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RANDOMISED CLINICAL TRIAL

Editor's Choice – The Abdominal Aortic Aneurysm Get Fit Trial: A Randomised Controlled Trial of Exercise to Improve Fitness in Patients with Abdominal Aortic Aneurysm

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WHAT THIS PAPER ADDS

Improving cardiopulmonary exercise testing parameters through exercise training in the abdominal aortic aneurysm (AAA) surveillance population could reduce cardiovascular risk, peri-operative morbidity and mortality, and improve health related quality of life (HRQoL). An evidence based exercise programme that achieves this is yet to be established. This study describes a 24 week, community based exercise programme in AAA surveillance patients which produced significant improvements in peak VO_2, anaerobic threshold, triglycerides, and HRQoL. This provides an evidence based exercise intervention which could be used in definitive multicentre randomised controlled trials with the ultimate aim of reducing peri-operative, cardiovascular, and all cause morbidity and mortality in this high risk patient group.

Objective: Ruptured abdominal aortic aneurysm (AAA) carries a mortality rate of up to 80%. Elective repair prevents rupture, but peri-operative mortality remains at 2% – 3%. This mortality rate and long term survival rate are associated with impaired peak oxygen uptake (peak VO_2), oxygen uptake at anaerobic threshold (AT) and ventilatory equivalent for CO_2 ($VECO_2$) at AT on cardiopulmonary exercise testing (CPET). Improving fitness to optimise these variables could improve peri-operative and long term survival, but the required exercise training suitable for patients with AAA has yet to be established. This randomised controlled trial aimed to evaluate the effectiveness of 24 week, patient directed, community based exercise on CPET measured fitness in AAA surveillance patients.

Methods: This was a prospective randomised controlled trial in a tertiary UK vascular centre conducted using CONSORT guidelines. Patients on AAA surveillance ($n = 56$) were randomly assigned to either (1) a 24 week community exercise programme (CEP) with choice of gym or home exercises, or (2) standard clinical care including advice on weight loss and exercise. The primary outcome was change in peak VO_2 at 24 weeks, with secondary outcomes including AT, $VECO_2$, cardiovascular biomarkers (lipid profile, pro-B-type natriuretic peptide, and high sensitivity C reactive protein, body mass index, and HRQoL. Follow up was at eight, 16, 24, and 36 weeks to evaluate duration of benefit. All analyses were performed on an intention to treat basis.

Results: CEP patients ($n = 28$) achieved mean (95% confidence interval [CI]) improvements from baseline in peak VO_2 of 1.5 (95% CI 0.5 – 2.5), 2.1 (95% CI 1.1 – 3.2), 2.3 (95% CI 1.2 – 3.3), and 2.2 (95% CI 1.1, 3.3) mL/kg/min at 8, 16, 24, and 36 weeks, respectively. These changes in CEP patients were significantly greater than those seen in control patients at 16 ($p = .002$), 24 ($p = .031$), and 36 weeks ($p < .001$). There were also significant improvements in AT, triglyceride levels, and HRQoL in CEP patients.

Conclusion: This CEP significantly improved those CPET parameters associated with impaired peri-operative and long term survival in patients following AAA repair. These improvements were maintained at 12 weeks following the end of the programme.

Keywords: Abdominal aortic aneurysm, Cardiopulmonary exercise testing, Cardiopulmonary fitness, Exercise training, Peri-operative medicine, Pre-habilitation

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INTRODUCTION

Abdominal aortic aneurysms (AAAs) affect 4% — 8% of men over 65 and cause 9 000 deaths annually in the UK, with similar trends seen across Europe.[1–3] Timely elective repair prevents rupture but with 30 day peri-operative mortality risks of 3.2% for open surgical repair and 0.4% for endovascular repair.[4] In hospital complications increase length of stay, significantly contribute to costs and impair subsequent quality of life.[5,6]

Cardiopulmonary exercise testing (CPET) measures aerobic fitness and is now established as a method for assessing peri-operative risk in patients prior to major surgery.[7–9] Clinically important CPET variables include peak oxygen uptake, usually at maximum effort (peak VO_2), VO_2 at the anaerobic threshold (AT), and the ventilatory equivalent ratio for carbon dioxide (VE/VCO_2). The Manchester CPET Study Group confirmed that these variables were associated with peri-operative mortality, morbidity, and even long term survival in patients undergoing AAA surgery.[10,11] These studies reported that patients with pre-operative peak VO_2 $<$ 15 mL/kg/min, AT $<$ 10.2 mL/kg/min, or VE/VCO_2 $>$ 42 were at increased risk of 30 and 90 day mortality following AAA repair.[11] Perhaps more notably, peak VO_2, VE/VCO_2, and the number of abnormal CPET variables independently predicted subsequent long term survival.[10] Patients with favourable CPET measures of fitness also experienced fewer complications and shorter hospital stays.

There is mounting evidence that pre-operative exercise training improves these CPET variables as well as reducing cardiovascular risk and improving health related quality of life (HRQoL).[12–14] In patients with heart failure, a 1.0 mL/kg/min decrease in peak VO_2 equated to ~16% increase in all cause mortality risk.[15] However, in this same population, every 6% *increase* in peak VO_2, reduced all cause mortality by ~7%, demonstrating that even modest improvements may be clinically important.[16]

A number of previous trials have established that exercise training is safe in people with AAA and does not influence AAA growth.[17] There have also been a number of trials investigating its impact on peri-operative morbidity and mortality following AAA surgery.[18–23] However, these trials have all suffered from a variety of issues including poor compliance, low numbers, and methodological flaws.[24] Furthermore, hospital based aerobic exercise training exceeding 12 weeks has yet to be studied in the UK despite previous research demonstrating that exercise training of between 20 and 24 weeks was required to achieve clinically meaningful, sustained gains in peak VO_2 in patients of similar age.[18,20–22,25] This study investigated whether an exercise programme specifically designed for people with AAA delivers sustainable and clinically meaningful improvements in fitness measured by CPET.

The hypothesis was that 24 week, patient directed community exercise training, at home or in a gym, will achieve greater improvements in fitness in people with AAA than the advice currently given in standard clinical practice.

MATERIALS AND METHODS

The research was carried out in accordance with the Declaration of Helsinki and approved by the North West — Greater Manchester Central Research Ethics Committee. It was registered in ClinicalTrials.gov under reference number NCT02997618. Written informed consent was obtained from all patients included in the study.

This was a prospective randomised controlled trial (RCT) based at Wythenshawe hospital, a large urban tertiary vascular centre, conducted between November 2017 and February 2020.

