Combined Resistance and Aerobic Exercise Intervention Improves Fitness, Insulin Resistance, and Quality of Life in Survivors of Childhood Haemopoietic Stem Cell Transplantation With Total Body Irradiation

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42 **Abbreviations table:**

Abbreviation	Full term or phrase
QoL	quality of life
HSCT	haemopoietic stem cell transplantation
TBI	total body irradiation
DEXA	dual energy X-ray absorptiometry
HOMA-IR	homeostatic model assessment of insulin resistance
$\dot{V}O_2$peak	peak rate of oxygen uptake
SF-36	36-Item Short Form Health Survey
SD	standard deviation
MMQL	Minneapolis-Manchester Quality of Life Instrument
GHD	growth hormone deficiency
GH	growth hormone
PRT	progressive resistance training programme
CNS	central nervous system
GVHD	graft versus host disease
ITT	insulin tolerance test
BMI	body mass index
BMISDS	body mass index standard deviation score
ECHO	echocardiogram
FVC	forced vital capacity

FEV1	forced expiratory volume in first second
SDS	standard deviation score
VT	ventilation threshold
Pulse O_2	the rate of oxygen uptake per heart beat ($\dot{V}O_2$/heart rate (HR))
HR	heart rate
RER	respiratory exchange ratio
ANOVA	one-way withinrepeated measures analysis of variance
FVCSDS	forced vital capacity standard deviation score
LSD	post-hocFisher's least significance difference method
GLUT-4	glucose transporter protein
AMPK	AMP-activated protein kinase
Akt	protein kinase B substrate
T2DM	type 2 diabetes mellitus
HRT	hormone replacement therapy

Abstract

Purpose: To investigate the effects of a supervised combined resistance and aerobic training programme on cardiorespiratory fitness, body composition, insulin resistance and quality of life(QoL) in survivors of childhood hematopoietic stem cell transplantation(HSCT) with total body irradiation(TBI).

Participants: HSCT/TBI survivors(*n*=20; 8 Female). Mean(range) for age at and time since HSCT/TBI was 16.7(10.9-24.5) and 8.4(2.3-16.0)yrs respectively.

Methods: After a 6-month run-in, participants undertook supervised 45-60-minute resistance and aerobic training twice-weekly for 6 months, with a 6-month follow-up. The following assessments were made at 0, 6(start of exercise programme), 12(end of exercise programme) and 18 months: Body composition via dual energy X-ray absorptiometry(DEXA), homeostatic model assessment of insulin resistance(HOMA-IR), cardiorespiratory fitness(treadmill based peak rate of oxygen uptake($\dot{V}O_2$peak) test), QoL questionnaires(36-Item Short Form Health Survey(SF-36) and Minneapolis-Manchester Quality of Life Instrument(MMQL).

Results: Results expressed as mean(SD) or geometric mean(range). There were significant improvements in $\dot{V}O_2$peak(35.7(8.9)vs.41.7(16.1)mL/min/kg, *P*=0.05), fasted plasma insulin(16.56(1.48-72.8)vs.12.62(1.04-54.97)mIU/L, *P*=0.03), and HOMA-IR(3.65(0.30-17.26)vs.2.72(0.22-12.89), *P*=0.02) after the exercise intervention. There were also significant improvements in the SF-36 QoL general health domain(69.7(14.3)vs.72.7(16.0), *P*<0.001) and the MMQL school domain (69.1(25.2)vs.(79.3(21.6), *P*=0.03) during the exercise intervention. No significant changes were observed in percentage body fat, fat mass or lean mass.

Conclusion: The supervised 6/12 combined resistance and aerobic exercise programme significantly improved cardiorespiratory fitness, insulin resistance and QoL in childhood HSCT/TBI survivors, with no change in body composition, suggesting a metabolic training effect on muscle. These data support a role for targeted physical rehabilitation services in this group at high risk of diabetes and cardiovascular disease.

Introduction

HSCT with TBI has significantly improved survival in childhood leukaemia but is associated with important long-term sequelae[1 2]. Survivors demonstrate central adiposity[3], reduced lean mass[4], and risk factors for the metabolic syndrome[5] including increased blood pressure[1], dyslipidaemia[5], insulin resistance, diabetes[6 3], and impaired β-cell function[7]. Growth hormone deficiency (GHD) after TBI also predisposes to these morbidities but they persist despite growth hormone (GH) treatment[8].

QoL in HSCT survivors is variable and whilst longer term studies are still needed in children[9], adults experience physical, cognitive and social difficulties, and fatigue[2 10]. Children with leukemia have reduced physical fitness, partly due to inactivity[10 11], but exercise has shown benefit, including to children after HSCT[12 13 14 15]. More generally, exercise programmes improve cancer treatment related fatigue and QoL [17 18 19].

Aerobic activity is the most commonly used intervention for reducing cardiovascular risk[16], and reduces visceral fat[17], insulin resistance[18], and blood pressure[19 20] in both adults and children. Progressive resistance training (PRT) also confers improvement in cardiovascular risk[20 21 22], and is becoming more widely utilised with potential benefit in increasing lean body mass[23 24] of particular relevance to HSCT/TBI survivors [25].

HSCT/TBI survivors therefore have a range of factors which may benefit from exercise rehabilitation including PRT. Our aim was to conduct a supervised combined aerobic and PRT in childhood survivors of HSCT/TBI, to examine effects on fitness, body composition, insulin resistance, and QoL.

