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Effect of supervised aerobic exercise rehabilitation on physical fitness and quality-of-life in survivors of critical illness: an exploratory minimized controlled trial (PIX study)

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Editor's key points

- Mental and physical health are reduced after discharge from an intensive care unit (ICU), often for a prolonged period.
- However, the effects of interventions to improve recovery after ICU have been limited.
- This study found that a supervised, hospital-based aerobic training intervention improved physical fitness at 9 weeks but this was not sustained.
- There was also a possible improvement in mental well-being at 26 weeks.
- This type of intervention is feasible and further studies are required.

Background. Evidence is limited for the effectiveness of interventions for survivors of critical illness after hospital discharge. We explored the effect of an 8-week hospital-based exercise-training programme on physical fitness and quality-of-life.

Methods. In a parallel-group minimized controlled trial, patients were recruited before hospital discharge or in the intensive care follow-up clinic and enrolled 8–16 weeks after discharge. Each week, the intervention comprised two sessions of physiotherapist-led cycle ergometer exercise (30 min, moderate intensity) plus one equivalent unsupervised exercise session. The control group received usual care. The primary outcomes were the anaerobic threshold (in ml O_2 kg^{-1} min^{-1}) and physical function and mental health (SF-36 questionnaire v.2), measured at Weeks 9 (primary time point) and 26. Outcome assessors were blinded to group assignment.

Results. Thirty patients were allocated to the control and 29 to the intervention. For the anaerobic threshold outcome at Week 9, data were available for 17 control *vs* 13 intervention participants. There was a small benefit (*vs* control) for the anaerobic threshold of 1.8 (95% confidence interval, 0.4–3.2) ml O_2 kg^{-1} min^{-1}. This advantage was not sustained at Week 26. There was evidence for a possible beneficial effect of the intervention on self-reported physical function at Week 9 (3.4; −1.4 to 8.2 units) and on mental health at Week 26 (4.4; −2.4 to 11.2 units). These potential benefits should be examined robustly in any subsequent definitive trial.

Conclusions. The intervention appeared to accelerate the natural recovery process and seems feasible, but the fitness benefit was only short term.

Clinical trial registration. Current Controlled Trials ISRCTN65176374 (http://www.controlled-trials.com/ISRCTN65176374).

Keywords: anaerobic threshold; cardiopulmonary exercise test; rehabilitation, exercise therapy

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In England, Wales, and Northern Ireland, more than 120 000 people a year require admission to an intensive care unit (ICU), with the majority (~78%) surviving to be discharged home.[1] The long-term consequences of a stay in the ICU for physical and mental health are well documented, with a reduced quality-of-life post-discharge.[2] The decreasing short-term mortality of critical illness focuses attention on efforts to improve the health status of survivors.[3]

Previous randomized controlled trials have focused on home-based or self-directed rehabilitation. A UK-based study reported substantial improvements in the physical function sub-scale of the 36-item Medical Outcomes Study Short Form (SF-36) at 8 weeks and 6 months, after a 6-week intervention involving a self-help rehabilitation manual.[4] The PRaCTICaL study of nurse-led follow-up after hospital discharge showed no substantial benefit of a self-directed, manual-based, physical rehabilitation programme on quality-of-life (SF-36) at 12-months.[5] In an Australian setting, an 8-week home-based physical rehabilitation programme demonstrated no substantial benefit for SF-36 physical function score or 6-min walk test distance at 8 or 26 weeks.[6] Similarly, a recent pilot trial of 12 weeks of home-based rehabilitation via telemedicine reported

comparable substantial improvements in both control and intervention groups on the timed up and go test (an objective measure of ambulation ability).[7]

Clearly, evidence for the effectiveness of interventions for survivors of critical illness after hospital discharge is limited. No studies have examined the effect of a supervised, hospital-based, aerobic training intervention on a precise, objective marker of aerobic fitness. The anaerobic threshold derived from cardiopulmonary exercise testing represents a salient primary outcome in this regard, as a marker of cardiorespiratory health reflecting the ability to carry out activities of daily living or prolonged exercise without undue fatigue.[8 9]

The aim of this study, therefore, was to explore the effectiveness of a supervised, hospital-based aerobic exercise-training intervention on the anaerobic threshold and quality-of-life in ICU survivors. We proposed that the intervention would accelerate the natural recovery process in the short term.