Patient population

Consecutive patients attending the AAA surveillance clinics (which also serve patients with other peripheral aneurysms, as well as endovascular aneurysm repair follow up) at Wythenshawe were screened for initial eligibility before being invited for baseline assessment which included CPET (Supplementary Appendix S1). This baseline CPET and all other study CPETs were performed using a standardised methodology (Supplementary Appendix S2). Following this, full eligibility was confirmed based on the eligibility criteria shown in Table 1.

Eligible, consenting patients were then allocated (1:1 ratio) to one of the interventions using computer randomisation (MinimPy v0.2) with minimisation to stratify for age ($<$ 75 years, $\geq$ 75 years), sex, body mass index (BMI) ($<$ 30, $\geq$ 30), and baseline peak VO_2 ($<$ 15 mL/kg/min, $\geq$15 mL/kg/min).

Interventions

Community based exercise. Patients randomised to exercise training were prescribed a community exercise programme (CEP) with the choice of exercising in a local gym or at home.

CEP patients attended a 90 — 120 minute induction at a local lifeLEISURE gym where they were shown how to perform a bespoke exercise programme designed for elderly patients. The evidence based rationale for the design of the programme is available in Supplementary Appendix S3. The exercise prescription consisted of warm up, aerobic, resistance, stretching, and cool down exercises (Supplementary Appendix S4). Modified versions of these exercises were also demonstrated to allow patients to perform the programme at home, should they choose to. Each patient was asked to exercise in 45 — 60 minute sessions, spread out over the week to a total of at least 150 minutes of exercise/week at a moderate intensity, based on a score of 12 — 14 using the validated Borg's rating of perceived exertion (Supplementary Appendix S5).[26] The total duration of the programme was 24 weeks, during which time the participants were given free access to lifeLEISURE gyms.

Control. Standard clinical care with advice on exercise, diet, and weight loss as currently given to patients on AAA surveillance.[27]

Table 1. Eligibility criteria used in the Abdominal Aortic Aneurysm (AAA) Get Fit randomised controlled trial evaluating the effect of exercise training on peak oxygen uptake in patients with small abdominal aortic aneurysms undergoing surveillance

Inclusion criteria	Exclusion criteria
Men with AAA ≥3.0 <5.0 cm and women with AAA ≥3.0 <4.5 cm	Patients deemed not fit for elective AAA repair (open or EVAR) even following exercise training and weight loss
Potentially fit for elective AAA repair (open or EVAR)	Unable or unwilling to undertake CPET or exercise training
Aged 60–85 years inclusive	Severe liver disease (INR >2, serum albumin <3.0 g/dL, bilirubin >50 μmol/L)
Willing and able to complete CPET and engage in gym and/or home based exercise training	Unstable angina occurring more than once daily, angina that is increasing in frequency or precipitated by progressively less exercise, angina at rest or of recent onset (<2 months)
	Poorly controlled AF (AF >90 bpm) or other dysrhythmia: untreated paroxysmal AF
	Moderate or severe aortic valve stenosis (peak systolic pressure gradient >40 mmHg or with an aortic valve area <1 cm^2)
	Pericarditis or myocarditis within the previous six months
	ST segment depression >2 mm on electrocardiogram during baseline assessment CPET
	Diagnosis or treatment for a malignancy, other than basal cell carcinoma, within the previous 12 months

CPET = cardiopulmonary exercise testing; EVAR = endovascular aneurysm repair; AF = atrial fibrillation; INR = international normalised ratio.

Follow up

CEP was prescribed for a total of 24 weeks with follow up at eight, 16, and 24 weeks. There was a final follow up at 36 weeks to assess changes in CEP patients once the programme had ended.

Outcomes

The primary outcome measure was change in peak VO_2 on CPET at 24 weeks.

Secondary outcome measures (recorded at eight, 16, 24, and 36 weeks) were the changes in:

1. Peak VO_2 on CPET at 8, 16 and 36 weeks.
2. The following CPET parameters:
   a. Peak VO_2 as a percentage of predicted maximum
   b. Anaerobic threshold
   c. Ventilatory equivalent for CO_2 at anaerobic threshold
   d. Number of subthreshold CPET parameters (defined as peak VO_2 < 15 mL/kg/min, AT<10.2 mL/kg/min, and VE/VCO_2 at AT > 42)
   e. Heart rate (HR) as a percentage of predicted maximum to assess for differences in exertion level at the end of the test between the groups.
   f. Work (watts) at peak VO_2 as a percentage of predicted maximum.
3. Cardiovascular risk biomarkers:
   a. Lipid profile
   b. Fibrinogen
   c. N-terminal pro-B-type natriuretic peptide (pro-BNP)
   d. High sensitivity C reactive protein (hs-CRP).
4. Anthropometric cardiovascular risk factors:
   a. BMI
   b. Waist to hip ratio.
5. HRQoL using the Medical Outcomes Study SF-36v2 HRQoL questionnaire. The overall score was reported as two separate scores: a physical component summary (PCS) and a mental component summary (MCS).[28]
6. Habitual physical activity using the Physical Activity Scale for the Elderly (PASE) questionnaire.[29]

Blinding the participants to their intervention was not possible for obvious reasons. However, the clinician performing all CPETs for this study was blinded to the randomisation assigned to each patient and to their previous results for all outcome measures. As CPET produces objective measures reported by its in built software, interpretation bias would only be a potential issue for AT. For this reason, AT measurements were repeated by an experienced, suitably accredited, independent assessor.

Questionnaires were posted to the patient to be completed in private, on the day of, but not at, each follow up appointment to minimise response bias.

Sample size. An increase in peak VO_2 (the primary outcome measure) by 1.5 mL/kg/min from the baseline CPET study equates to a theoretical reduction in all cause mortality of ~8.3% based on previous studies in people with AAA and other cardiovascular disease.[10,15] This was considered a clinically meaningful change by both the study team and the patient and public involvement group. Assuming the standard deviation of 1.5 mL/kg/min in peak VO_2 from these same studies, a total of 56 patients (28 in each group) was needed to achieve 80% power with statistical significance at the 5% level allowing for a 35% ($n = 20$) attrition rate.

Statistical methods. The statistical plan was agreed between the authors and the Medical Statistics Department at the University of Manchester prior to the start of the study.