Method

Ethical Approval: This study was conducted in accordance with the Declaration of Helsinki following approval by the NHS South West Frenchay Research Ethics Committee. Written informed consent was obtained from all participants.

Participants: Children/adolescents followed up after HSCT/TBI for haematological malignancy at a single regional centre between 1993-2004 were identified via the endocrine database and the Leukaemia registry. Eligible participants were those on GH replacement for GHD (to control for GH status)[26 27]. Participants were approached by their late effects team and 24 consented to participate. All were >1 year post-HSCT/TBI or any oncology or steroid treatment.

All were on GH treatment for >6months before study enrolment, for GHD diagnosed by standard insulin tolerance test (ITT) after documentation of poor growth. Demographic and oncology treatment data of participants are shown in Table 1.

Study Design: A within-subject longitudinal repeated measures study, frequently used in Sports science research[28]. Baseline data collection was performed at study entry (time1) and after a 6-month period of habitual activity and GH treatment (time2) to assess changes over time not attributable to the subsequent exercise intervention. A 6-month supervised aerobic and PRT followed with data collection at the end of the intervention (time3) and again, after a further 6-months (time4).

Data Collection: At each time point included auxology, body composition assessment with DEXA, HOMA-IR, cardiorespiratory fitness $\dot{V}O_2$peak test, and QoL questionnaires (SF-36 and MMQL).

Auxology: Height was measured to the nearest mm using a wall-mounted Harpenden® stadiometer (Holtain, Crymych, UK) calibrated daily, body weight to the nearest 0.1kg using a single set of scales (Seca®,Hamburg, Germany), both using standard auxology procedures[29]. Pubertal status was assessed using standard Tanner staging[30], by a single observer (ND). For males, only pubic hair and virilisation of the external genitalia were used, as testicular volume is not a reliable marker of puberty due to sertoli cell damage. Body mass index (BMI) was calculated as weight/height^2(kg/m^2) and converted to body mass index standard deviation score (BMISDS) using Cole's method[31].

Body Composition: DEXA fan-beam technique (Lunar Prodigy DF+15048 series, GE Healthcare, Madison, Wisconsin, USA) was used to differentiate whole body fat, lean mass, and percentage trunk fat.

QoL questionnaires: All participants (those<16 years with parental assistance) completed SF-36, a generic health related QoL measure for adults with chronic disease including cancer survivors[32] and those with GHD[33]. The SF-36 is well validated, widely used, and comprises 36 questions on general health and well-being during the previous 4 weeks. Data are presented as T scores i.e. are normalised with mean(SD) of 50(10). Higher scores indicate better quality of life. One or more SDs below the population mean demonstrates poor QoL. MMQL is a specific measure for childhood cancer survivors <18 years, demonstrated to show validity and reliability, with versions for youth, adolescents, and parents and carers of children. It is a comprehensive, multidimensional self-report instrument across 5 scales including physical, emotional, social, school and body image. It is the only questionnaire assessing satisfaction with appearance, potentially an important aspect for childhood cancer survivors[34]. Previous studies have shown that

childhood cancer survivors show similar overall QoL to controls with mean scores of 4/5 or 80%[34].

Assays: Laboratories were Clinical Pathology Accredited. Plasma samples for glucose were assayed within 4hrs (Olympus AU640 or AU2700 clinical chemistry analyser, Olympus, Hamburg, Germany). A commercially available ELISA kit (Human Insulin KAP1251 (MDC 0.15µIU/mL and CV 5.3%), BioSource Europe S.A., Nivelles, Belgium) was used to determine plasma insulin concentrations. The maximum time to assay was 24 months using plasma/serum samples frozen at -80^{o}C.

HOMA-IR: Venous blood (3mL), collected between 08:00 and 10:00 following overnight fasting for 8 to 12 hr were analysed for plasma glucose and insulin concentrations. HOMA-IR was calculated as: fasted plasma insulin concentration(mIU/L) x fasted plasma glucose concentration(mmol/L)/22.5[35].

Exercise intervention: Participants were required to perform 45-60 minutes of exercise at least twice, but preferably three times per week. KT, an exercise physiologist experienced in training children and young people and special groups, designed the generic programme, which was supervised by ND and local gym trainers with appropriate qualifications for children and young people to ensure individual participant safety. ND monitored attendance and progress. Patient feedback and study retention demonstrated that the participants enjoyed the exercise programme and found it valuable. In order to minimise the potential for an adverse cardiac event, each participant underwent an echocardiogram (ECHO), conducted and assessed by a cardiologist before proceeding with the intervention. All received an induction programme and were supervised at every session. They were asked to perform at least 15 minutes of self-

selected aerobic activity at moderate intensity (60-70% of maximum HR) followed by ≥30 minutes of PRT using body weight or standard machine-based PRT equipment and involving at least 9 major muscle groups, at resistance loads of 60-80% 1RM. The programme involved a standard range of flexion and extension exercises tailored to the individual. Initially, participants performed 1 set of 18-20 repetitions, progressing over 6-months to 3 sets of 10-12 repetitions for each muscle group. This approach minimised lean tissue loss initially, and maximised the likelihood of safe gains in lean mass. At baseline and every 6 weeks, 1 repetition maximum (1RM) strength tests (leg press and chest press) were undertaken by qualified instructors to monitor gains in skeletal muscle strength.

Isometric exercise was avoided due to the risk of cardiomyopathy from TBI and anthracycline toxicity.

