A systematic review of exercise as a therapeutic intervention to improve Quality of Life and Cancer Related Fatigue in Paediatric Cancer Care

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Abstract

Objective: To review the evidence that personalised physical activity is a feasible and acceptable means of significantly improving quality of life (QoL) and cancer related fatigue (CRF) in childhood cancer. Methods: Seven databases/registers were searched for studies evaluating exercise interventions in paediatric cancer (2013-2023). Studies included patients ages 3-25 years, with any cancer type, undergoing exercise interventions during active treatment. Thirteen studies (551 participants) were included. Primary outcome measures analysed were CRF and QoL. Results: Three of eight studies (N=105) measuring CRF revealed significant reduction in total fatigue score (p=0.001, 0.01, 0.026). All others demonstrated a non-significant reduction in CRF in the intervention group (mean -5.7 (±8.82 pooled SD)). One of ten papers (N=99) measuring QoL reported significant improvement (p=0.014), with non-significant favourable outcomes (mean change +3.47) in all remaining studies. No adverse events were reported. Conclusion: Physical activity is a feasible way to improve CRF and QoL in children undergoing cancer treatment.

A systematic review of exercise as a therapeutic intervention to improve Quality of Life and Cancer Related Fatigue in Paediatric Cancer Care.

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Results: Three of eight studies (N=105) measuring CRF revealed significant reduction in total fatigue score (p=0.001, 0.01, 0.026). All others demonstrated a non-significant reduction in CRF in the intervention group (mean -5.7 (±8.82 pooled SD)). One of ten papers (N=99) measuring QoL reported significant improvement (p=0.014), with non-significant favourable outcomes (mean change +3.47) in all remaining studies. No adverse events were reported.

Conclusion: Physical activity is a feasible way to improve CRF and QoL in children undergoing cancer treatment.

Key words: paediatric exercise oncology; cancer related fatigue; quality of life; strength; fitness

Research Question: Is personalised physical activity a feasible, acceptable and effective means of improving quality of life (QoL) and cancer related fatigue (CRF) in pediatric cancer patients?

INTRODUCTION:
Childhood cancer and its treatment have both immediate and long-term adverse consequences on physical capacity and quality of life (QoL). In addition to the burden of disease itself, side-effects of treatment include fatigue, peripheral neuropathy, muscle weakness and pain. Over half of survivors develop at least one chronic health condition within 20 years of diagnosis, with late effects including reductions in bone density, sarcopenia and cardiovascular morbidity. Up to 75% of childhood cancer survivors experience multiple chronic health conditions by age 50, with reports of a 1.8 times greater risk of diabetes mellitus compared to siblings, and increased rates of osteoporosis and cardiometabolic disease. In addition to physical sequelae, the Childhood Cancer Survivor Study identified that up to 29% of children experienced long-term reduction in emotional functioning and capacity for attention and increased rates of anxiety and...
depression\textsuperscript{17}. These effects were significantly higher in children who were overweight or obese post-treatment\textsuperscript{6}, with survivors who did not exercise experiencing higher levels of cancer-related fatigue (CRF) and depressive symptoms compared to those who remained active\textsuperscript{44}.

**Physiological benefits of exercise during treatment.**

Exercise is essential for maintaining general health in children, increasing cardiopulmonary fitness, lean body mass, bone mineral density, gait, balance, and co-ordination and leading to both short and long-term reductions in obesity, anxiety and depression\textsuperscript{47}. Psychosocial skills can be developed through sport and activity. A 25-30\% reduction in all-cause mortality has been reported in otherwise healthy individuals meeting minimum exercise recommendations\textsuperscript{49}.

Evidence suggests that physical activity reduces after childhood cancer diagnosis and does not return to baseline post treatment\textsuperscript{38}. Only around 50\% of children with cancer meet minimum physical activity guidelines. This statistic is similar in healthy populations, which may help us infer some of the attitudes towards exercise in young children and their parents. Although one barrier to children with cancer accessing physical activity is concern about safety, evidence suggests the risk is very low when exercise is undertaken in appropriate settings and individually modified. A recent literature review reported a 0.02\% incidence of adverse events, all of which were mild in nature with a short-lived self-limiting reduction in functioning\textsuperscript{11}. All occurred outside the acute phase of treatment in the setting of sports camps/groups, with incidence being lower than that incurred in a healthy population. The most frequently reported side-effect of exercise was muscle soreness, which can be considered a normal effect of a new exercise programme and managed by moderations in volume and intensity.