Methods

Participants and sample size

Patients admitted to the ICU of one of two large teaching hospitals were invited to participate. Eligible patients were aged 18–65 yr, had received a minimum of 3 days of ventilator support (for the emergency management of trauma or sepsis), and had been discharged home within 6 months of hospital admission. The study exclusion criteria were the inability to climb a flight of stairs, enrolment in another rehabilitation programme, and medical contraindication to cardiopulmonary exercise testing.[10] Patients were recruited either before discharge from hospital or in the ICU follow-up clinic. Eligible patients providing written informed consent were enrolled in the study 8–16 weeks after leaving hospital. This time window was deliberately broad to maximize recruitment. The trial was approved by the Newcastle and North Tyneside 1 Research Ethics Committee on January 16, 2008 (ref.: 07/H0906/137) and registered with Current Controlled Trials (ref.: ISRCTN65176374).

Given that this was an exploratory trial, a formal sample size estimation is not presented herein. Our target sample size of ~60 patients was chosen to be large enough to be representative of the target population and to provide sufficient information to inform a subsequent definitive trial.[11]

Study design

This was an exploratory parallel-group minimized controlled trial that compared the effect of an 8-week exercise intervention, delivered after hospital discharge, with current usual care of follow-up by appropriate medical and surgical specialties but no formal rehabilitation programme.

Allocation

Participants were allocated to control or intervention arm using minimization to ensure balance between trial arms for potentially important prognostic factors assigned a priori.[12] We minimized on three factors; age (18–39 *vs* 40–65 yr), sex, and cause of entry to ICU (sepsis *vs* trauma). Allocation was concealed from those assessing eligibility and recruiting patients, with eligible patients allocated remotely via e-mail by the trial statistician. Importantly, the research nurses in charge of recruitment were unaware of the specific minimization factors being used and so could not deduce future group assignments by keeping track of the past-allocations to control or intervention groups. Minimization was performed using the Minim software[13] with a 1:1 allocation ratio and equal weighting for the three minimization factors. Participants could not be blinded to the group assignment, but outcome assessors were.

Intervention

The exercise intervention consisted of two hospital-based, physiotherapist-led supervised sessions per week. Participants were encouraged to add one unsupervised session each week of the same duration and intensity (e.g. a 30-min walk at a moderate pace). During the supervised sessions, participants exercised individually or in pairs for 40 min (including 5 min each of warm-up and cool-down) on a cycle ergometer (Life Fitness C Series C9i/C7i Exercise Bike, Life Fitness, Ely, UK). The exercise intensity was equivalent to levels 12–14 on the 6–20-point Borg scale of perceived exertion.[14] This intensity corresponds to moderate exercise, in which participants feel that the exertion is 'somewhat hard', and closely approximates the intensity at the anaerobic threshold.[15] The pedal resistance was increased progressively over the course of the intervention in line with improvements in fitness to maintain the same relative intensity (perceived exertion) throughout.

Outcome measures

The primary outcomes were the relative oxygen consumption at the anaerobic threshold (assessed during a cardiopulmonary exercise test on a cycle ergometer) and health-related quality-of-life using the SF-36 (version 2, UK norm-based) physical function and mental health sub-scales.[16] Of these, we define the anaerobic threshold as the outcome of main interest and importance, as it is a precise objective measure free from the threat of 'ascertainment bias' inherent in patient-reported outcomes. Data were collected after group allocation (before the start of the intervention period: baseline), at Week 9 (after the 8-week intervention), and at 26 weeks after randomization (18 weeks after the end of the intervention period). The time point of primary interest was Week 9. Baseline measures were secured 8 and 16 weeks post-hospital discharge.