Baseline demographics were described using simple summary statistics. An independent samples t test was used to check for differences in continuous variables after performing Levene's test of equal variance to determine the appropriate calculation. Dichotomous variables were compared using the

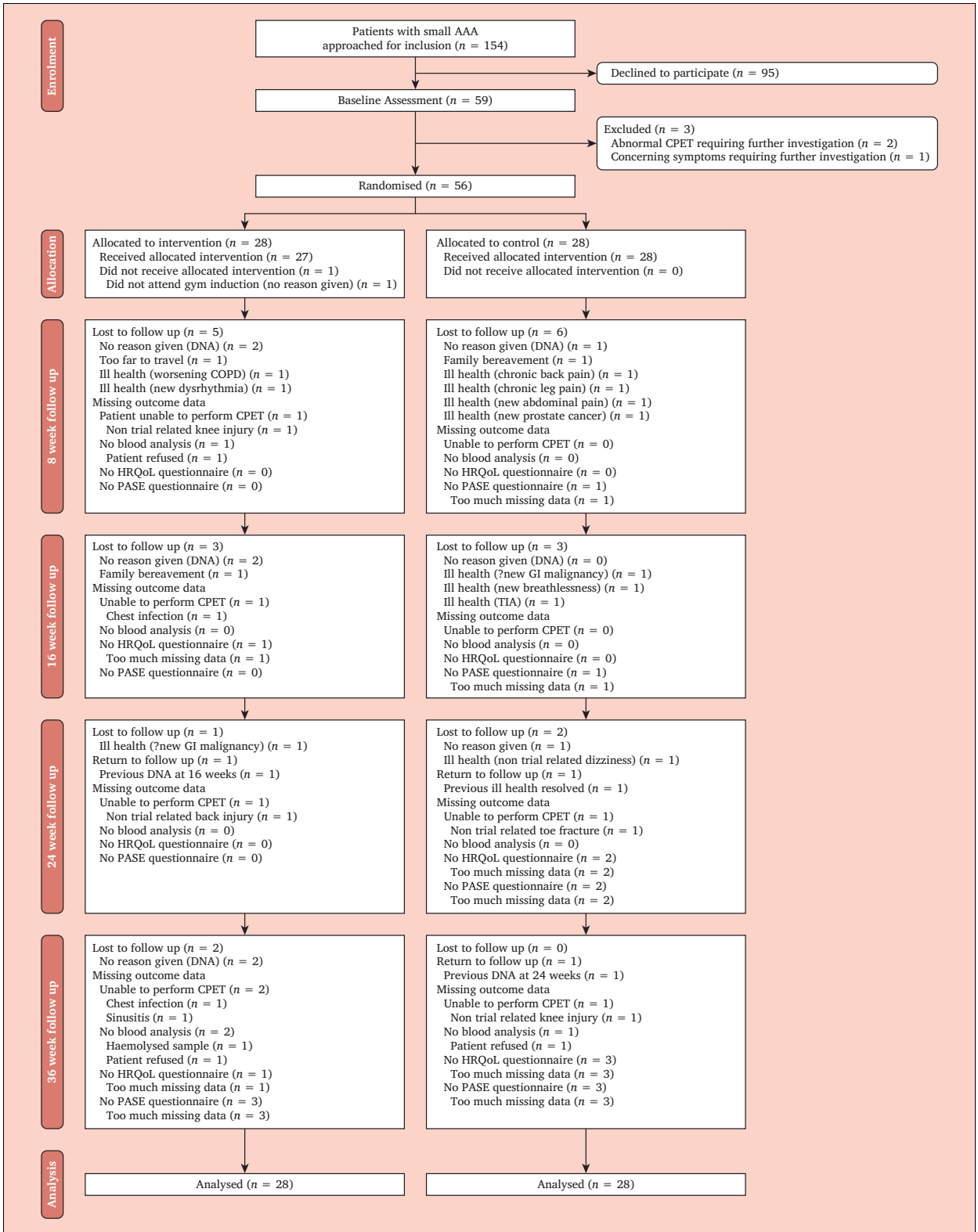

Figure 1. Consolidated standards of reporting trials (CONSORT) diagram of participant flow in the Abdominal Aortic Aneurysm (AAA) Get Fit randomised controlled trial evaluating the effect of exercise training on peak oxygen uptake in patients with small abdominal aortic aneurysms undergoing surveillance, including loss to follow up and the reasons for this. Of the 154 patients with small AAA approached for inclusion, 59 (38.8%) agreed to participate, of whom a further three were excluded due to abnormalities found during baseline assessment. Attrition rates were 19.6% ($n = 11$) at eight weeks, 30.4% ($n = 17$) at 16 weeks, 32.1% ($n = 18$) at 24 weeks, and 33.9% ($n = 19$) at 36 weeks. The majority of participants who dropped out contacted the research team to explain the reasons why they could no longer continue. COPD = chronic obstructive pulmonary disease; CPET = cardiopulmonary exercise testing; DNA = did not attend; GI = gastrointestinal; HRQoL = health related quality of life; PASE = Physical Activity Scale for the Elderly; TIA = transient ischaemic attack.

chi squared test or Fisher's exact test. All significance testing was two tailed at a 5% level. All analyses were performed on an intention to treat basis. Random effects linear mixed models for repeated measures were used to compare the two groups over time.[30] Time was modelled as a discrete factor (as the repeated measures variable) in order to capture non-linear behaviour. This produced an interaction effect between groups and time which allowed for an overall test of the shape of the profiles in each group and comparison of CEP and control over the full follow up time period. Using this model, *post hoc* contrasts were generated to compare changes from baseline between groups to allow further interrogation of where interactions took place. No clinically significant differences in primary baseline demographics were found between those who dropped out after baseline assessment and those who remained in the study. The interaction effects between groups and time for each variable were reported as *p* values. Changes from baseline and comparisons between exercise and control groups were reported as mean with associated confidence intervals (95% CI) and *p* values where appropriate. Absolute marginal mean values, calculated using the described statistical model, were reported as means with 95% CI to provide additional clinical context to the changes.

These analyses were undertaken in Stata 15.1 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC) and a 5% significance level was assumed. All graphs, figures, and tables were created using Microsoft Office Excel 2016. (Microsoft Corporation. 2018. Microsoft Excel).

The study has been prepared for dissemination in accordance to the Consolidated Standards of Reporting Trials (CONSORT) statement.[31]

RESULTS

Recruitment and participant flow

A total of 59 of 154 (38.3%) consecutive eligible AAA surveillance patients agreed to participate and attended baseline assessment. Three patients were excluded following baseline assessment, all requiring referral to cardiology. A total of 56 patients were randomised on a 1:1 basis to either patient directed, community based exercise (CEP) ($n = 28$) or standard clinical care (control) ($n = 28$).

The CONSORT diagram of participant flow, including loss to follow up (and the reasons for this), can be seen in Figure 1. There were no reported harms or unintended effects in either group at any time interval.

Baseline data

The 56 randomised patients had a mean (standard deviation [SD]) age of 72.8 (5.7) years, with 86% male sex and 98% Caucasian. Mean AAA diameter (SD) on consent to the trial was the same at 3.8 (0.5) cm in both groups.

Baseline mean (SD) peak VO_2 was 15.2 (3.8) mL/kg/min in the CEP patients and 18.1 (5.9) mL/kg/min in control patients; a mean difference of 2.8 (95% CI 0.2 − 5.5) mL/kg/min. Baseline triglycerides were also greater in CEP patients than control patients ($p = .023$). There were no other important differences in baseline characteristics between the groups (Table 2 and Supplementary Appendix S6).