Exercise may be an accessible and acceptable means of improving therapeutic, physical, and psychosocial outcomes\textsuperscript{5,10} for children undergoing cancer treatment. A recent literature review\textsuperscript{51} summarized improvements in participant outcome measures in parameters including increased strength, cardiorespiratory fitness and functional mobility, improved quality of life, emotional functioning, mental health and well-being, and reduced fatigue. Nielsen \textit{et al} \textsuperscript{34} found 30–60-minute training sessions incorporating aerobic and strength work combined with 2 weekly play-based sport sessions, maintained baseline cardiopulmonary fitness in children undergoing cancer treatment compared to significant decline in controls. Relative V\textsubscript{O}2 max (a measure of aerobic capacity) significantly improved beyond baseline in the intervention group six months following treatment. A recent Cochrane review\textsuperscript{5} found improvements in body composition and metabolic parameters in survivors of childhood cancer following exercise interventions, with significant reductions in cardiometabolic risk factors (lipid profiles, systolic blood pressure, fasting glucose) in survivors of 10+ years with as little as a 16 week home based exercise intervention. To our knowledge there is no existing review that summarizes data on the effects of exercise on QoL and CRF outcomes with a focus on identifying factors that prevent protocols being implemented in standard care.

**Aims:**

This systematic review aims to investigate the feasibility of an exercise intervention to improve quality of life (QoL) and cancer-related fatigue (CRF) in paediatric patients undergoing active treatment for any cancer type.

**METHODS:**

This systematic review was conducted in accordance with PRISMA guidelines.

**Eligibility criteria:**

Criteria for inclusion and exclusion respectively can be found in table 1.

**Information sources:**

The databases PubMed, MEDLINE, Embase, Science Direct, CINAHL, Central and Web of Science were
searched in September 2023. The Cochrane Library and the National Institute of Health Clinical Trials Registry platform were also searched to identify systematic reviews, meta-analyses and ongoing trials.

Nine databases and registers (supplementary file 4) were searched for studies evaluating exercise interventions in paediatric cancer patients undertaken within the last 10 years (2013-2023). Attempts were made to source data from ongoing studies where appropriate.

Data was collated through database searching, full text search and data extraction. Analysis was performed using the RoB 2 Cochrane bias review tool\(^\text{15}\) (figure 2, 3, 4, 5). Synthesis of results for meta-analysis was performed by pooling standard deviations of the primary end point from within the intervention group (not including long-term follow up due to confounding de-training effect) using data from studies that employed the PedsQL Multi-dimensional Fatigue scale and PedsQL QoL Inventory respectively.

**Search Strategy:**

To search for both standard terms and alternative phrases, Boolean operators were used (refer to search strategy summary in appendix). The question entered to search databases was ‘Is (Physical Activity OR exercise), feasible OR acceptable to improve (quality of life OR QoL OR PedsQL) in pediatric* or paediatric* OR childhood cancer’, with separate search terms utilised where search powers permitted.

Exact search terms depended on available database searching capabilities.

Efforts were made to search for all these terms, using both free text searches and title/abstract searching.

Refinements were made to search only papers published between 2013-2023.

Conference notes and chapters were excluded from initial search. Duplicates from other databases were excluded.

Available literature was then scanned via title, abstract and full text in sequence to identify suitability for full data extraction.

Please refer to supplementary file 4 (PRISMA flowchart) for clarity of the search methods used.

Guidelines for Paediatric Exercise Oncology (The International Paediatric Exercise Oncology Guidelines (IPEOG)\(^\text{52}\) and Network ActiveOncoKids\(^\text{14}\) and systematic reviews with similar search questions were also reviewed to identify other sources of evidence.

Detailed breakdown of the search strategy may be found in S4. Many duplications were found secondary to our database search. Reports were sought through trial libraries or relevant guideline sites with limited success as most were not at the stage of reporting data. Some, such as the FORTE-e trial\(^\text{1}\), are large scale interventions which will add to the current knowledge base in view of their replicability and power.

**Selection Process:**

Two reviewers (Holly Sheldon-Wilson and Imogen Shaw) independently screened all titles and abstracts of studies identified, and assessed all studies included for full text. Disagreements were solved by discussion or a third reviewer.

**Data Collection Process:**

Data extractions were independently conducted by two reviewers (Holly Sheldon-Wilson and Imogen Shaw), with disagreements resolved by discussion.

**Data items:**

The following information was extracted for each study: design, year of publication, number of patients, age at inclusion, gender, time since diagnosis, primary cancer diagnosis, details of exercise intervention (nature, frequency, duration etc), adverse effects of exercise intervention, outcome tool, quality of life outcome
measure, cancer related fatigue outcome measure, secondary outcome measures (aerobic capacity, strength, flexibility), adverse events and analysis method. Please see table 1 for a summary of the extracted data.