Secondary outcomes secured at each time point were peak oxygen uptake, additional quality-of-life measures using the EuroQol-5D (EQ-5D) index (UK time trade-off value set) and 100 mm visual analogue scale,[17] and mood disorder using the Hospital Anxiety and Depression Scale.[18] Also, at the time of recruitment to the study, participants were asked to estimate their pre-morbid quality-of-life using the SF-36 instrument.

Cardiopulmonary exercise tests

The cardiopulmonary exercise tests were conducted on a cycle ergometer (Lode Corrival; BV Medical Technology, Groningen,

The Netherlands) using the MedGraphics Ultima gas exchange system (Tewkesbury, UK), according to the guidelines of the American Thoracic Society/American College of Chest Physicians.[10] The participants performed 3 min of unloaded cycling at 60 rpm, after 3 min of resting habituation on the cycle ergometer. The pedal resistance was then increased steadily to increase the workload at between 10 and 20 W per minute, with the aim of attaining the participant's predicted maximum exercise level in ~10 min. Participants exercised to volitional exhaustion.

The anaerobic threshold (V-slope method[19]) and peak oxygen uptake were read independently from each test by two investigators (G.D. and S.J.H.). When there was disagreement, the readers examined the test output in detail together and reached a consensus. The graphs of VO_2 and VCO_2 against time were first examined to confirm that the VCO_2 was consistently less than the VO_2 before the start of exercise. If not, the participant was judged to have been hyperventilating before the start of exercise. In these circumstances. the observed anaerobic threshold is an artifactually low pseudo-threshold[20] and was therefore recorded as 'indeterminate'.

Data analysis

The effect of the intervention was evaluated using an analysis of covariance (multiple regression) model. The Week 9 or 26 outcome was the dependent variable and trial arm (intervention and control) was the independent variable. The baseline value of the outcome, the three minimization variables, and study site were included as covariates. This model provides the difference between groups for the outcome in question, accounting appropriately for any chance imbalance between arms at baseline.[21] The minimization factors (age, sex, and cause of entry to ICU) must be included as covariates in the analysis for valid estimation of the intervention effect.[22] It is also recommended that the study site be included in the analysis as a fixed effect, as ignoring site differences results in less precise estimates of the intervention effect (wider confidence intervals).[23] For the physical function outcome, baseline mental health score was included as an additional covariate, as mental health is a non-specific predictor of outcome in this context.[24 25] That is, poorer mental health is associated with worse physical function in both groups, and by chance baseline mental health was higher in the control group; Table 1.

For the primary outcomes, patients with data available for Week 9 or 26 but with missing baseline data were included in the analysis to avoid violating the intention-to-treat principle.[26] This issue arose for the anaerobic threshold outcome, for which there were five such patients (three control, two intervention) at Week 9 and seven (three control, four intervention) at Week 26. These patients had participated as planned in the study but it so happened that their anaerobic threshold was considered to be indeterminate when the baseline cardiopulmonary exercise test was read. This problem was addressed by imputing the missing baseline values before conducting the main analysis. This method involves predicting the

Table 1 Sample baseline characteristics. Data are mean (SD) unless stated; the median and inter-quartile range (IQR) are presented for grossly skewed variables. APACHE, acute physiology and chronic health evaluation; ICNARC, Intensive Care National Audit and Research Centre; ICU, intensive care unit; LOS, length of stay; AT, anaerobic threshold; PF, physical function sub-scale; MH, mental health sub-scale; VAS, visual analogue scale; HADS, hospital anxiety and depression scale. For AT, $n=21$ control: 15 intervention. For peak oxygen uptake, HADS, EQ-5D, SF-36 PF, and timing of baseline measures post-discharge variables, $n=25$ control: 21 intervention. For SF-36 MH, $n=25$ control: 20 intervention. Additional details on specific reasons for ICU admission and comorbidities are provided in Supplementary Table S1