Cardiopulmonary exercise testing outcomes

Changes in CPET parameters between the CEP and control patients with statistical analysis of any differences are shown in Table 3.

Peak oxygen uptake (primary outcome measure). Overall, there was a significant interaction effect for peak VO_2 between group and time ($p = .003$). CEP patients achieved significantly greater improvements in peak VO_2 than control patients from 16 weeks onwards, including a difference of 1.6 (95% CI 0.1 − 3.1) mL/kg/min ($p = .031$) at the primary outcome interval of 24 weeks. The greatest divergence between CEP and control patients was 2.7 (95% CI 1.2 − 4.2) mL/kg/min ($p < .001$) at 36 weeks.

CEP patients achieved significant improvements in mean peak VO_2 of 1.5 (95% CI 0.5 − 2.5), 2.1 (95% CI 1.1 − 3.2), 2.3 (95% CI 1.2 − 3.3), and 2.2 (95% CI 1.1 − 3.3) mL/kg/min at eight, 16, 24, and 36 weeks from baseline respectively. In absolute terms, peak VO_2 rose from 15.2 (95% CI 13.3 − 17.2) to 17.5 (95% CI 15.5 − 19.5) mL/kg/min at 24 weeks, an improvement that was maintained at 36 weeks. The changes in peak VO_2 from baseline never achieved statistical significance in control patients at any follow up interval.

CEP achieved a steady improvement in peak VO_2 over the first 16 weeks followed by a relative plateau (Fig. 2).

Peak oxygen uptake as percentage of predicted maximum. Reporting peak VO_2 as a percentage of predicted maximum allows for an individual patient's ability. Again, there was a significant interaction effect ($p < .001$). The changes seen in CEP patients were significantly greater than those seen in control patients at 16 ($p = .001$), 24 ($p = .025$), and 36 weeks ($p < .001$) and had almost reached significance as early as eight weeks ($p = .050$). CEP achieved significant improvements at all time intervals from baseline, and by 36 weeks had improved from 67.6% (60.4 − 74.8) to 79.7% (71.9 − 87.5), almost equivalent to the 80% that would be expected in a healthy population.[32] In contrast, peak VO_2 trended to decline in control from 77.0% (69.8 − 84.2) at baseline to 74.0% (66.3 − 81.6) at 36 weeks.

Anaerobic threshold. Even though the interaction effect between group and time for AT did not quite reach significance ($p = .051$) there was a significant contrast in the improvements seen in CEP patients compared with control by 36 weeks ($p = .002$). There were significant improvements in mean AT from 9.8 (95% CI 8.9 − 10.7) mL/kg/min baseline at all time intervals in the CEP patients reaching 11.3 (95% CI 10.3 − 12.3) mL/kg/min at 36 weeks, an increase of 1.5 (95% CI 0.8 − 2.3) mL/kg/min. This AT was significantly greater than the threshold (< 10.2 mL/kg/min) associated with impaired perioperative survival. There were no significant changes in AT in control patients (Fig. 3).

Table 2. Baseline characteristics of 56 patients enrolled in the Abdominal Aortic Aneurysm (AAA) Get Fit randomised controlled trial evaluating the effect of exercise training on peak oxygen uptake in patients with small abdominal aortic aneurysms undergoing surveillance

	Overall (n = 56)	CEP patients (n = 28)	Control patients (n = 28)	Mean (95% CI) or % difference	p value*
Patient characteristics					
Age − y	72.8 ± 5.7	73.3 ± 5.3	72.4 ± 6.2	−0.9 (−3.9 − 2.2)	.56
Sex	48 (85.7)	24 (85.7)	24 (85.7)	0	1.0
Caucasian ethnicity	55 (98.2)	27 (96.4)	28 (100)	3.4	.31
AAA size − cm	3.8 ± 0.5	3.8 ± 0.5	3.8 ± 0.5	0.1 (−0.2 − 0.3)	.64
Past medical history					
Hypertension	34 (60.7)	17 (60.7)	17 (60.7)	0.0	1.0
Type 2 diabetes	8 (14.3)	3 (10.7)	5 (17.9)	7.2	.71
Cholesterol	40 (71.4)	20 (71.4)	20 (71.4)	0.0	1.0
Peripheral arterial disease	12 (21.4)	5 (17.9)	7 (25)	7.1	.52
Current smoker	9 (16.1)	3 (10.7)	6 (21.4)	10.7	.47
Ex-smoker	36 (64.3)	19 (67.9)	17 (60.7)	−7.2	.58
Angina	6 (10.7)	4 (14.3)	2 (7.1)	−7.14	.67
Myocardial infarction	7 (12.5)	5 (17.9)	2 (7.1)	−10.71	.42
Coronary artery bypass graft	5 (8.9)	3 (10.7)	2 (7.1)	−3.6	1.0
Cardiac stent	6 (10.7)	4 (14.3)	2 (7.1)	−7.1	.67
Cerebrovascular accidents, stroke or TIA	9 (16.1)	6 (21.4)	3 (10.7)	−10.7	.47
Previous malignancy	10 (17.9)	7 (25)	3 (10.7)	−14.3	.16
Osteoarthritis	29 (51.8)	16 (57.1)	13 (46.4)	−10.7	.42
Asthma	4 (7.1)	2 (7.1)	2 (7.1)	0.0	1.0
Chronic obstructive pulmonary disease	6 (10.7)	3 (10.7)	3 (10.7)	0.0	1.0
Clinical examination					
BMI − kg/m^2	27.7 ± 3.6	27.8 ± 4.1	27.6 ± 3.0	−0.2 (−2.2−1.7)	.81
Waist:hip ratio	0.96 ± 0.1	0.96 ± 0.07	0.95 ± 0.07	−0.01 (−0.04−0.03)	.73
CPET variables					
Peak VO_2 − mL/kg/min	16.6 ± 5.1	15.2 ± 3.8	18.1 ± 5.9	2.8 (0.2−5.5)	.037
Peak VO_2 − % of predicted maximum	72.3 ± 19.2	67.6 ± 20.7	77.0 ± 16.7	9.4 (−0.7−19.4)	.068
Anaerobic threshold − mL/kg/min	10.2 ± 2.3	9.8 ± 2.1	10.8 ± 2.5	1.0 (−0.2−2.3)	.11
VE/VCO_2 at AT	29.7 ± 6.5	29.8 ± 6.9	29.5 ± 6.2	−0.3 (−3.8−3.2)	.87
≥2 subthreshold CPET variables	19 (33.9)	14 (50)	5 (17.8)	−32.2	.011
Heart rate at peak VO_2 − % of predicted maximum	82.6 ± 14.4	80.8 ± 13.1	84.4 ± 15.6	3.7 (−4.0−11.4)	.34
Watts at peak VO_2	111.7 ± 41.8	102.0 ± 35.8	121.3 ± 45.6	19.3 (−2.7−41.3)	.084
Watts at peak VO_2 − % of predicted maximum	87.6 ± 25.3	81.0 ± 25.8	94.1 ± 23.4	13.1 (−0.1−26.3)	.051
Health related quality of life					
HRQoL physical component score	46.9 ± 10.7	45.9 ± 10.5	48.0 ± 11.1	2.1 (−3.8−8.0)	.48
HRQoL mental component score	53.6 ± 8.6	53.9 ± 8.2	53.3 ± 9.3	−0.6 (−5.3−4.1)	.80
Habitual physical activity					
PASE score	167.0 ± 89.0	158.3 ± 92.5	175.8 ± 86.2	17.5 (−30.4−65.4)	.47