**Synthesis methods:**

Data was summarised by collecting pre and post intervention data where possible, presented in Tables 2 and Supporting File 3, and Figures 1 and 2. Due to heterogeneity in the data available, it was not possible to acquire pre and post testing values for all studies. Some studies employed immediate follow up post intervention and long-term. In this instance the primary end point from within the intervention group (not including long-term follow up due to confounding de-training effect). Meta-analysis was not performed due to the paucity of data employing the PedsQL Multi-dimensional Fatigue scale and PedsQL QoL Inventory respectively.

**Assessment of the quality of included studies and risk of bias** was performed using the RoB2 Cochrane bias review tool (Figures 1, 2, 3, 4).

**RESULTS**

After a thorough search of published work, grey literature, and trial registries, 11 published studies were accepted for final data extraction (S4). Although the search could not be replicated exactly across different databases due to limitations in search tools, efforts were made to search for all pseudonyms or alternative spellings of the key terms (see appendix 1- search strategy summary).

In addition to this, 4 ongoing trials that met inclusion criteria were identified. Although none had published data available, 4 had protocols indicating that results will be relevant to this review at trial end.

Despite a considerable number of papers returned, many were discounted due to not meeting inclusion criteria. Literature reviews were more prevalent than trials, with other intervention-based studies rejected for reasons including not being specific to a pediatric population and being in the recruitment or intervention stage. Several studies were discounted at the stage of full text analysis due to lack of reporting.

We were unable to perform statistical interpretation of the data available due to the heterogeneity in methods, outcome tool and reporting. This re-enforces the need for more standardized research approaches that allow easier translation to practice.

**Study Characteristics**

Details of the selected studies are shown in Table 2.

A summary of study characteristics may be found in Supporting File S1.

A total of 13 studies (551 patients) reported QoL and CFR as outcome measures, using validated Peds QL questionnaires. Ten studies measured QoL and eight measured CRF using the Peds QL tool. Data from these studies was used to conduct the analysis. A detailed description of the studies including the intervention, primary/secondary outcomes and adverse effects is presented in Supporting file S2.

Another common theme was the prevalence of studies focused on a survivor population only. While exercise-based interventions are established in adult oncology (Cancer Research UK), the novelty of the concept of exercise in pediatric cancer is reflected in the limited evidence for physical activity during treatment.

**Certainty of evidence and risk of bias**

**Sample Population and Allocation**

A full Cochrane bias review of the final papers was undertaken to assess various domains of quality (See figure 1, 2, 3 and 4) for traffic light and summary plots demonstrating scoring using the rob2 tool.

Population sizes were typically small, ranging from 16-70 participants. Several papers discussed difficulties during the recruitment phase for reasons including parental concern over risks to the child’s health and the timing of approaching family and the patient. Recruitment criteria in many trials required parental
consent prior to commencing treatment to acquire baseline fitness measurements prior to confounding effects of initiating chemotherapy. This required approaching families during a particularly sensitive period, where they may be less receptive to information surrounding a trial that would not influence treatment. Passive recruitment methods such as flyers on the ward and early discussions with other members of the multidisciplinary team (MDT) allowed families to acquire information in a less intrusive manner.

There was heterogeneity of sample population ages across trials, with the lower age limit of participants ranging from 3-15 years and the upper age limit from 16-25 years. The age-related differences in baseline physical and metabolic function and the range of age-appropriate physical activity interventions are considerable, as is the child’s capacity to comply with a prescribed intervention. To reduce confounding effects of age many interventions stratified the intervention to include age-appropriate variations.

Most study designs had robust methods of allocation of participants to intervention and control groups, using randomization processes such as random number generators (D1 in Figure 1 and 3). Those scoring higher risk of bias either did not include a control group and therefore did not randomly allocate, or in the case of Spreafico et al., allocated intervention and control group based on individual participants’ preference or desire to exercise, which clearly creates risk of bias.

**Data Analysis**

Most papers used a t-test to compare differences in intervention and control groups at time zero and the end of the intervention, reporting *p*-value and 95% confidence intervals as measures of significance. A one-way ANOVA was most often used to compare variation between groups. Most studies used a power calculation initially to decide on a suitable sample size, often also accommodating for some dropout due to effects of the disease of treatment. Many trials presented analyses as per Intention to Treat (ITT). Those reporting As per Protocol (APP) were deemed less reliable, especially where reasons for attrition were vague which made it difficult to ascertain the influence of treatment versus intervention.