Variable	Control ($n=30$)	Intervention ($n=29$)
Age in years [mean (range)]	40.5 (19–60)	42.7 (18–65)
Sex (number female/male)	11/19	10/19
Diagnosis (number with trauma/sepsis)	13/17	15/14
APACHE-II	16.4 (7.8)	15.9 (7.9)
ICNARC physiology score	23.2 (9.5)	18.4 (8.2)
ICU LOS (days) [median (IQR)]	15 (7–23)	15 (10–23)
Total hospital LOS (days) [median (IQR)]	35 (26–50)	45 (31–93)
Timing of baseline measures post-hospital discharge (weeks)	11.1 (2.6)	10.3 (1.9)
Number of ventilator days [median (IQR)]	10 (5–19)	12 (8–18)
AT (ml O_2 kg^{-1} min^{-1})	10.4 (2.8)	10.4 (3.5)
SF-36 PF	37.4 (13.1)	36.7 (13.2)
SF-36 MH	48.8 (11.6)	43.0 (13.1)
SF-36 PF pre-morbid estimate	50.0 (10.9)	50.0 (12.2)
SF-36 MH pre-morbid estimate	50.0 (12.1)	48.7 (11.6)
Peak oxygen uptake (ml O_2 kg^{-1} min^{-1})	17.7 (6.9)	17.8 (7.7)
EQ-5D index [median (IQR)]	0.725 (0.516–0.814)	0.689 (0.258–0.822)
EQ-5D VAS	64 (23)	61 (26)
HADS-Anxiety [median (IQR)]	7.0 (2.5–11.0)	7.0 (4.0–12.0)
HADS-Depression [median (IQR)]	3.0 (1.0–7.5)	5.0 (2.0–8.5)

missing baseline values from the other covariates in the model (excluding treatment arm) using linear regression.[27] The treatment effect (intervention minus control) is presented with its 95% confidence interval. Analyses were conducted using the Stata® software (version 12.1, Stata Corp., College Station, TX, USA). Residual plots were inspected to confirm that models were correctly specified. In line with expert recommendations, we make no adjustments herein for multiple comparisons.[28]

Results

The participant flow through the trial is illustrated in Figure 1.

Recruitment took place between June 2008 and November 2010, with 26-week follow-up measures completed by May 2011. The trial terminated at the end of the grant funding period with the target sample size approximated. Baseline characteristics for each arm of the trial are given in Table 1. Additional details on specific reasons for ICU admission and comorbidities are provided in the Supplementary material. The groups were well-balanced at baseline for the majority of variables.

There were small-moderate chance imbalances for the Intensive Care National Audit and Research Centre (ICNARC) physiology score, the SF-36 mental health sub-scale score,