Exercise test outcome measurements: Forced vital capacity (FVC) and forced expiratory volume over the first second (FEV1) were measured using spirometry. Results were expressed as standard deviation scores (SDS) adjusted for age, gender and stature[36]. A modified Balke 2 protocol was used[37] to measure $\dot{V}O_2$peak; participants walked/jogged on a motorised treadmill belt with incremental changes in speed and inclination every two minutes until volitional exhaustion. Respiratory data collected including the rates of oxygen uptake and carbon dioxide elimination ($\dot{V}CO_2$). $\dot{V}O_2$peak is traditionally expressed either in absolute terms (L/min) or relative to body mass (mL/min/kg), the latter assuming a constant relationship between lean mass and fat mass[38]. It is conventional to express measured $\dot{V}O_2$peak data relative to body mass[39] when comparing with published normal data for age and gender[40] and absolute $\dot{V}O_2$peak values were

187 divided by body weight to yield relative data. The ventilatory threshold (VT) was
188 assessed by the V-slope method[41] and refers to the point where aerobic metabolism is
189 supplemented by anaerobic mechanisms during progressive exercise, and can be
190 expressed as occurring at a percentage of $\dot{V}O_2$peak. Pulse O_2 is the rate of oxygen uptake
191 per heart beat ($\dot{V}O_2$/heart rate (HR)) and is a measure of circulatory efficiency increasing
192 with stature, and therefore age, in childhood. Respiratory exchange ratio (RER) is the
193 ratio $\dot{V}CO_2/\dot{V}O_2$. Peak exercise tests were considered truly at peak if at least two of the
194 following criteria were satisfied: a plateau (≤2 mL/min/kg) in the $\dot{V}O_2$ profile over the
195 final two exercise stages, HR ≥95% age-predicted maximum (220beats/min –
196 chronological age) and/or RER ≥1.10. Exercise test outcome measures were $\dot{V}O_2$, $\dot{V}CO_2$,
197 VT, Pulse O_2 and HR.
198 **Statistical analyses:** Statistical analyses were performed using IBM SPSS version 17.0
199 (IBM Corporation, New York, USA). Statistical significance was accepted at $P \leq 0.05$.
200 Normally distributed data were expressed as mean(SD). Skewed data were expressed as
201 geometric mean(range) and log-transformed(log10) to normalise the distribution and
202 facilitate the correct use of parametric statistical testing for between time comparisons.
203 Parametric data were compared overall using repeated measures analysis of variance
204 (ANOVA) followed by pairwise comparisons using the post-hoc Fisher's least
205 significance difference (LSD) method. As there were randomly missing data points, a
206 repeated measures analysis using the 'SAS mixed procedure' was used for between time
207 comparisons using ANOVA. This method uses a maximum likelihood method and
208 automatically excludes missing data by using mixed modelling. In this data the strength
209 of correlations between data at different time points did not vary significantly.

Proportions were compared using Chi-square or Fishers Exact tests when appropriate for smaller sample sizes.

Results

Twenty-four participants consented to the study and 20(8 females:12 males) completed the supervised combined aerobic and PRT. Exercise diaries demonstrated 85% attended at least twice weekly and 35% attended 3 times weekly over the 6-month period): 4 were unable to complete the intervention (sickness =2; time constraints =2). Sixteen completed post-exercise intervention data collection (4 unavailable due to relocation out of region). None had conditions which precluded exercise; 6 had reduced fractional shortening on ECHO attributed to subclinical anthracyline toxicity.

Baseline data (time1)

Cardiorespiratory fitness: Six participants displayed forced vital capacity standard deviation score (FVCSDS) <-3 suggesting restrictive lung deficits with mean maximal ventilation (FVCx40) reduced to <75% expected in healthy young people. However, as $\dot{V}O_2$ is the rate-limiting step, maximal ventilation is not usually reached during an exercise test. Peak ventilation as a proportion of the predicted maximal ventilation (FVCx40) was mean(SD) 58.6(18.8)%. Only one patient exercised at maximal ventilatory capacity with a FVCSDS of -5.78.

$\dot{V}O_2$peak divided by body mass was reduced at baseline (mean 35.7mL/min/kg) compared to published normal values for age and sex (females 39-45mL/min/kg and males 49-50mL/min/kg)[40].

Body Composition: Female participants had significantly higher body fat and trunk fat than males: female body fat mean(SD) 41.7(8.2)%vs.male 24.3(13.5)%,P<0.001; female

trunk fat 42.8(10.7)%vs.male 24.7(14.0)%,*P*=0.004). Female participants also had higher body fat than published UK normal data for females of the same age[42]. HOMA-IR values were greater (mean(range) 3.65(0.30-17.26)) than the published upper limit of normal (2.0= mean plus 2 SD)[43]. Sex differences were apparent in both fasted plasma insulin and HOMA-IR values, with higher levels in females: fasted plasma insulin mean (range) 25.0 (6.5-50.0)vs.9.5 (2.6-68.3)μIU/mL,*P*=0.013; HOMA-IR mean(range) 5.0(1.3-11.1)vs.2.2(0.5-18.3),*P*=0.047.

Baseline data (time2)

End of run in period: There were no changes in cardio-respiratory fitness, body composition or insulin resistance during the run-in period (see Table 2) when participants were engaging in their usual level of habitual activity.

Impact of Exercise Intervention (times2-3)

Body composition and insulin resistance: There were no significant changes in fat mass, lean mass or percentage body fat (Table 2) but significant improvements in markers of insulin resistance such as fasted plasma insulin concentrations (*P*=0.026) and HOMA-IR (*P*=0.024) following the exercise intervention, and maintained at time3vs.4(*P*=0.60 and *P*=0.06) respectively (Table 2, Figure 2).