Data are presented as n (%) or mean ± standard deviation, unless stated otherwise. AAA = abdominal aortic aneurysm; BMI = body mass index; CEP = community exercise programme; CI = confidence interval; HRQoL = health related quality of life; PASE = Physical Activity Scale for the Elderly; VE/VCO_2 at AT = ventilatory equivalent for carbon dioxide at anaerobic threshold; VO_2 = oxygen uptake.
* The p value refers to univariable comparison between the community exercise programme and the control group.

Ventilatory equivalent for carbon dioxide at anaerobic threshold. The interaction effect between the groups and time for VE/VCO_2 was non-significant (p = .53) nor were there any significant contrasts in the changes between the groups at any time interval. However, VE/VCO_2 at AT in CEP patients had improved significantly by 16 weeks, a change of −2.6 (95% CI −4.1 − −1.1) from a baseline of 29.8 (95% CI 27.7 − 31.9) to 27.2 (95% CI 25.0 − 29.5), these improvements were then maintained at 27.3 (95% CI 25.0 − 29.6) by 24 weeks; and had improved further to 26.8 (95% CI 24.4 − 29.1) at 36 weeks. There were again no significant changes from baseline in control patients. The improvements seen with CEP meant that the mean (95% CI) VE/VCO_2 at AT had fallen to < 30, the threshold above which gas exchange is considered impaired, from 16 weeks onwards. This was not achieved in the control patients at any time.

Other cardiopulmonary exercise testing parameters. Heart rate at peak VO_2 (a surrogate for exercise intensity) was similar in CEP and control patients at all follow up intervals, suggesting that the above changes in the CPET variables were not attributable to differences in patient effort This is demonstrated by the non-significant interaction effect (p =

Table 3. Changes in cardiopulmonary exercise testing parameters observed in the 56 patients enrolled in the Abdominal Aortic Aneurysm (AAA) Get Fit randomised controlled trial evaluating the effect of exercise training on peak oxygen uptake in patients with small abdominal aortic aneurysms undergoing surveillance

	CEP patients (n = 28)			Control patients (n = 28)			Contrast in changes between the groups (95% CI)	p value
	n	Mean (95% CI)	Mean change from baseline (95% CI)	n	Mean (95% CI)	Mean change from baseline (95% CI)		
Peak VO_2 − mL/kg/min, threshold for impaired peri-operative and long term survival <15 mL/kg/min								
Interaction effect (group × time)								.004†
Baseline	28	15.2 (13.3−17.2)		28	18.1 (16.1−20.0)			
8 weeks	21	16.7 (14.7−18.7)	1.5 (0.5−2.5)*	22	18.3 (16.3−20.3)	0.2 (−0.7−1.2)	1.2 (−0.1−2.6)	.069
16 weeks	19	17.4 (15.3−19.4)	2.1 (1.1−3.2)*	19	17.9 (15.9−19.9)	−0.2 (−1.2−0.8)	2.3 (0.9−3.8)†	.002†
24 weeks	19	17.5 (15.5−19.5)	2.3 (1.2−3.3)*	18	18.7 (16.7−20.8)	0.7 (−0.4−1.7)	1.6 (0.1−3.1)†	.031†
36 weeks	15	17.5 (15.4−19.5)	2.2 (1.1−3.3)*	18	17.6 (15.6−19.6)	−0.5 (−1.5−0.5)	2.7 (1.2−4.2)†	<.001†
Peak VO_2 − % of predicted maximum, threshold expected in normal healthy population >80% mL/kg/min								
Interaction effect (group × time)								<.001†
Baseline	28	67.6 (60.4−74.8)		28	77.0 (69.8−84.2)			
8 weeks	21	73.2 (65.7−80.7)	5.6 (1.2−10.0)*	22	76.5 (69.0−83.9)	−0.5 (−4.8−3.8)	6.1 (0.0−12.3)	.050
16 weeks	19	77.0 (69.3−84.6)	9.4 (4.7−14.0)*	19	75.1 (67.5−82.6)	−1.9 (−6.4−2.6)	11.3 (4.8−17.7)†	.001†
24 weeks	19	76.9 (69.2−84.5)	9.3 (4.6−13.9)*	18	78.6 (71.0−86.3)	1.7 (−3.0−6.4)	7.6 (1.0−14.2)†	.025†
36 weeks	15	79.7 (71.9−87.5)	12.1 (7.2−17.0)*	18	74.0 (66.3−81.6)	−3.0 (−7.6−1.6)	15.1 (8.4−21.9)†	<.001†
Anaerobic threshold − mL/kg/min, threshold for impaired peri-operative survival <10.2 mL/kg/min								
Interaction effect (group × time)								.051
Baseline	28	9.8 (8.9−10.7)		27	10.8 (9.9−11.7)			
8 weeks	21	10.7 (9.7−11.6)	0.9 (0.3−1.5)*	22	11.2 (10.2−12.1)	0.4 (−0.3−1.0)	0.5 (−0.4−1.4)	.25
16 weeks	19	10.7 (9.7−11.7)	0.9 (0.2−1.6)*	19	10.9 (10.0−11.9)	0.1 (−0.6−0.9)	0.8 (−0.2−1.8)	.14
24 weeks	19	10.8 (9.8−11.8)	1.0 (0.3−1.7)*	18	11.2 (10.1−12.2)	0.4 (−0.4−1.1)	0.7 (−0.4−1.7)	.21
36 weeks	15	11.3 (10.3−12.3)	1.5 (0.8−2.3)*	18	10.7 (9.7−11.7)	−0.1 (−0.9−0.6)	1.7 (0.6−2.7)†	.002†
VE/VCO_2 at AT, threshold for impaired peri-operative and long term survival >42, threshold for impaired gas exchange >30								
Interaction effect (group × time)								.53
Baseline	28	29.8 (27.7−31.9)		28	29.5 (27.4−31.6)			
8 weeks	21	28.9 (26.8−31.1)	−0.9 (−2.1−0.3)	22	29.9 (27.7−32.1)	0.4 (−0.8−1.6)	−1.3 (−3.0−0.5)	.15
16 weeks	19	27.2 (25.0−29.5)	−2.6 (−4.1−−1.1)*	19	28.3 (26.1−30.5)	−1.2 (−2.7−0.2)	−1.4 (−3.4−0.7)	.19
24 weeks	19	27.3 (25.0−29.6)	−2.5 (−4.1−−1.0)*	18	28.2 (25.9−30.5)	−1.3 (−2.9−0.2)	−1.2 (−3.4−1.0)	.28
36 weeks	15	26.8 (24.4−29.1)	−3.0 (−4.7−−1.4)*	18	28.2 (25.9−30.5)	−1.3 (−2.9−0.3)	−1.7 (−4.0−0.6)	.14
Heart rate at peak VO_2 − % of predicted maximum, expected minimum for maximum exertion test >80								
Interaction effect (group × time)								.16
Baseline	28	80.8 (75.6−85.9)		28	84.4 (79.2−89.6)			
8 weeks	21	81.5 (76.1−86.9)	0.8 (−2.1−3.7)	22	87.6 (82.3−93.0)	3.2 (0.3−6.1)*	−2.4 (−6.5−1.6)	.24
16 weeks	19	84.5 (79.0−90.0)	3.8 (0.4−7.1)*	19	85.0 (79.5−90.4)	0.5 (−2.7−3.8)	3.2 (−1.4−7.9)	.17
24 weeks	19	83.4 (77.9−88.9)	2.7 (−0.7−6.0)	18	86.5 (81.0−92.1)	2.1 (−1.3−5.5)	0.6 (−4.2−5.4)	.82
36 weeks	15	84.0 (78.4−89.7)	3.3 (−0.3−6.9)	18	87.4 (81.9−92.9)	2.9 (−0.4−6.3)	0.3 (−4.6−5.3)	.89
Work at peak VO_2 − % of predicted maximum, expected minimum in normal population >80								
Interaction effect (group × time)								.001†
Baseline	28	81.0 (70.7−91.3)		28	94.1 (83.8−104.4)			
8 weeks	21	92.7 (82.2−103.3)	11.7 (6.8−16.6)*	22	97.2 (86.7−107.6)	3.0 (−1.7−7.8)	8.7 (1.9−15.5) †	.013†
16 weeks	19	100.0 (89.2−110.8)	19.0 (13.0−25.0)*	19	97.1 (86.4−107.8)	3.0 (−2.9−8.9)	16.0 (7.6−24.4) †	<.001†
24 weeks	19	104.3 (93.4−115.1)	23.3 (16.9−29.7)*	18	101.0 (90.1−111.9)	6.9 (0.5−13.3)*	16.4 (7.3−25.4)	<.001†
36 weeks	15	102.2 (91.1−113.4)	21.2 (14.3−28.2)*	18	99.8 (88.9−110.7)	5.7 (−0.8−12.3)	15.5 (5.9−25.1)†	.001†