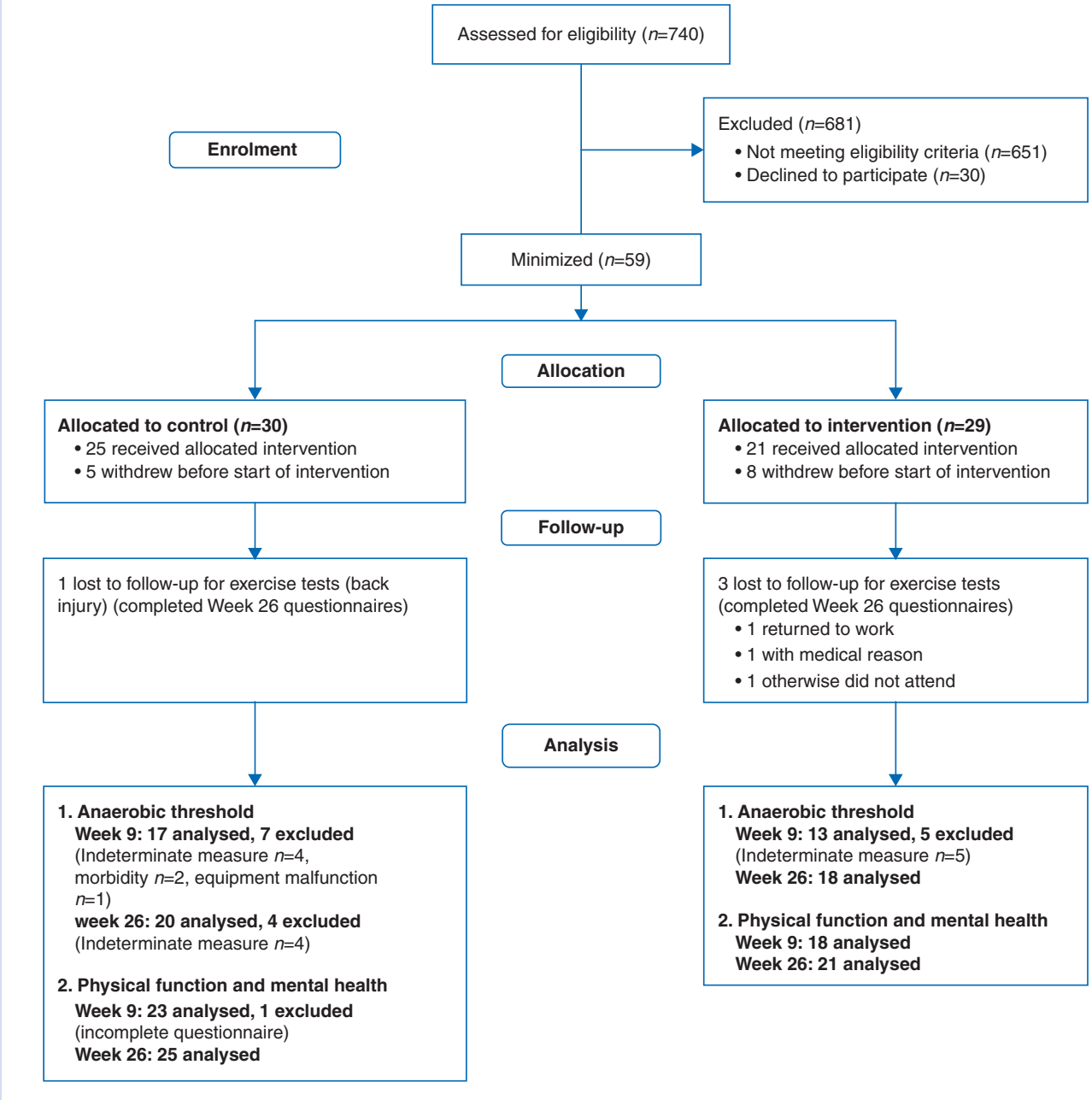

Fig 1 The CONSORT participant flow diagram for primary endpoints.

and total hospital length of stay. The mean ICNARC physiology score in the control group was around half a standard deviation (SD) higher than the population average,[1] whereas that in the intervention arm was more typical of the ICU patient population. Similarly, the mean SF-36 mental health sub-scale score was approximately half an SD higher in the control arm *vs* the intervention group. The median total hospital length of stay was 10 days longer in the intervention group *vs* control.

Approximately half of those receiving the intervention completed all 16 supervised exercise sessions (mean=12) and all 8 unsupervised sessions (self-reported brisk walking; mean=6). Residual plots for all primary and secondary analyses revealed that linear modelling of untransformed raw data was robust. Table 2 presents the effects of the intervention on the primary outcomes. Analysis was by the original assigned groups.

There were no harms or other unintended effects of the intervention. The analysis of the secondary outcomes is presented in Table 3; we place no inferential emphasis on these results and they are provided as descriptors only.

Anaerobic threshold outcome

At Week 9, there was a small beneficial mean effect of the intervention on the anaerobic threshold (Table 2) of around half an SD (Table 1). However, this advantage was not sustained at the Week 26 time point, where we observed a trivial mean difference between groups of <1 ml O_2 kg^{-1} min^{-1}.