**Methodology**

Six of eight papers sourced for CRF outcomes utilized the PedsQL Fatigue Scale. One used a Chinese population specific version, and another an older validated scale (The Child/Adolescent Fatigue Questionnaire). There was more variation in outcome measures for QoL. Six of ten used the PedsQL QoL questionnaire, one used the Chinese specific equivalent, one used the KINDL questionnaire, and another the PROMIS tool. More standardized outcome measures across research would have allowed better synthesis of quantitative data.

There was also heterogeneity in the time of measurement reflecting difference in durations of exercise interventions across studies. Exercise interventions were conducted between 1 and 7 times each week, for a total number of weeks ranging from 1 to 21.

Assessments were typically done at baseline and within 4 weeks of finishing the protocol, with 9 of the 13 final papers completing a follow-up assessment at 6 weeks or more. Two trials were deemed lower quality in this area: one used multiple time points to report data, and Spreafico et al performed QoL and CRF assessments at intervention end only, thus creating a higher risk of reporting bias. Given the nature of cancer treatments and inevitable decline in physical functioning and wellbeing, longer follow-up, and standardized time points to compare the rate and amount of decline are essential to create replicable data.

**Intervention and Protocol**

A common challenge across trials is difficulty limiting performance bias, as participants and trainers could not be blinded to their allocation to the exercise or non-exercise group. Some maintained single blinding between participant allocation and those analyzing data, reducing observer bias. All studies reported on physical activity interventions appropriate for individual age, ability and fitness, both at baseline and prior to individual session. Some trials (e.g. Bogg et al.) utilized a qualified exercise professional to tailor sessions towards the child’s needs. This incorporated baseline fitness, physician’s medical approval prior to each
session and use of Rate of Perceived Exertion (RPE) scales, heart rate and direct verbal feedback to guide appropriate intensity. Others (e.g., Masoud et al.) tool a more opportunistic approach, with a range of games available and children and parents educated on recognizing a light-moderate effort on the RPE scale.

Adherence to protocol and intervention

Measuring adherence to the planned protocol was difficult across most studies. The higher scoring trials for this domain described thorough adherence monitoring methods to ascertain the degree of compliance. Hooke et al. designed an intervention in which children wore an activity monitor and were encouraged to walk every day. This allowed collation of objective data, as any number of steps on a given day meant the child had met the criteria for exercising. More uncertainty was found in studies in which there was limited reporting of the completion of required intervention goals. These studies limited their exercise protocols to a time goal, stating that sessions were individually modified to reflect the patient’s capacity and wellbeing on a session-by-session basis. Whilst it is acknowledged broadly that the child’s symptoms and motivation are important when deciding intensity, volume and type of exercise, vague intervention guidelines make replication difficult.

Documenting reasons for stopping exercise is essential to ascertain whether an intervention could be responsible for dis-engagement or lead to harm. Whilst most trials included scored highly in this domain, some (e.g., Stossel et al.) did not give clear reasons for loss of every participant.

In terms of analysis methods, seven reports used ITT analysis, including all patient data irrespective of whether they completed the trial, with four of the final papers using APP analysis. This confers a higher risk of attrition bias and is more prone to confounding.

Quality of Life

Ten studies measured QoL using the Peds QL (n=6), EORTC-QLQC30 (n=1), Chinese Paediatric QoL Inventory (n=1), PROMIS (n=1) and KINDL tool (n=1), reporting on a total of 442 patients. Mean change in score from baseline post intervention for the exercise group (calculated from four studies using PedsQL) was +3.47 with one reaching significance.

Mean change in score from baseline for the control group (calculated from three studies using PedsQL) was -0.58.

Fiuza-Luces could not be quoted in this raw data set due to larger values than the maximum PedsQL score system.

Two papers (N=89) measuring QoL (Supporting file 3) as an outcome reported a significant improvement in QoL score, P =<0.05 and p = 0.011. Smith et al could not be included in data analysis as the PROMIS tool did not allow for a single measure for comparative purposes. Non-significant favorable outcomes reported in all remaining studies.

S3 also displays the results from the control group, with no significant change from baseline in any of the studies. As Bogg et al and Diorio et al did not utilize a control group there in so comparative data available. Spreafico et al conducted QoL assessments for controls only at baseline, and for the intervention group only at post 6-week intervention, resulting in no assessment of change over time.

Although decline was noted across both groups in line with the nature of disease and treatment, trend of decline was larger in the control group.