CEP = community exercise programme; CI = confidence interval; VE/VCO_2 at AT = ventilatory equivalent for carbon dioxide at anaerobic threshold; VO_2 = oxygen uptake.
* Denotes statistically significant change from baseline.
† Denotes statistically significant change from control.

.16). The mean heart rate at peak exercise was > 80%, the expected minimum for a maximum exertion test at every time interval in both treatment and control patients, demonstrating that end exercise VO_2 was an appropriate measure of peak VO_2.[32]

Mean (95% CI) work at peak VO_2 as a percentage of predicted maximum increased significantly with time in CEP patients as their fitness improved, with a significant interaction effect between groups and time (p = .001) and significant contrast between the changes in the groups seen

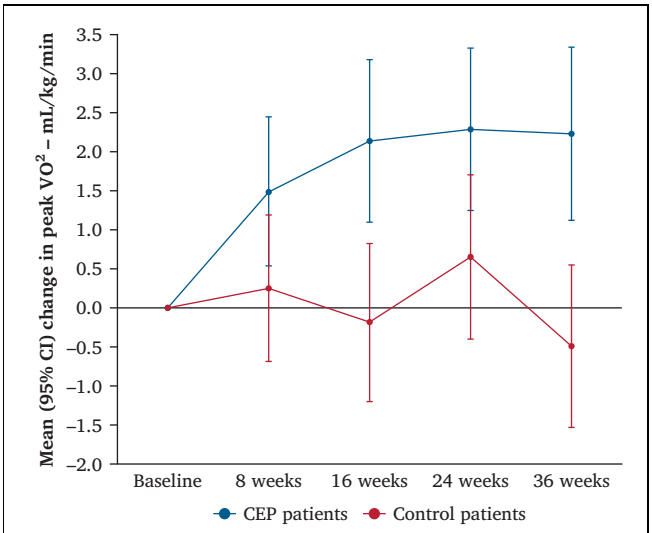

Figure 2. Changes in peak oxygen uptake (VO_2) in the Abdominal Aortic Aneurysm (AAA) Get Fit randomised controlled trial evaluating the effect of exercise training on peak oxygen uptake in patients with small abdominal aortic aneurysms undergoing surveillance, demonstrating significant improvements in community exercise programme (CEP) patients ($n = 28$) from baseline. These improvements were linear up to 16 weeks and then plateaued. The increase seen at the end of the exercise programme (24 weeks) was 2.3 (1.2 − 3.3) mL/kg/min, which was maintained at 2.2 (1.1 − 3.3) mL/kg/min at 36 weeks. There was no significant improvement seen from baseline in control patients ($n = 28$). A significant contrast in the changes in favour of an improvement in CEP patients was seen at 16 ($p = .002$), 24 ($p = .031$), and 36 weeks ($p < .001$). CI = confidence interval.