Quality-of-life outcomes

Consistent with the anaerobic threshold outcome, mean self-reported physical function appeared to be higher in the intervention group at Week 9. Table 2 reveals that most of 95% confidence interval lies on the positive side, suggestive of a beneficial effect. However, the confidence interval also reveals that the true population effect could range from a trivial negative (harmful) effect of −0.1 SD to a moderate beneficial effect of 0.6 SD. At Week 26 the mean difference between groups for physical function was negligible. For mental health, there was no substantial difference between groups at Week 9, but a suggestion of a small beneficial effect of the intervention at Week 26. Again, the uncertainty revealed by the confidence interval indicates that the likely range for the true population effect on mental health at this time point is from trivial negative to moderate beneficial.

Discussion

Our main finding is that the intervention resulted in a small beneficial effect on physical fitness (anaerobic threshold) at 9 weeks. The minimum clinically important difference for the anaerobic threshold has yet to be firmly established, but we believe that an increase of this magnitude is a

Table 2 Effects on primary outcomes adjusted for baseline value. The adjusted mean value for each group at each time point is shown, with the numbers analysed in parentheses. AT, anaerobic threshold; PF, physical function sub-scale; MH, mental health sub-scale. *Also adjusted for baseline SF-36 mental health

Primary Outcome	Time point (week)	Control	Intervention	Difference (95% confidence interval)
AT (ml O_2 kg^{-1} min^{-1})	9	10.7 (17)	12.5 (13)	1.8 (0.4–3.2)
	26	12.1 (20)	12.7 (18)	0.6 (−1.6 to 2.8)
SF-36 PF*	9	40.1 (23)	43.5 (18)	3.4 (−1.4 to 8.2)
	26	46.6 (25)	46.7 (21)	0.1 (−6.0 to 6.2)
SF-36 MH	9	47.9 (23)	49.8 (18)	1.9 (−3.9 to 7.7)
	26	46.6 (25)	51.0 (21)	4.4 (−2.4 to 11.2)

Table 3 Effects on secondary outcomes adjusted for baseline value. The adjusted mean value for each group at each time point is shown, with the numbers analysed in parentheses. EQ-5D index, EuroQol-5D index (UK time trade-off value set); EQ-5D VAS, EuroQol-5D 100 mm visual analogue scale; HADS-Anxiety, Hospital Anxiety and Depression Scale Anxiety; HADS-Depression, Hospital Anxiety and Depression Scale Depression

Outcome	Time point (weeks)	Control	Intervention	Difference (95% confidence interval)
Peak oxygen uptake (ml O_2 kg^{-1} min^{-1})	9	20.5 (21)	21.1 (18)	0.6 (−1.8 to 3.0)
	26	20.4 (23)	22.0 (21)	1.6 (−1.0 to 4.2)
EQ-5D index	9	0.684 (23)	0.700 (18)	0.016 (−0.104 to 0.137)
	26	0.712 (25)	0.669 (21)	−0.043 (−0.174 to 0.088)
EQ-5D VAS	9	70.3 (22)	70.1 (18)	−0.2 (−8.7 to 8.3)
	26	74.1 (24)	70.0 (20)	−4.1 (−14.9 to 6.7)
HADS-Anxiety	9	6.6 (23)	6.7 (18)	0.1 (−1.6 to 1.8)
	26	7.0 (25)	6.3 (21)	−0.7 (−2.9 to 1.5)
HADS-Depression	9	4.9 (23)	4.1 (18)	−0.8 (−2.1 to 0.5)
	26	4.8 (25)	4.0 (21)	−0.8 (−2.6 to 1.0)

clinically meaningful effect. It appears that the exercise-training programme was sufficient to accelerate the natural recovery process in the short term and superimpose a beneficial physiological adaptation in the intervention group *vs* controls. This finding contrasts with a recent trial in which no substantial benefit was observed for 6-min walk test distance after a home-based endurance and strength training intervention.[6] Plausible explanations for this difference in results include possibly greater compliance with the intervention and a higher overall intensity of exercise training in our study. It should be noted that the focus of the intervention in the Elliott and colleagues[6] study was to optimize functional recovery during the first few months after a critical illness, as participants were recruited—and baseline outcome measures secured—within 1 week of hospital discharge. This time frame contrasts markedly with that in the current study and presents a competing hypothesis for the differences in findings.