Cardiorespiratory fitness: There were significant improvements in $\dot{V}O_2$ peak(mL/min/kg) (time2vs.3), which were maintained at time3vs.4(*P*=0.05) (Table 2, Figure 1). There were no further improvements during the follow-up period (time3vs.4) when participants were not in a formal exercise programme. Pulse O_2 increased significantly with training (*P*=0.026). VT occurred at mean(SD) 72.0(11.9)%$\dot{V}O_2$peak and did not change with training. Significant gains in strength were identified from 1RM

testing: mean(SD) 81.5(40.4)%,*P*<0.001 increase in leg strength and 90.4(78.9)%,*P*<0.001 increase in chest strength.

QoL: There were significant improvements in the SF-36 QoL general health domain during the exercise intervention: mean(SD)(69.7(14.3)vs.72.7(16.0),*P*<0.001), which were maintained at time3vs.4,*P*<0.05 (Figure 3). Data from the SF-36 QoL questionnaire identified significant improvements before the exercise intervention in physical health (85.2(13.8)vs.91.5(11.4),*P*=0.007); physical role (84.1(17.7)vs.94.4(9.5),*P*=0.012); emotional role (80.9(22.2)vs.91.3(16.6),*P*=0.023); social (84.1(24.1)vs.93.1(11.8),*P*=0.048); and total (69.1(25.2)vs.72.9(22.9),*P*=0.007) domains. Data from the MMQL QoL questionnaire showed improvements in the school domain (time2vs.time3) (69.1(25.2)vs.79.3(21.6),*P*=0.034). The MMQL also identified significant improvements in the physical health domain 12 months after the start of the 6-month exercise intervention (time2vs.time 4) 66.4(25.3)vs.79.4(16.7),*P*=0.029), but not immediately after the exercise intervention (time2vs.time3).

Discussion

This study reports a successfully implemented 6-month combined resistance and aerobic exercise intervention programme in young people after HSCT/TBI and demonstrated improved outcomes for insulin resistance, cardiorespiratory fitness, and some aspects of QoL.

Cardiorespiratory fitness ($\dot{V}O_2$peakmL/min/kg) was lower at baseline than predicted values for age and sex in UK children[17]. $\dot{V}O_2$peak is closely correlated to lean body mass, therefore, expressing $\dot{V}O_2$peak relative to body mass (rather than lean body mass) may be expected to show reduced $\dot{V}O_2$peak in HSCT/TBI survivors due to their abnormal body

composition with reduced lean mass and increased adiposity. GHD also reduces cardiorespiratory fitness, and GH treatment improves cardiorespiratory fitness and body composition but not strength in adults with GHD[44]. All study participants had been established on GH treatment for at least 6 months prior to baseline assessment (time1) to control for the effects of GH with usual activity before the exercise programme.

There were no changes in cardio-respiratory fitness, body composition or insulin resistance during the six month period before the intervention. There was a significant improvement in cardiorespiratory fitness seen during the exercise intervention. This may have been a larger effect due to reduced baseline cardiorespiratory fitness, related, in part, to de-conditioning from treatment. Significant improvement in Pulse O_2 suggests improved circulatory efficiency. VT occurred at mean(SD) 72(11.9)%$\dot{V}O_2$peak. This refers to the point where aerobic metabolism is supplemented by anaerobic mechanisms during progressive exercise. In healthy adults, published data suggests VT occurs between 45-65% $\dot{V}O_2$peak. In the study group, there was no change in VT expressed as a percentage of $\dot{V}O_2$peak, however, as $\dot{V}O_2$peak increased significantly after the exercise intervention, VT occurred at a higher VO_2. VT as %$\dot{V}O_2$peak is known to be increased in GH deficient adults (73%) and contributes to fatigue during activities of daily living[44 45]. The improvements seen in $\dot{V}O_2$peak without a change in %VT may still improve fatigue.

There were significant gains in leg and chest strength identified by the 1RM tests. This is not seen with GH treatment alone[44], consistent with the lack of change seen during the run in period, and both GH treatment and exercise are required to regain full strength and fitness in GHD participants.

A reduction in fat mass, an increase in lean mass or a reduction in percentage body fat may be expected to contribute to enhanced cardiorespiratory fitness and muscular strength, but significant changes in body composition were not seen during the 6-month training period. It may be that a larger sample, a longer intervention period, and/or longer follow-up are required to identify significant changes in body composition.

As expected, the study group demonstrated higher HOMA-IR values at baseline compared to published normal data for adults and adolescents. In >1000 US adolescents, two thirds of whom had normal BMI, the mean(SEM) HOMA-IR for girls was 2.93(0.11)vs.2.82(0.11) for boys[46]. These data are comparable for the male study participants whereas the female participants had a higher HOMA-IR. HSCT/TBI has been shown to be associated with increased abdominal adiposity and diabetes risk, related both to increased insulin resistance and reduced β-cell function[7]. Body composition after HSCT/TBI is abnormal with increased visceral and intra-muscular fat and reduced subcutaneous fat and lean mass[7]: this might specifically contribute to development of the metabolic syndrome and insulin resistance due to a failure of the adipose tissue to expand, as seen in lipodystrophy[47]. It is also well known that increased insulin resistance is associated with central adiposity, and with GHD and GH replacement both in adults and children[48 49]. All participants were receiving GH replacement therapy for the duration of the study, potentially impacting on baseline insulin and HOMA-IR levels, but this cannot have influenced the improvement in insulin resistance with exercise as GH treatment remained constant throughout. The significant reductions in insulin and HOMA-IR recorded during the exercise intervention are consistent with other reports of reduced insulin resistance with either aerobic[18] or resistance training [50 51].