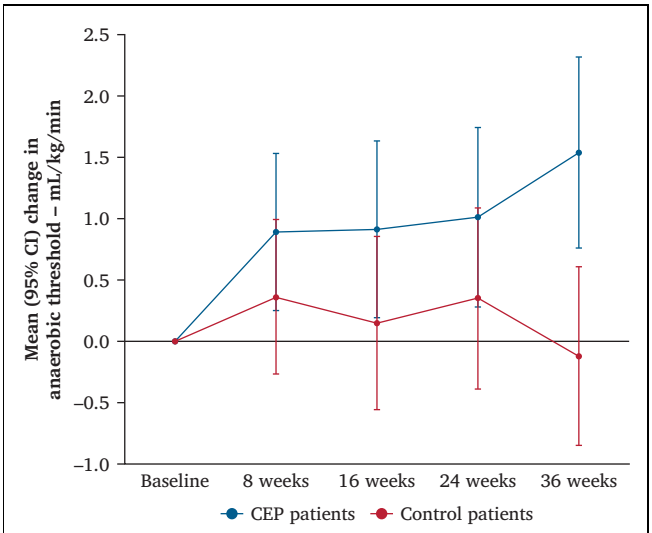

Figure 3. Changes in anaerobic threshold from baseline in the Abdominal Aortic Aneurysm (AAA) Get Fit randomised controlled trial evaluating the effect of exercise training on peak oxygen uptake in patients with small abdominal aortic aneurysms undergoing surveillance, showing a significant improvement in the anaerobic threshold (AT) from baseline at all time intervals in the community exercise programme (CEP) group. Conversely, there were no significant changes in AT in the control group at any time interval. By 36 weeks there was a significant contrast in the changes between CEP patients and control patients ($p = .002$). CI = confidence interval.

at each follow up interval. Although control patients were also advised to take exercise, there were no significant increases in the work these patients could achieve up until a marginally significant increase at 24 weeks, 6.9% (0.5 − 13.3) which had become non-significant again by 36 weeks 5.7% (−0.8 − 12.3).

Cardiovascular risk biomarkers

Triglycerides (normal range < 1.6 mmol/L) were the only cardiovascular risk biomarker which had a significant interaction effect between the groups and time ($p = .007$). This was caused by the significant fall in CEP patients from an abnormal baseline of 2.09 (3.41 − 4.19) to a normal value of 1.58 (1.22 − 1.94) by 36 weeks, a change of −0.51 (−0.80 − −0.21) mmol/L. This fall was −0.71 (−1.12 − −0.31) mmol/L ($p = .001$) greater than the insignificant change in control subjects.

The only other significant finding was in change in mean total serum cholesterol (normal range < 5.0 mmol/L). Although the interaction effect between the groups and time was non-significant ($p = .40$), there *was* a significant fall from a baseline in the CEP patients of 4.69 (4.25 − 5.13) to 4.33 (3.85 − 4.81) mmol/L by 36 weeks, a change of −0.36 (−0.68 − −0.05) mmol/L. There was no significant change in serum cholesterol in the control patients.

There were no significant interaction effects or contrasts between the groups in fibrinogen, pro-BNP, or hs CRP at any time interval in either CEP or control patients.

Changes in cardiovascular risk biomarkers are summarised in Supplementary Appendix S7.

Anthropometric markers of cardiovascular risk

There were no significant interaction effects between group and time in either BMI or waist:hip ratio. However, there was a minor reduction in BMI of −0.6 (−1.0 − −0.1) by 36 weeks though this was not a significant contrast with the change seen in CEP patients 0.4 (−0.1 − 0.8) ($p = .097$). There were no other significant changes in BMI nor waist:hip ratio in either group (Supplementary Appendix S7).

Health related quality of life and habitual activity levels

There was a significant interaction effect between groups and time in the HRQoL PCS score ($p = .037$) with a contrast in the change of the score in CEP compared with control patients of 5.5 (1.2 − 9.8) ($p = .013$) by 36 weeks (Table 4). The difference was due to an increase in the PCS (normal population minimum value of 45.0) in CEP patients from a baseline of 45.9 (42.1 − 49.8) to 47.7 (43.5 − 52.0) and a fall in PCS in control patients from 48.0 (44.0 − 52.0) to 44.3 (40.0 − 48.7).

The improvement in MCS (normal population minimum value of 45.0) for CEP patients from a baseline of 53.9 (50.7 − 57.1) to 56.4 (52.7 − 60.1) failed to achieve statistical significance ($p = .32$) with no change in control patients and this was also reflected in the non-significant interaction effect ($p = .66$).

Table 4. Changes in health related quality of life and physical activity scores of the 56 patients enrolled in the Abdominal Aortic Aneurysm (AAA) Get Fit randomised controlled trial evaluating the effect of exercise training on peak oxygen uptake in patients with small abdominal aortic aneurysms undergoing surveillance

Health related quality of life and habitual physical activity	CEP patients (n = 28)			Control patients (n = 28)			Contrast in changes between the groups (95% CI)	p
	n	Mean (95% CI)	Mean change from baseline (95% CI)	n	Mean (95% CI)	Mean change from baseline (95% CI)		
HRQoL PCS, minimum threshold for normal population = 45								
Interaction effect (group × time)								.037†
Baseline	28	45.9 (42.1–49.8)		28	48.0 (44.0–52.0)			
8 weeks	22	47.6 (43.6–51.5)	1.6 (−0.6–3.9)	22	47.6 (43.5–51.7)	−0.4 (−2.7–1.9)	2.0 (−1.2–5.3)	.22
16 weeks	18	47.7 (43.5–51.8)	1.7 (−1.0–4.5)	19	47.4 (43.3–51.6)	−0.6 (−3.3–2.2)	2.3 (−1.6–6.2)	.25
24 weeks	19	45.4 (41.3–49.5)	−0.5 (−3.4–2.3)	16	47.8 (43.5–52.1)	−0.2 (−3.2–2.8)	−0.3 (−4.4–3.8)	.89
36 weeks	16	47.7 (43.5–52.0)	1.8 (−1.2–4.9)	16	44.3 (40.0–48.7)	−3.7* (−6.7–−0.6)	5.5 (1.2–9.8)†	.013†
HRQoL MCS, minimum threshold for normal population = 45								
Interaction effect (group × time)								.66
Baseline	28	53.9 (50.7–57.1)		28	53.3 (50.0–56.5)			
8 weeks	22	55.2 (51.8–58.6)	1.4 (−1.4–4.2)	22	52.3 (48.8–55.7)	−1.0 (−3.8–1.8)	2.4 (−1.6–6.3)	.24
16 weeks	18	55.0 (51.4–58.6)	1.1 (−1.9–4.1)	19	51.5 (47.9–55.0)	−1.8 (−4.8–1.2)	2.9 (−1.3–7.2)	.17
24 weeks	19	55.8 (52.3–59.4)	2.0 (−1.0–4.9)	16	53.8 (50.1–57.5)	0.5 (−2.6–3.7)	1.4 (−2.9–5.7)	.52
36 weeks	16	56.4 (52.7–60.1)	2.6 (−0.6–5.7)	16	53.6 (49.9–57.3)	0.3 (−2.8–3.5)	2.3 (−2.2–6.7)	.32
Physical activity scale for the elderly, mean ± standard deviation score in 70–75 year olds = 102.4 ± 53.7								
Interaction effect (group × time)								.91
Baseline	28	158.3 (125.8–190.7)		28	175.8 (143.4–208.3)			
8 weeks	21	175.4 (139.3–211.5)	17.1 (−18.7–52.9)	21	178.4 (142.2–214.6)	2.6 (−33.3–38.4)	14.5 (−36.2–65.2)	.58
16 weeks	19	159.4 (122.0–196.9)	1.1 (−36.0–38.3)	18	189.7 (151.4–227.9)	13.8 (−24.1–51.8)	−12.7 (−65.8–40.4)	.64
24 weeks	18	161.5 (123.4–199.7)	3.3 (−34.6–41.1)	16	173.6 (133.8–213.4)	−2.2 (−41.7–37.3)	5.5 (−49.3–60.2)	.85
36 weeks	14	153.5 (111.9–195.1)	−4.8 (−46.1–36.6)	16	165.6 (125.9–205.4)	−10.2 (−49.7–29.3)	5.4 (−51.8–62.6)	.85

