as that reported within a systematic review of uptake and adherence to SEPs.[17] Similarly, HIIT completion rates were comparable to those reported in the systematic review (75%), but were higher than recently reported for the usual-care SEP provided in one of our centers (50%),[18] with the latter likely being most reflective of the completion rates for "real-world" routine care exercise programs as opposed to clinical research settings. Overall, this suggests that our HIIT program is feasible, and comparable to usual-care SEPs for patient eligibility/recruitment rates, and potentially superior for completion rates.

It should also be noted that the recruitment rate may have been impacted by the COVID-19 pandemic. More than one-half of the sample (28 participants) was recruited during COVID-19. It is therefore hugely positive that we were able to recruit to target during a global pandemic with lockdown restrictions. It would also be reasonable to suggest that the recruitment rate may have been higher, exceeding that of SEPs, if the study was conducted without the COVID-19 pandemic, given that some patients did cite this as a reason for non-participation.

With regards to tolerability, all but three participants were able to tolerate the HIIT program and study procedures, and the three reasons for intolerability were not related to IC. The remaining participant withdrawals were also not related to the study.

Furthermore, the withdrawal rate (15%) was similar to that seen in a HIIT program in patients with coronary artery disease,[38] and >80% of sessions were completed in full at the required intensity. This is in contrast to HIIT studies in other populations, with the SAINTEX-CAD study reporting that patients exercised at lower than prescribed intensities, over longer interval periods of 4 minutes.[38] However, SAINTEX-CAD utilized a higher HIIT training zone of 90% to 95% of peak heart rate, whereas the current study adopted a training zone of ≥85%. Indeed, the SAINTEX-CAD study reported that patients exercised at a mean intensity of 88% of peak heart rate, which would be within the HIIT intensity prescribed in the current study. Clearly, this outlines the need for a universal 'HIIT' definition, such as that adopted in recent systematic reviews,[28,39] which aligns closely to that used here. Regardless, our data support the tolerability of this HIIT intervention, especially given that participants chose to continue after the initial 6-week duration.

In total, there were nine AEs related to the intervention or study procedures, although these were mild, resolved quickly, and were not unexpected for an intervention of this nature. Indeed, light-headedness is not uncommon in young, healthy adults performing sprint interval training,[40] meaning that the AE profile found here was not dissimilar to that seen in younger, healthy populations. None of these events led to a review/change in study procedures. Additionally, there were

no serious AEs related to the intervention or study procedures.

It is plausible that this study and its high-level screening procedures prevented AEs from occurring. First, one participant had a positive CPET, indicative of myocardial ischaemia, and was therefore excluded and referred for further investigation. If this participant was to undergo a standard SEP, CPET may not have been routinely performed, as it is not considered necessary due to the safety profile of SEPs.[41] Therefore, this myocardial ischemia may not have been detected. Second, a participant experienced an unexplained worsening of dyspnea. This was quickly identified, followed by appropriate referral and management, preventing a potential SAE. Accordingly, this study provides an early indication that HIIT may be safe for patients with IC, although further evidence is required, including direct comparison to a usual-care SEP. We also maintain our previous recommendation that any exercise program adopting HIIT in patients with IC, should include a baseline CPET with exercise ECG screening.[29]

Those who completed HIIT had improvements from baseline in objective and subjective measures with the 95% CI intervals for IC distance, maximum walking distance, and a number of QoL domains not crossing zero, providing a signal of potential efficacy. However, this study was not designed nor powered to provide substantive evidence of clinical benefits. Regardless, the results are promising as the improvement in maximum walking distance with a cycle-based HIIT intervention represents a moderate minimal clinically important difference[42] and is comparable to that of the usual-care, 12-week, SEP based on walking/circuit training provided in one of our centers.[18] The results also support the findings of our previous systematic review, which suggested that short-term, low-volume HIIT has the potential to provide symptomatic and clinical benefit.[28]

Importantly, these improvements were provided in one-half the amount of time required for a usual-care SEP. The time-efficiency of this HIIT intervention when compared with usual-care SEPs reduces patient burden. It also means that the intervention may be easier to deliver for providers. This may translate into cost savings at both the patient and provider level.

The above findings are also supported by qualitative data, which highlighted that, from a patient perspective, our HIIT program is largely acceptable, and patients who complete the program report a benefit.

Overall, our supervised short-term HIIT program appears feasible, tolerable, acceptable, and potentially safe for patients with IC. It may also provide clinical and symptomatic benefits. An appropriately powered randomized controlled trial comparing our HIIT program with usual-care SEPs is now required to assess its clinical and cost effectiveness.