Previous studies have also reported improvements in insulin resistance without body composition changes[52] suggesting that initial improvements relate to improved metabolic function of muscle. The mechanisms whereby exercise improves insulin resistance are complex[53 54] and were not directly measured in this study. Both insulin and exercise promote an increase in glucose uptake in skeletal muscle, and involve an increase in translocation of the main glucose transporter protein (GLUT-4) from the intracellular space to the cell membrane[55]. However, insulin and exercise have been shown to act through different pathways, enabling insulin resistant individuals to increase glucose uptake with exercise. There is evidence that improvements in insulin sensitivity associated with exercise training are also related to changes in the expression and/or activity of proteins involved in insulin signal transduction in skeletal muscle such as the AMP-activated protein kinase (AMPK) and the protein kinase B (Akt) substrate AS160[56]. Increased lipid oxidation and/or turnover related to upregulation of the oxidative capacity of skeletal muscle and the expression of proteins involved in mitochondrial biogenesis is likely to be a further mechanism improving insulin sensitivity with training[57], Significant gender differences were seen in the study with higher insulin and HOMA-IR in females, consistent with increased body fat and greater incidence of insulin resistance in females during childhood and adolescence[58 59 60]. However, obese adolescent and adult males have a greater risk of type 2 diabetes mellitus (T2DM) and of the metabolic syndrome than obese females due to greater visceral fat[61 62]. Female participants in this study had greater visceral adiposity than males and also higher body fat than published data for normal UK females of the same age. The use of oestrogen replacement therapy for treatment-related ovarian failure after HSCT/TBI in females may be a factor and

untreated premature ovarian failure is itself associated with increased metabolic disease[63]. Oral hormone replacement therapy (HRT) may promote a greater increase in insulin resistance than trans-dermal HRT but data supporting this are typically from studies in older post-menopausal women and may not be applicable to young women with premature ovarian failure[64 65].

The general health domain of SF-36 showed significant improvement during the exercise intervention and during the 6-month follow-up period. The magnitude of this improvement, however, was less than 1 SD: the size of a change usually accepted as conferring clinically relevance. Although this improvement is positive and consistent with what would be expected with exercise training in young people, the SF-36 may not be a sensitive enough tool in this sample size to detect a clinically relevant change. In addition the young people in this study reported higher QoL scores than those typically seen in adults and therefore a positive change may be more difficult to detect Other SF-36 domains showed significant improvements before the exercise intervention started time1-time2). This suggests that taking part in the study, rather than the specific effects of the exercise intervention, was of benefit, or that there was familiarisation with the questionnaire between the time points. MMQL data showed significant improvements in the school domain during the exercise intervention, and MMQL physical health and school domains also improved between time 2 and time 4, but it is not clear whether this can be attributed to the exercise intervention alone. A number of studies employing exercise interventions have shown improvements in QoL in healthy participants[66], cancer patients on therapy[67 68], and cancer survivors[69]. The stated rationales include improvements in fitness, self-esteem, body image and resistance to fatigue.

There are some limitations of this study. It was not practical to apply the whole study, including the intervention, to a control group but the longitudinal design controlled for the effects of growth and growth hormone over the baseline period. One question is whether there could be a bias to the more motivated individuals completing the study. However, we found that reasons for not completing the study were illness and moving out of the area which were unrelated to motivation. In addition the participants gave very positive feedback regarding taking part, which is supported by the positive findings in the QoL scores across the baseline period.

Summary: Survivors of HSCT/TBI in childhood were shown to have reduced cardiorespiratory fitness, associated with increased adiposity and de-conditioning. Female survivors were more affected than males at baseline, exhibiting increased insulin resistance and greater visceral fat. A 6-month combined resistance and aerobic exercise programme resulted in positive changes in cardiorespiratory fitness, measures of insulin resistance and some measures of QoL without changes in body composition. These data support the use of physical rehabilitation programmes to reduce metabolic and cardiovascular risk in HSCT/TBI survivors.

386

387 **Compliance with Ethical Standards:**

388 ND received research grants for this study from Above and Beyond Charitable Trustees
389 and Novonordisk. All of the authors declare that they have no conflict of interest.

390 Ethical approval: All procedures performed in studies involving human participants were
391 in accordance with the ethical standards of the institutional and/or national research
392 committee and with the 1964 Helsinki declaration and its later amendments or
393 comparable ethical standards.

394 Informed consent: Informed consent was obtained from all individual participants
395 included in the study and was properly documented.

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398 Data Availability statement: The data that support the findin*gs of this study are available from*
399 *the corresponding author upon reasonable request.*

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Legends;

Figure 1. Mean (SD) $\dot{V}O_2$peak a time 1 to time 4 indicating an improvement in aerobic fitness following the exercise intervention (between time 2 and time 3).

Figure 2. Log HOMA-IR at time 1 to time 4 indicating improved insulin resistance after the exercise intervention (between time 2 and time 3).

Figure 3. Quality of life (QoL) scores at time 1 to time 4 indicating improved in QoL after the exercise intervention (between time 2 and time 3).

