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Effects of physical activity interventions on physical activity and health outcomes in young people during treatment for cancer: a systematic review and meta-analysis of randomised controlled trials

Ellie Langworthy , Kajal Gokal, Victoria E Kettle, Amanda J Daley

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Centre for Lifestyle Medicine and Behaviour, Loughborough University, Loughborough, UK

Correspondence to
Ellie Langworthy;
e.j.langworthy@lboro.ac.uk

ABSTRACT

Objective Physical activity may improve health and reduce the adverse effects of cancer and/or its treatment in young people, therefore, interventions that promote physical activity are important. This systematic review and meta-analysis aims to synthesise evidence from randomised controlled trials (RCTs) that have assessed the effectiveness of physical activity interventions on health outcomes in young people undergoing cancer treatment.

Design Systematic review with meta-analyses.

Data sources Embase, PubMed, Medline, PsycINFO, PsychArticles, SPORTDiscus, Scopus, Web of Science and The Cochrane Library were searched from inception to January 2022.

Eligibility criteria for selecting studies Studies were eligible for inclusion if they were RCTs, recruited young patients with cancer receiving cancer treatment and tested an aerobic physical activity intervention. Title/abstract reports were screened against the review eligibility criteria.

Results Searches revealed seven eligible trials that had recruited 317 participants. No differences were found in minutes per day of participation in moderate to vigorous intensity physical activity (MD 2.61, 95% CI −3.67 to 8.89, p=0.42), total physical activity (standardised mean difference, SMD 0.35, 95% CI −0.39 to 1.09, p=0.35) or fatigue (SMD −0.50, 95% CI −1.03 to 0.02, p=0.06). Sensitivity analyses where trials with a high risk of bias were excluded, revealed significant effects for total physical activity (SMD 0.87, 95% CI 0.17 to 1.57, p=0.02) and fatigue (SMD 0.74, 95% CI −1.13 to −0.35), p=0.0002).

Conclusion Evidence regarding the effects of physical activity interventions on the health of young people undergoing treatment for cancer is limited and mixed, where results from high-quality trials showed some promise.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ While cancer in young people is relatively rare, it is one of the top causes of death among young people, causing several adverse side effects.

⇒ Evidence suggests that physical activity is effective in improving health outcomes in adults undergoing treatment for cancer, but it is unclear if they are similarly effective in young people receiving treatment for cancer.

WHAT THIS STUDY ADDS

⇒ This review found some evidence that physical activity interventions may be useful in improving health outcomes in young people during treatment for cancer, but this is based on limited evidence, and further high-quality trials are required.

INTRODUCTION

Cancer in children, adolescents and young adults (hereafter referred to as young people) poses a relatively rare, yet highly distressing experience for individuals diagnosed with the disease.[1] Although the incidence of cancer in young people is lower than the case for older populations, incidence rates are increasing.[2] Cancer remains one of the top causes of death among young people, responsible for around 250 deaths every year.[3]

Young people undergoing cancer treatment face an array of difficulties, not least having to endure the adverse side effects of cancer treatment. This includes side effects such as pain, fatigue, nausea and loss of strength, which can persist beyond the completion of treatment.[4 5] Whether beginning during treatment or developing later, young people with cancer face additional age-related challenges.[6] As the early years of life represent critical and complex stages of development, being diagnosed with cancer will often disrupt developmental processes, which can adversely impact young people's physical and mental health.[6 7] This can put young people at risk of experiencing depression, problems with memory and learning, treatment-related infertility and early

menopausal symptoms, and impact their social and educational attainment.[6 7]

The additional burden of treatment-related side effects can reduce the physical functioning and quality of life of young patients with cancer.[5] This contributes to high levels of physical inactivity, with evidence showing that young patients with cancer are less physically active than before treatment and compared with their healthy peers.[8 9] Reduced levels of physical activity perpetuate fatigue which in turn may further reduce physical and mental health.[10 11] Investigating the effectiveness of interventions that reduce both the short-term and long-term effects of cancer and cancer treatment has therefore been identified as one of the top 10 research priorities for young people with cancer.[12]

Physical activity during cancer treatment

Interventions that promote physical activity during cancer treatment may benefit young people by attenuating adverse treatment effects, while also contributing to the maintenance of a broader healthy lifestyle, at a time when it is critical that their health status is not compromised. In adults, strong evidence supports the role of physical activity in reducing cancer-related fatigue, anxiety and depression and improving health-related quality of life and physical function.[13] Some studies have indicated this may also be the case for children.[14 15]

All patients with cancer, regardless of age, are encouraged to avoid complete inactivity and remain physically active, where possible aiming to follow the physical activity guidelines issued for their age group.[16] This means completing 60 min of moderate to vigorous intensity physical activity (MVPA) per day for children and adolescents (5–17 years) and 150–300 min of moderate-intensity aerobic physical activity per week for adults (18–64 years).[16] Both age groups should also complete exercises that strengthen muscles and aim to reduce the amount of time spent sitting or lying down.[16] With 23% and 13% of children (6–12 years) and adolescents (13–17 years) in the general population meeting these guidelines, achieving these quantities of physical activity is evidently a challenge, even for those not undergoing treatment for cancer.[17] The high incidence of physical inactivity, alongside the evidence in support of physical activity during cancer treatment, highlights the importance of finding effective interventions to support young people to engage in regular physical activity during their treatment for cancer and beyond.