Limitations. This study is not without limitations. First, participants were recruited from patients referred to a usual-care SEP. It is therefore possible that patients who chose to take part in this study would also have chosen to take part in a usual-care SEP and were not encouraged by the time-efficiency of the HIIT program. The small sample and lack of a comparator group are also limitations. However, proof-of-concept work is vital to ensure the intervention and inclusion criteria are appropriate, to inform the design of future large-scale clinical and cost effectiveness trials. Additionally, within this cohort, there was a smaller proportion of female participants compared with larger exercise trials in patients with IC. Although the reason for this is not clear, it should be considered in future trials to identify if gender-specific barriers to HIIT exist.

Finally, information on socio-economic status, race, and ethnicity was not collected in this study. However, these important factors should be considered in future trials, with the support of equality and diversity guidance, to ensure these groups are represented.

CONCLUSIONS

This proof-of-concept study has demonstrated that HIIT is feasible, tolerable, and acceptable for patients with IC, with uptake and completion rates that are at least similar to usual-care SEPs. It has also provided an early indication that HIIT is safe for patients with IC, while also being potentially efficacious. A definitive randomized controlled trial of HIIT vs usual-care SEPs is warranted.

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AUTHOR CONTRIBUTIONS

Conception and design: SP, AH, BR, GM, CH, MT, AN, LI, SC, HH, JL, MR, IC
Analysis and interpretation: SP, CH
Data collection: SP, AH, JP, AW, BR, GM, SI
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Critical revision of the article: AH, JP, AW, BR, GM, CH, MT, AN, LI, SC, HH, JL, MR, IC, SI
Final approval of the article: SP, AH, JP, AW, BR, GM, CH, MT, AN, LI, SC, HH, JL, MR, IC, SI
Statistical analysis: SP, CH
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Overall responsibility: SP

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Additional material for this article may be found online at www.jvascsurg.org.

Supplementary Table I (online only). CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	1
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	3-4
	2b	Specific objectives or research questions for pilot trial	4
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	5
Participants	4a	Eligibility criteria for participants	4
	4b	Settings and locations where the data were collected	Protocol page 2
	4c	How participants were identified and consented	Protocol page 4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5 and protocol page 4
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	5-6 and protocol pages 6-7
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	N/A
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	N/A
Sample size	7a	Rationale for numbers in the pilot trial	6
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	N/A
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	N/A
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	N/A
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	N/A
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	N/A
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	6 and protocol page 7

(Continued on next page)

Supplementary Table I (online only). Continued.

Section/Topic	Item No	Checklist item	Reported on page No
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	Fig 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Fig 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7
	14b	Why the pilot trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table I
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	Tables
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	Tables
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	Tables
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	8
	19a	If relevant, other important unintended consequences	N/A
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	12
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	N/A
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	9-12
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	N/A
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	4
Protocol	24	Where the pilot trial protocol can be accessed, if available	Referenced throughout
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	2
	26	Ethical approval or approval by research review committee, confirmed with reference number	Protocol page 7

Supplementary Table II (online only). The TIDieR (Template for Intervention Description and Replication) Checklist*: Information to include when describing an intervention and the location of the information

Item number	Item	Where located	
		Primary paper (page or appendix number)	Other (details)
	BRIEF NAME		
1.	Provide the name or a phrase that describes the intervention.	Title	_____
	WHY		
2.	Describe any rationale, theory, or goal of the elements essential to the intervention.	Page 4	_____
	WHAT		
3.	Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (eg online appendix, URL).	Pages 4-5	Protocol paper page 4.
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	Pages 4-5	Protocol paper page 4.
	WHO PROVIDED		
5.	For each category of intervention provider (eg psychologist, nursing assistant), describe their expertise, background and any specific training given.	Page 5	_____
	HOW		
6.	Describe the modes of delivery (eg face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.	Page 5	_____
	WHERE		
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	_____	Protocol paper page 2.
	WHEN and HOW MUCH		
8.	Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose.	Pages 4-5	Protocol paper page 4.
	TAILORING		
9.	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.	Page 5	Protocol paper page 4.
	MODIFICATIONS		
10.	If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).	Page 5	_____
	HOW WELL		
11.	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.	Page 5	Protocol paper pages 4 and 6.
12.	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.	Page 7	_____

Supplementary Table III (online only). Pre- and late-follow-up (4- and 12-week) outcomes, with mean difference for those that completed the program