Table 1. Demographics and treatment details of participantsTable 2. Changes in $\dot{V}O_2$max, Pulse O_2, percentage body fat and insulin resistance indicating significant improvements in outcomes after the exercise intervention (between time 2 and time 3, pairwise comparisons 2 vs. 3).

Normally distributed data is expressed as mean (standard deviation) whereas skewed data* is expressed as geometric mean (range). Parametric data were compared overall using one-way analysis of variance (ANOVA) followed by pairwise comparisons using post-hoc Fisher's least significance difference (LSD) tests. Skewed data* was log transformed to attain a normal distribution before parametric testing. Sample size in pairwise comparisons: 1 vs. 2 (n= 24), 2 vs. 3 (n= 20), 3 vs. 4 (n= 16). Statistically significant P values are shown in bold.

Table 1. Demographics and treatment details of participants

Demographics and treatments	number of participants	
Mean (range) age	24	16.7(10.9-24.5)yrs
Mean (range) times since HSCT/TBI	24	8.4(2.3-16.0)yrs
Conditioning cyclophosphamide	24	total dose 120mg/kg
Conditioning campath	24	total dose 50mg
Conditioning TBI	24	total dose 14.4Gy; 8 fractions
CNS boost irradiation	8	6Gy; 4 fractions
Previous cranial irradiation	2	18Gy and 24Gy
GVHD post-transplant	12	oral steroids (*n*=6) topical steroids (*n*=6)
Dose of GH treatment for GHD	24	children 5mg/m^2/week adolescents 6.5mg/m^2/week transition 0.6-1.0mg daily
Thyroxine	6	
Oestrogen	8/10 females	
Testosterone	5/14 males	
Pubertal status	2 pre-pubertal, 5 pubertal 13 post-pubertal.	

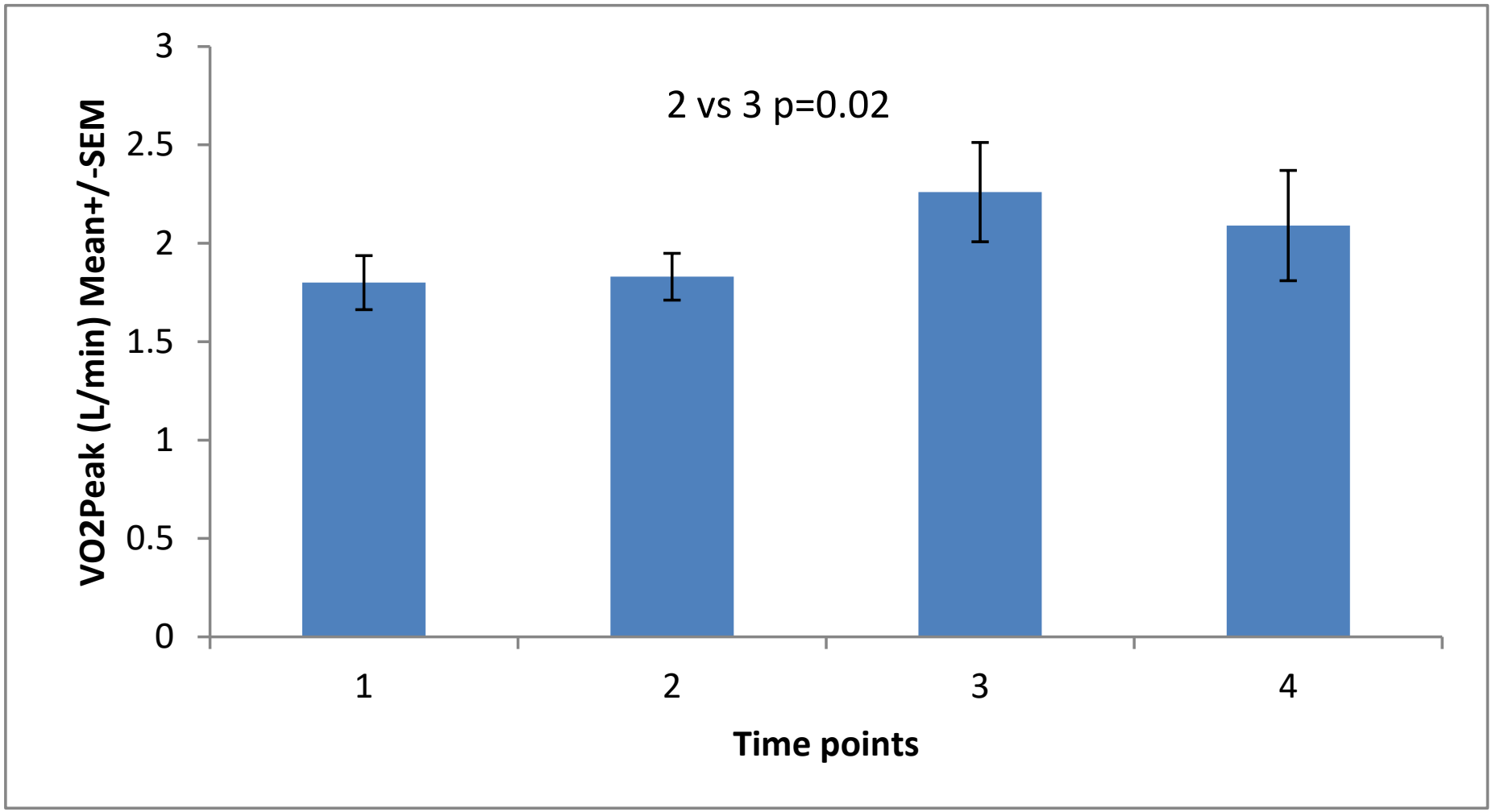
Haemopoietic stem cell transplantation (HSCT/TBI), central nervous system (CNS), graft versus host disease (GVHD), growth hormone (GH), growth hormone deficiency (GHD).