This systematic review and meta-analysis aims to synthesise the evidence on the effectiveness of physical activity interventions during treatment in young patients with cancer on physical activity levels, fatigue, quality of life and sedentary behaviour. Understanding the size of such effects is also important to guide future health policy on this question.

METHODS

A systematic review with meta-analysis of randomised controlled trials (RCTs) and quasi-RCTs (here referred to as RCTs) was conducted. The protocol was registered on PROSPERO (CRD42022311892) and is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[18]

Eligibility criteria

Studies were eligible for inclusion if they met the following inclusion criteria: (A) were either RCTs or quasi-RCTs; (B) recruited young patients with cancer aged 0–39 years who were completing cancer treatment; (C) measured physical activity as an outcome and (D) included a comparator group that did not include physical activity. Interventions not designed to promote aerobic-based physical activity or were solely focused on mindfulness exercise or body conditioning (eg, yoga or tai-chi) were excluded. Online supplemental table S1 shows the full eligibility criteria. A broad age range was included in this review as the cut-off to define what age range constitutes an adolescent, and young person differs across countries. For example, in the UK, between 13 and 24 years denote an adolescent/young person,[19] whereas in the USA and Canada, between 15 and 39 years is used.[20]

Database search

Between 10 December 2021 and 15 January 2022, the following databases were systematically searched using individualised search strategies: EMBASE, PubMed, Medline, PsycINFO, PsychArticles, SPORTDiscus, Scopus, Web of Science and The Cochrane Library. Grey literature was also searched using BASE. The key search terms included words related to cancer, physical activity, RCT/quasi-RCTs, and children, adolescents and young adults (online supplemental table S3). All searches were completed from inception, with no language restrictions applied. Subsequently, the reference lists of relevant studies searched to check for additional potentially eligible trials. Retrieved studies were imported into COVIDENCE (Veritas Health Innovation, Melbourne, Australia).[21] Before the final analyses, a 6-month search of PubMed was conducted on 13 May 2022 to check for any eligible studies that had recently been published.

Study selection

Duplicates were automatically identified and removed by COVIDENCE. Two independent reviewers screened study titles and abstracts from EL, AJD, KG and VEK. EL retrieved the full texts of potentially eligible studies. They were then assessed independently by EL, AJD or KG using the inclusion and exclusion criteria. The researchers were blinded to each other's decisions. When disagreements arose, they were discussed between the two researchers and resolved by consensus, with a third reviewer consulted if consensus could not be reached.

Data extraction

EL extracted and summarised data about the characteristics of included studies (online supplemental table

S1). EL and VEK independently extracted outcome data used for the meta-analysis before comparing the data. Any disagreements between the reviewers were resolved through discussion and consulting the original study reports. If disagreements persisted, a third reviewer was consulted.

Quality of evidence assessment

The Cochrane Risk of Bias Tool V.2 (RoB2) was used to independently assess the risk of bias (RoB) by EL and VEK or KG.[22] This tool addresses five different domains: randomisation, deviation from intended interventions, incomplete outcome data, measurement of outcome data and selective outcome reporting. An outcome of 'low' RoB, 'some concerns' or 'high' RoB is generated by the tool's algorithm for each domain, with an overall judgement also given. Where available, study protocols and trial registries were used to help assess the RoB. Studies with attrition of >25% were determined to have a high RoB. Discrepancies between researchers were identified by the ROB tool. Subsequently, the two authors discussed disagreements with the full text consulted to reach a consensus.

Outcomes

The primary outcomes were the difference in the change in the participation of MVPA (minutes/day) and total physical activity (all intensities) between trial groups from baseline to final follow-up. The secondary outcomes were mean differences in sedentary behaviour (minutes/day), fatigue and quality of life scores between trial groups from baseline to final follow-up.