The small benefit for anaerobic threshold was not sustained at Week 26. The data suggest that after stopping the intervention at Week 9 the control group essentially caught up with the physical fitness levels of the intervention group, with the latter maintaining their Week 9 fitness. This effect can be seen from the mean anaerobic threshold values in Table 2 for Week 26; the control group mean is 12.1 ml $O_2\,kg^{-1}\,min^{-1}$ *vs* 12.7 ml $O_2\,kg^{-1}\,min^{-1}$ in the intervention group. A larger trial, with precise objective monitoring of 24-7 physical activity energy expenditure, is required to define and explain any longer term effect of the intervention.

For self-reported physical function, there was a suggestion of a potential small beneficial effect at Week 9, consistent with the small benefit for objectively measured physical fitness; however, our exploratory study was not large enough to define this effect precisely, with a wide confidence interval around the mean observed effect. Again, this possible benefit was not apparent at Week 26, with similar mean physical function scores in both groups. This finding provides further support for our contention that the intervention is of most benefit for physical fitness/function in the short term, accelerating the natural recovery process; by Week 26 the groups are essentially equivalent as natural recovery prevails.

Our results revealed the importance of adjusting for any group differences in mental health when evaluating the effect of interventions on self-reported physical function. It has been shown that patients with worse mental health report more physical limitations, even after adjustment for objectively measured physical function.[25] Failure to adjust for the substantially higher baseline mental health score observed in the control group would bias the effect on physical function in favour of the control group, thus masking the true effect of the intervention. Indeed, re-running the analysis without baseline mental health as a covariate reduced the mean effect on self-reported physical function (intervention minus control) from a possibly small beneficial effect of 3.4 units (Table 2) to a trivial 1.1 units. We, therefore, urge investigators to account for self-reported mental health when comparing groups for self-reported physical function.

Interestingly, there was a suggestion of a potential small beneficial effect for self-reported mental health at Week 26, though again this effect was not precisely defined, as indicated by the relatively wide confidence limits. The intervention was stopped at Week 9, at which point there was apparently no substantial benefit for mental health. Complexity theory indicates that we should not expect the effects of interventions to be immediate or linear.[29] Indeed, beneficial effects on mental health might not manifest until the participants are no longer frequenting the clinical hospital setting in which they experienced their ICU stay. Further investigation of this potential 'delayed effect' of the intervention on mental health is warranted in a large definitive trial.

Comparing our quality-of-life findings with previous trials is difficult because of different methods and follow-up durations. Only one trial has shown substantial improvements in self-reported physical function, observed at 8 weeks and 6 months.[4] However, in that study it appears that pre-intervention physical function was not assessed and the equivalence of the groups at baseline is therefore unknown, potentially confounding the results.

It is important to acknowledge limitations to our study. First, this is an exploratory trial and the sample size is small leading to imprecision in estimation of some of the intervention effects. Secondly, there were substantial missing data. For the variable of primary interest (anaerobic threshold) at the Week 9 time point, follow-up data were available for 30 of 59 patients. Some of this loss to follow-up was beyond our control, including withdrawals before the start of the intervention, return to work, and morbidity (Fig. 1). However, a substantial proportion of Week 9 follow-up data ($n=9$ patients) was lost because of an indeterminate measure of anaerobic threshold (see Methods section). The anaerobic threshold was also indeterminate at baseline for a small number of patients. This phenomenon occurred because of hyperventilation pre-test, likely consequent to anxiety and/or poor accommodation to the mouthpiece. We might, therefore, have underestimated the amount of habituation required to stabilize the pre-test respiratory exchange ratio below unity in this patient population. Thirdly, there was no specific psychological or cognitive component to the intervention. Subject to feasibility and cost-effectiveness concerns, multicomponent interventions involving cognitive, physical, and functional training might be effective for targeting the post-intensive care syndrome broadly.[7] Fourthly, our eligibility criteria restricted the sample to patients admitted to the ICU with either sepsis or trauma. The effect of our intervention on a more diverse critical illness population is unknown and should be examined in a definitive trial. Fifthly, partly attributable to our eligibility criteria, our sample is relatively young compared with the general mean age of patients admitted to ICU of 61 yr.[1] The effect of our intervention—and compliance to it—in an older patient population is uncertain, and should also be evaluated in a definitive trial. Sixthly, the exercise intensity was prescribed using the patients' perceived exertion. Although the rating of perceived exertion and physiological measures of exercise intensity are strongly correlated, and the rating of 12–14 adopted in the current study is broadly coincident with the