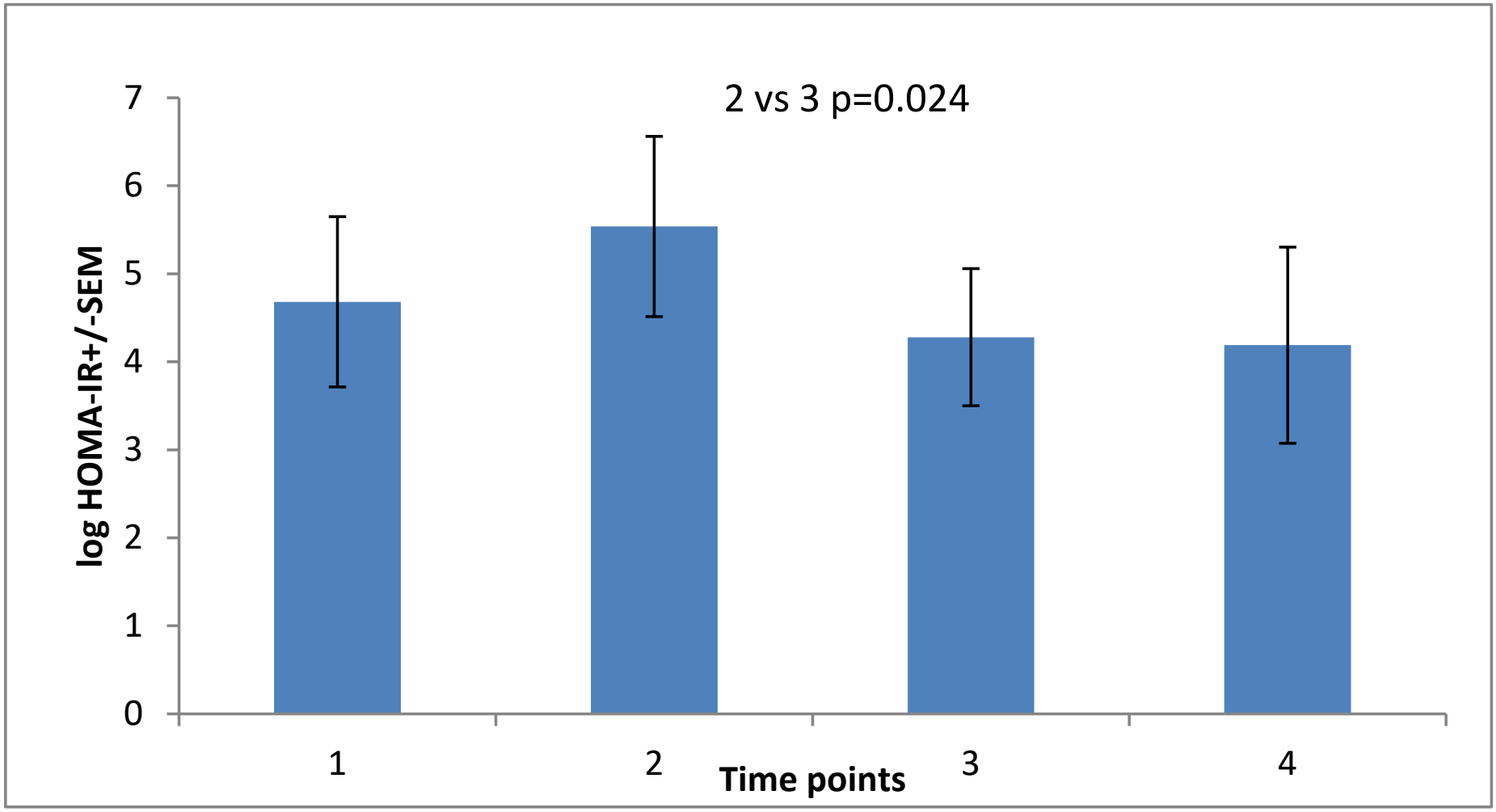
TABLE 2. Demonstrating Changes in $\dot{V}O_2$peak, Pulse O_2, Body Composition and Insulin Resistance