CEP = community exercise programme; CI = confidence interval; HRQoL = health related quality of life; MCS = mental component summary; PASE = Physical Activity Scale for the Elderly; PCS = physical component summary.
* Denotes statistically significant change from baseline.
† Denotes statistically significant change from control.

There were no significant changes in self reported habitual physical activity on PASE questionnaire scoring at any follow up interval.

DISCUSSION

The AAA Get Fit Trial was designed to explore the effectiveness of a 24 week programme of community based exercise in AAA surveillance patients. Over the full follow up of 36 weeks, the CEP group achieved significant improvements compared with the control group in peak VO_2, peak VO_2 as a percentage of predicted maximum, work at peak VO_2, triglycerides, and the physical component of HRQoL. The CEP group had also achieved significantly greater improvements in AT than controls by 36 weeks. Importantly, the CEP group achieved significant improvements from baseline in all the CPET measures associated with perioperative and long term survival by 24 weeks, including peak VO_2 (primary outcome measure), AT, and VE/VCO_2. Furthermore, these improvements were maintained or even improved upon at 36 weeks, 12 weeks after the prescribed programme had stopped. The 15.1% improvement in peak VO_2 seen in CEP patients would theoretically equate to a 17.6% reduction in all cause mortality, based on evidence provided from a similar patient group.[16] There were no changes in heart rate at peak VO_2 between CEP and control patients at any time interval, suggesting the changes can be attributed to true improvements in cardiopulmonary fitness rather than differences in patient effort on CPET. In control patients, most CPET parameters trended to deterioration, adding to previously published evidence that patient fitness for surgery *declines* while on surveillance.[33]

The results of this RCT support previously published evidence that exercise training in AAA patients is well tolerated and effective.[19] There were no serious adverse events with CEP and, in fact, the study methodology allowed previously undetected, significant cardiovascular disease to be found and treated in three patients. Baseline patient characteristics were as expected for an UK AAA surveillance population, and although there were relatively low rates of statin (69.6%) and antiplatelet/anticoagulant (75.0%) use, this merely highlighted the already known wider problem of suboptimal best medical management in the AAA surveillance population.[34] Attrition rates were lower than those seen in other exercise studies in people with AAAs, demonstrating that this type of exercise was acceptable and improves compliance, though future studies should employ methods to attempt to improve this further.[20,21,23] This was the UK's first study on exercise

training of more than 12 weeks in people with AAA, and the results confirm previous research in elderly patients that training should be for longer than 20 weeks to achieve meaningful gains in peak VO_2.[25] The rate of improvement in CPET measures achieved by the CEP patients confirms that exercise needs to be for at least 16 weeks and that a strategy of 24 weeks achieves improved fitness for at least a further 12 weeks. Considering the median time on surveillance in this population is over three and a half years, there would be more than sufficient time to implement this length of programme as part of preparation prior to elective or even semi-urgent surgery.[35] Furthermore, exercise training also provides wider benefits which impact all patients on AAA surveillance. Regular exercise has been shown to promote anti-atherogenic modifications in vascular function, improve cardiac parasympathetic regulation, and protect against the damaging effects of reperfusion. It also reduces inflammation, stimulates angiogenesis, and reverses sarcopenia. These changes all act to reduce cardiovascular related mortality, which is the main cause of death in individuals with AAA regardless of whether they undergo surgical repair.[36,37] This is particularly important when it is considered that in the same population only 23.8% of the surveillance population underwent surgery and provides further support to the methodology of targeting such interventions at the AAA surveillance population.[35]

Limitations of this study include that peak VO_2 at baseline (and subsequently number of participants with two or more adverse CPET parameters) was significantly greater in control subjects than in the CEP patients. This occurred despite minimising on randomisation for peak $VO_2 > $ or $<$ 15 mL/kg/min (equivalent to the threshold associated with peri-operative survival). What effect this would have on the patients' ability to improve their fitness is open to conjecture. However, other CPET parameters which were not significantly different at baseline followed similar trends to those seen in peak VO_2, which suggests the effect was not important. Furthermore, the results include described changes from baseline and these were used as a reference level contrast that attempts to account for any difference in baseline value.

Another limitation, in common with all RCTs, was that patients who agree to take part in research tend to be more motivated than those that refuse. Although both recruitment and attrition rates were better than those achieved by previous research on exercise training in patients with AAA, the majority of patients (61.2%) still declined to take part, and with no significant differences in demographics between those who did and did not agree to take part, it is difficult to explore specific reasons for this.[21,22] However, efforts to improve this rate would need to be made to maximise effectiveness in clinical practice.

Another important consideration is how an exercise programme could be implemented into AAA surveillance within the confines of a public health system, such as the National Health Service. Poor provision of well evidenced exercise services in peripheral arterial disease has demonstrated that funding, resource, and patient compliance are probable barriers to implementation.[38] The proposed patient directed and community based exercise training programme is one that should be cheaper and easier to deliver for large populations compared with traditional hospital based supervised exercise. This approach also encourages patients to exercise at a location and time convenient to them, which should improve compliance. It would also enable "hub" vascular centres to deliver the same standard of exercise training to their "spoke" areas, solving one of the problems resulting from the centralisation of vascular services. However, it is appreciated that a full cost effectiveness analysis would be crucial prior to widespread implementation.

The European Society for Vascular Surgery highlights the importance of exercise in managing cardiovascular risk in patients with AAA, but also states that previously published evidence is of poor quality and non-specific.[39] The results from this trial address this issue and should now inform definitive multicentre RCTs with the aim of investigating the effect of improving CPET parameters with CEP on all potential clinical outcomes in AAA surveillance patients, including peri-operative morbidity and mortality, cardiovascular risk, HRQoL, and all cause mortality. Such studies would also need to include robust cost effectiveness analyses and may ultimately provide evidence to support the widespread implementation of CEP to improve outcomes for all individuals with AAA.

CONFLICT OF INTEREST

None.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2022.07.005.

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