Cancer Related Fatigue

Six studies measured cancer related fatigue (CRF) using the Peds QL tool, reporting on a total of 283 patients. Mean change in the exercise group (calculated from 6 studies using PedsQL fatigue scale) was -5.89 from baseline post-intervention with three reaching significances (p=0.001, 0.01, 0.26).
Mean change in the control group (calculated from 5 studies using PedsQL fatigue scale) was +2.28 from baseline.

In total eight studies measured CRF, one using the Chinese fatigue scale and another using the Child or Adolescent Fatigue questionnaire.

Three studies (supporting file 3) found a significant reduction of total fatigue score (p = 0.001, 0.01, 0.026)\(^{18,26,45}\). All other papers displayed a lower CRF score in the intervention group with a although none reached significance. S3 also displays the results from the control group, showing no significant change from baseline. Of note is that data from Masoud et al is a cross group analysis displaying intergroup significance, but pre-statistical data is not available for post-intervention. Similarly, as Spreafico et al only conducted post intervention/ standard care assessments there is no time analysis possible.

Adverse events

Of the 13 studies identified in this review, 11 reported no serious adverse events and 2 did not report any information of non/incidence. The only exercise specific incidents reported were by Stössel\(^{45}\), describing three falls during an exercise session that did not result in injury. Some studies specifically reported levels of compliance: Bogg\(^4\) found 50% of patients completed the full program, Masoud\(^{26}\) found 100% of the intervention group completed all sessions, and Munsie\(^{30}\) and Smith\(^{42}\) both found 91% completed the exercise program. Sessions were not completed for reasons including medical exemption, other services such as physiotherapy, treatment interruptions, inability to attend hospital, fatigue, and/or no specific reason. Reasons for study withdrawal included lack of motivation or tiredness, medical withdrawal, death, and only one patient reported without reason. Please see S1 for a breakdown of reasons provided by each study.

Several ongoing studies identified have comprehensive and thorough methodology and longer follow-up testing, including Munsie et al\(^{30}\), Kauhanen et al\(^{20}\) and the pan-European FORTE-e trial\(^1\). Although these remain in progress at the time of writing and could not be evaluated within this review, the larger samples and longer time spans are promising and will help provide evidence lacking in the current data pool.

DISCUSSION

Despite the paucity of high quality randomized controlled trials, this review provides evidence that an exercise intervention could result in significant improvements in QoL and reduction in CRF in childhood cancer.

It is known that children experience impairment in QoL and fatigue, both during and after cancer treatment. Patients have difficulty regaining baseline physical function and remain at increased risk of preventable late effects and co-morbidities long after treatment is complete\(^{46}\).

Despite the heterogenous inclusion criteria, studies repeatedly show that physical activity can contribute to a slower decline in both measures reviewed, and also lead to improvement in other measures of functional health such as lean muscle mass, functional capacity and VO2 peak\(^{5,34,46}\). Reported adverse events were almost always reasonably attributed to the disease process/treatment, with a meta-analysis finding an incidence rate of 0.02\(^{11}\), indicating that personalized exercise programmes are safe in a paediatric cancer population.

Limitations

We have discussed the clinical heterogeneity between studies prior to aggregating data and conducting an analysis. A meta-analysis was deemed unsuitable due to the heterogeneity of testing protocols limiting the data pool available for the PedsQL fatigue scale or CRF scores. One limitation of this study is that the results are based on studies in children of various ages, with various types of cancer, employing a diverse range of exercise interventions. In view of this, the observed outcomes may differ between diagnostic groups and may be dependent on the type of intervention employed.

Implications for practice and research

This review supports the recommendations of the International Paediatric Oncology (iPOEG) guidelines that all children with cancer should be given the opportunity to exercise safely\(^{52}\), providing evidence that
routine implementation of physical activity programmes could improve QoL and CRF in this vulnerable population. Future studies are needed to evaluate the benefit of personalized physical activity programmes to prevent decline in CRF and QoL and improve other short and long-term physical and psychological outcome measures. More standardised intervention protocols also need to be evaluated to enable replicability across treatment centers.

Conclusion

Physical activity is a feasible and safe means of improving both CRF and QoL in children undergoing treatment for cancer. Evidence shows that various durations and disciplines of exercise improve scores for both QoL and CRF, with several trials reporting statistically significant benefits in both parameters. Further research, including randomised controlled trials, is needed to make evidence-based recommendations for targeted therapeutic exercise programmes to benefit this vulnerable population.

CONFLICT OF INTEREST STATEMENT

The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The views expressed in the submitted article are the authors own and not an official position of the institution. No funders had any role in the design of this study, in the collection of data, the analysis, the interpretation of data, or the dissemination of data.

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