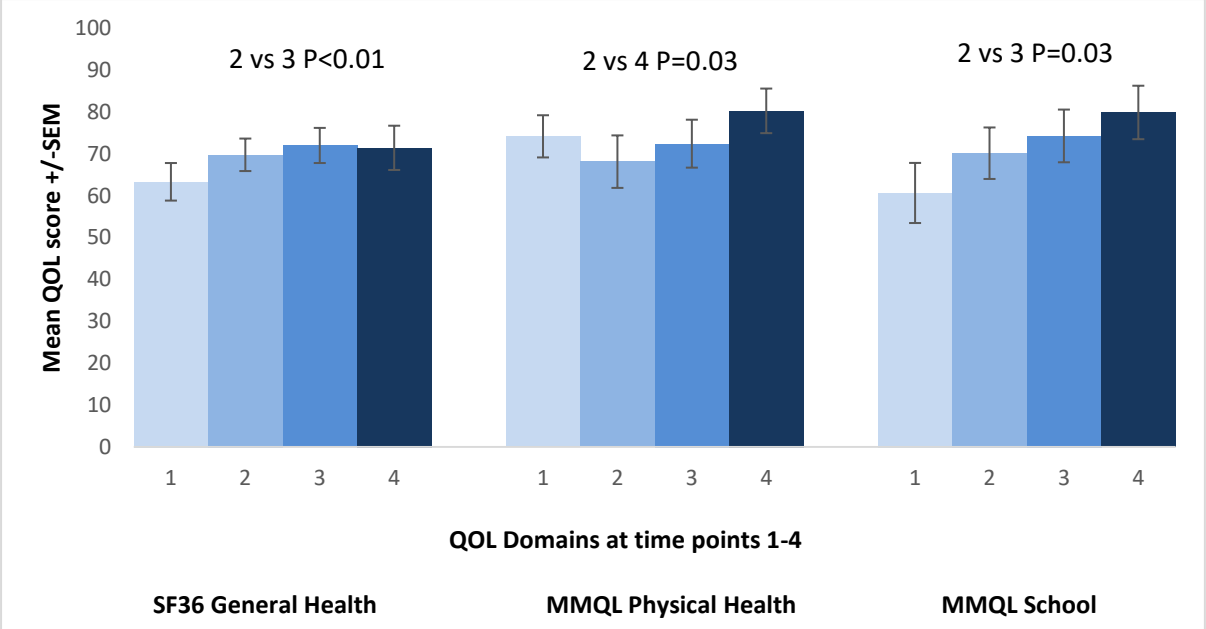
Outcome measure	Mean (SD) or Geometric mean (range)*				ANOVA *P* value	Pairwise comparison: *P* value
	Time 1	Time 2	Time 3	Time 4		
$\dot{V}O_2$peak (L/min)	1.80 (0.70)	1.83 (0.57)	2.26 (1.04)	2.09 (1.01)	**0.002**	1 vs. 2: 0.29 **2 vs. 3: 0.020** 3 vs. 4: 0.78
$\dot{V}O_2$peak/kg (mL/min/kg)	35.7 (11.8)	35.7 (8.9)	41.7 (16.1)	38.4 (8.1)	0.20	1 vs. 2: 0.87 **2 vs. 3: 0.05** 3 vs. 4 (0.46)
PulseO_2 (mL/beat/min)	9.8 (3.0)	10.1 (2.8)	12.2 (4.8)	10.8 (5.1)	**0.036**	1 vs. 2: 0.76 **2 vs. 3: 0.026** 3 vs. 4: 0.61
Fat mass (kg)	16.62 (11.26)	16.44 (11.39)	15.87 (11.43)	16.30 (11.67)	0.997	1 vs. 2: 0.96 2 vs. 3: 0.86 3 vs. 4: 0.91
Lean mass (kg)	31.58 (7.22)	34.67 (9.14)	35.70 (9.67)	36.72 (10.83)	0.323	1 vs. 2: 0.26 2 vs. 3: 0.71 3 vs. 4: 0.74
Percentage body fat	31.1 (15.0)	29.5 (13.9)	28.3 (14.0)	26.6 (13.2)	0.27	1 vs. 2: 0.76 2 vs. 3: 0.83 3 vs. 4: 0.20

BMISDS	-0.07 (1.63)	-0.08 (1.53)	-0.28 (1.68)	-0.40 (1.79)	**0.07**	1 vs. 2: 0.93 **2 vs. 3: 0.03** 3 vs. 4: 0.41
Fasted Plasma Insulin* (mIU/L)	13.84 (2.61-68.30)*	16.56 (1.48-72.80)*	12.62 (1.04-54.97)*	11.93 (0.84-80.38)*	**0.050**	1 vs. 2: 0.13 **2 vs. 3: 0.03** 3 vs. 4: 0.60
HOMA-IR*	3.00 (0.53-18.31)*	3.65 (0.30-17.26)*	2.72 (0.22-12.89)*	2.67 (0.20-16.67)*	0.77	1 vs. 2: 0.24 **2 vs. 3: 0.02** 3 vs. 4: 0.06

Peak rate of oxygen uptake ($\dot{V}O_2$peak), rate of oxygen uptake per heart beat (Pulse O_2), standard deviation (SD), body mass index standard deviation score (BMISDS), homeostatic model assessment of insulin resistance (HOMA-IR), repeated measures analysis of variance (ANOVA).Normally distributed data is expressed as mean (SD) whereas skewed data* is expressed as geometric mean (range). Parametric data were compared overall using repeated ANOVA followed by pairwise comparisons using post-hoc Fisher's least significance difference (LSD) tests. Skewed data* was log transformed to attain a normal distribution before parametric testing. Sample size in pairwise comparisons: 1 vs. 2 (*n*= 24), 2 vs. 3 (*n*= 20), 3 vs. 4 (*n*= 16). Statistically significant *P* values are shown in bold


2 vs 3 p=0.02
VO2Peak (L/min) Mean+/-SEM
3
2.5
2
1.5
1
0.5
0
1
2
3
4
Time points


2 vs 3 p=0.024
log HOMA-IR+/-SEM
0
1
2
3
4
5
6
7
1
2
3
4
Time points


2 vs 3 P<0.01
2 vs 4 P=0.03
2 vs 3 P=0.03
Mean QOL score +/-SEM
100
90
80
70
60
50
40
30
20
10
0
1
2
3
4
QOL Domains at time points 1-4
SF36 General Health
MMQL Physical Health
MMQL School