intensity at the anaerobic threshold,[15 30] patients might have been exercising below, at, or less likely above this threshold. Future studies should seek to confirm the fidelity of the exercise intervention using objective physiological measures in addition to ratings of perceived exertion. Seventhly, there were small-moderate chance imbalances between groups at baseline for the ICNARC physiology score and total hospital length of stay. However, these variables were not included as covariates in the analysis as neither was predictive of any of the outcomes. The fact that these variables are not prognostic is possibly because patients discharged from hospital are at a broadly similar level of recovery irrespective of how sick they were to begin with (ICNARC) or their total length of stay. Finally, we acknowledge that there are many other potentially relevant outcome variables useful in determining functional recovery from critical illness, and these must be considered for any future definitive trial. For example, with 10–12 days of artificial ventilation, it is likely that a substantial proportion of patients would have experienced a degree of acute lung injury. Therefore, outcome data on resting and exercise respiratory parameters might be useful. Muscle strength and power would also be relevant outcomes, because of the muscle wasting consequent to critical illness.[31] In this regard, a more broadly focused intervention package, incorporating resistance training and aerobic training, might be more effective for functional recovery.

The intervention was well-tolerated, compliance was good, and implementing the exercise-training programme appears feasible. Further research is needed to build on the encouraging results of this exploratory trial. More sustainable fitness benefits might accrue with an intervention longer than 8 weeks. Alternatively, as the time course of adaptation in anaerobic threshold was not explored in the current study, future work should address this issue to see whether an intervention shorter than 8 weeks would be effective. Potentially, a short intervention could be delivered intermittently to maximize benefit over the longer term (e.g. 2–4 weeks on, 2–4 weeks off). Lower volume, higher-intensity interventions should also be explored, subject to due safety considerations in this heterogeneous patient population. The programme of research should address the level of habituation required to cardiopulmonary exercise testing in this patient population to prevent missing data for the anaerobic threshold because of pre-test hyperventilation. In addition, more work is required to help determine the optimum multicomponent intervention package (cognitive, psychological, physical, and functional) to maximize effectiveness and cost-effectiveness.

Finally, the current study focused exclusively on rehabilitation after hospital discharge. An emerging body of work is also examining the effectiveness of early mobilization and physical rehabilitation within the ICU[32] and research is needed to address the need for a tailored and integrated care package both pre- and post-discharge from hospital.[33]

Conclusions

We have shown that an 8-week supervised hospital-based aerobic exercise rehabilitation programme led to a small benefit in physical fitness that accelerated the natural recovery process in the short term. The results are encouraging and support the need for an iterative programme of work to develop and evaluate the effectiveness and cost-effectiveness of interventions for ICU survivors.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Authors' contributions

A.M.B. drafted the manuscript, contributed to the design of the study, and performed the statistical analyses. Original study concept was by S.B. and G.D. G.D. was Chief Investigator for the project, S.B. was Principal Investigator (PI) at James Cook University Hospital and S.J.H. was PI at Leeds General Infirmary. All the authors contributed to the critical revision of the manuscript for important intellectual content and read and approved the final manuscript.

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Declaration of interest

None declared.

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