Variable	Baseline (*n*=16)	4-weeks Post-intervention (*n*=16)	Mean difference	Baseline (*n*=24)	12-weeks Post-intervention (*n*=24)	Mean difference
ICD (m)	147.0 ± 110.1	212.7 ± 173.8	65.7 (−0.3–131.7)	154.6 ± 100.5	276.0 ± 214.7	121.4 (48.1–194.7)
MWD (m)	354.0 ± 197.8	450.7 ± 242.8	96.7 (40.0–153.4)	376.8 ± 219.3	448.1 ± 240.9	71.2 (25.8–116.6)
VascuQoL pain score	4.0 ± 1.2	4.8 ± 1.3	0.8 (0.4–1.3)	3.7 ± 1.2	4.6 ± 1.3	0.9 (0.5–1.3)
VascuQoL social score	5.2 ± 1.6	5.5 ± 1.6	0.3 (−0.4–1.0)	5.2 ± 1.6	5.4 ± 1.7	0.2 (−0.4–0.9)
VascuQoL activities score	4.4 ± 1.2	4.9 ± 1.2	0.5 (0.1–0.9)	4.4 ± 1.2	4.7 ± 1.1	0.2 (−0.2–0.6)
VascuQoL symptom score	4.9 ± 1.2	5.3 ± 1.2	0.4 (0.04–0.9)	4.8 ± 1.3	5.2 ± 1.2	0.4 (−0.05–0.9)
VascuQoL emotional score	5.3 ± 1.2	5.7 ± 1.3	0.4 (−0.02–0.8)	5.2 ± 1.3	5.5 ± 1.1	0.3 (−0.03–0.7)
VascuQoL total score	4.7 ± 1.1	5.2 ± 1.2	0.5 (0.1–0.9)	4.6 ± 1.1	5.0 ± 1.1	0.4 (0.02–0.8)
SF-36 physical functioning	52.2 ±17.6	61.7 ± 19.9	9.4 (3.1–15.8)	53.8 ± 18	61.5 ± 20.3	7.7 (1.3–14.1)
SF-36 role physical	52.8 ± 22.3	63.9 ± 24.5	11.1 (4.0–18.2)	53 ± 23.4	57.3 ± 23.4	4.3 (−4.2–12.7)
SF-36 pain	49 ± 21.3	55.6 ± 20.3	6.6 (−2.1–15.3)	47.6 ± 20.4	57.5 ± 23.6	9.9 (0.9–18.9)
SF-36 general health	52.7 ± 20.4	54.6 ± 18.1	1.9 (−4.1–8.0)	54.7 ± 20.6	53.2 ± 19.5	−1.5 (−6.6–3.5)
SF-36 vitality	54.6 ± 18.2	54.9 ± 20.7	0.2 (−7.7–8.1)	53.3 ± 18.1	54.8 ± 22.0	1.4 (−5.2–8.0)
SF-36 social functioning	77.8 ± 24.5	79.9 ± 25.4	2.1 (−6.8–10.9)	77.5 ± 24.7	76.5 ± 27.8	−1.0 (−11.7–9.7)
SF-36 role emotional	72.7 ± 24.9	77.3 ± 26.5	4.6 (−3.9–13.2)	73.7 ± 25.2	77.7 ± 26.5	4.0 (−6.6–14.6)
SF-36 mental health	75.8 ± 13.2	78.9 ± 17.4	3.1 (−4.3–10.4)	76.8 ± 13.9	78.0 ± 18.6	1.2 (−4.7–7.0)
SF-36 physical component summary	38.5 ± 7.1	41.7 ± 7.5	3.3 (1.4–5.1)	38.6 ± 6.7	41.0 ± 8.6	2.4 (0.1–4.8)
SF-36 mental component summary	52.3 ± 9.2	52.5 ± 10.0	0.2 (−3.2–3.6)	52.4 ± 8.9	52.3 ± 11.2	−0.2 (−3.4–3.0)
$\dot{V}O_{2peak}$ (mL·kg^{-1}·min^{-1})	17.7 ± 4.0	16.9 ± 4.6	−0.9 (−1.9 – 0.2)	17.4 ± 3.9	17.8 ± 4.1	0.4 (−0.5 – 1.2)
VAT (mL·kg^{-1}·min^{-1})	10.5 ± 1.9	9.8 ± 2.1	−0.8 (−1.4 – −0.1)	10.5 ± 1.9	10.1 ± 2.2	−0.3 (−1.1 – 0.4)
Peak power output (W)	110.3 ± 43.7	112.0 ± 44.5	1.7 (−3.1 – 6.4)	110.3 ± 43.7	114.1 ± 45.5	3.8 (−1.2 – 8.8)

ICD, intermittent claudication distance; *mL·kg^{-1}·min^{-1}*, millilitres per kilogram per minute; *MWD*, maximum walking distance; *QoL*, quality of life; *VascuQoL*, vascular quality of life questionnaire; *SF-36*, Short-Form 36; *VAT*, Ventilatory Anaerobic Threshold; *$\dot{V}O_{2peak}$*, peak oxygen consumption; *W*, watt.
Values are given as mean ± SD with mean difference given with 95% confidence intervals.