Data synthesis

Study information such as study reference, setting and design, intervention design and delivery, participant characteristics, comparator information and outcomes measures were extracted from study reports. The mean, SD and the number of participants for the intervention and comparator groups at baseline and follow-up were extracted for each review outcome. These data were used to calculate the mean change from baseline and SD of the change using a standardised formula.[23] Where trials reported data as minimum, maximum and medians, this was used to calculate the mean and SD using standardised formulas (SD).[24 25] Where studies measured fatigue using inverse scales, that is, a higher score indicated lower fatigue, the results were multiplied by −1, so lower scores indicated lower fatigue.[26 27] Where studies reported moderate and vigorous-intensity physical activity separately, these means were added together, and the SD was calculated to give an overall moderate vigorous-intensity physical activity score.[28]

Where studies did not report an overall score for quality of life, with results from each subscale given separately, an average score was calculated by summating the scores and then dividing them by the number of subscales, and SD was calculated.[29] Where studies only reported data at follow-up, we checked there was no evidence to suggest that baseline data differed substantially between groups and follow-up data were used in the analyses.[27 29] For trials that reported multiple physical activity outcomes, the most relevant measurement in relation to the outcome was used for the meta-analysis, with device-based measurements chosen over self-reported data.[27] RevMan V.5.4 (Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark)[30] was used to conduct inverse variance meta-analyses for all outcomes.

Random effects models were used as a range of interventions had been tested in the included trials. For each outcome, the weighted mean, or standardised mean difference (SMD), and 95% CIs were calculated. The SMD was calculated for total physical activity, fatigue and quality of life, as the tools to measure each outcome differed between studies. The effect size was interpreted using Cohen's d, where 0.2 represents a small effect, 0.5 represents a moderate effect and 0.8 represents a large effect.[31] The variability in effect estimates that is due to the heterogeneity rather than sampling error (chance) is also reported using the I^2 statistics. Sensitivity analyses were completed for each outcome to examine the impact of removing trials with a high RoB and by age with trials recruiting older people (18–39 years) removed.

RESULTS

Study selection

The search strategy yielded 3719 reports, including 1694 duplicates, with 2025 unique reports screened. Of these, 44 reports were eligible and sought for retrieval. A total of 38 full texts were obtained and screened. Of these, six were conference abstracts with no published full texts and were therefore excluded, resulting in seven eligible reports included in this review. The screening process is summarised in figure 1.

Study characteristics

The included trials were conducted in the USA (n=2),[28 32] China (n=1),[33] Spain (n=1),[34] Germany (n=1),[26] Finland (n=1)[27] and in USA and Canada (n=1).[29] All seven studies were RCTs.[26–29 32–34] No quasi-RCTs were included. Studies randomised a total of 317 participants, with most randomising less than 50 participants (n=6).[26–28 32 34] The youngest recruited participants were 3 years of age.[27] Most studies used 18 years as their upper age limit (n=4)[26 29 33 34] other studies used 10 years (n=1)[32] or 16 years (n=1).[27] Only one study that recruited 44 participants included participants over 18 years, recruiting those aged 18–39 years.[28] Studies included participants with acute lymphoblastic leukaemia (ALL) only (n=2),[29 32] any cancer (n=3),[26 28 33] extracranial solid tumour (n=1)[34] or either ALL or cancer outside the central nervous system (n=1).[27] Most participants were receiving chemotherapy, either solely (n=2)[28 34] or as part of their treatment regimen (n=5).[26 27 29 32 33]

The duration of interventions ranged from 6 weeks[26] to 2.5 years.[29] Interventions were either home based

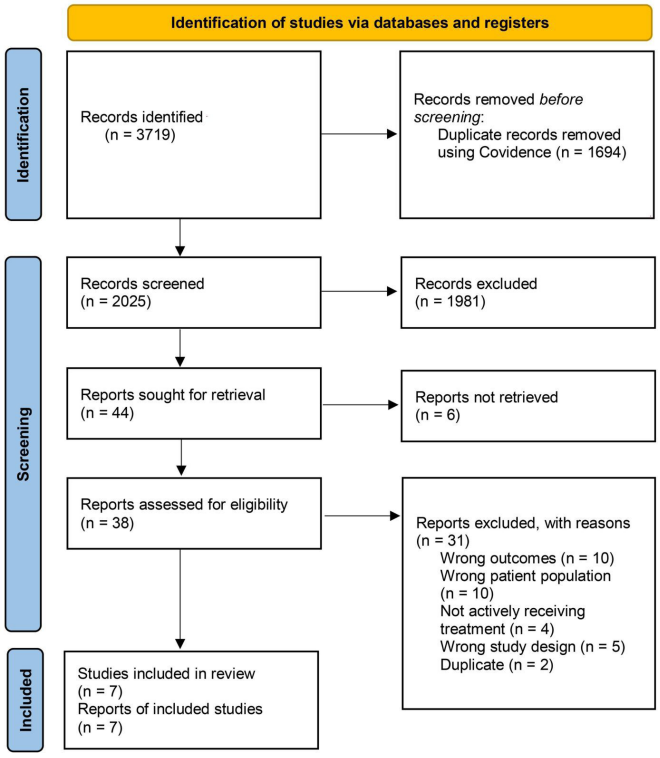

Figure 1 PRISMA diagram showing the process for study selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

(n=3)[28 32 33] hospital based (n=1)[34] or a combination of both (n=3).[26 27 29] Studies measured physical activity using accelerometers (n=3),[28 29 34] subjective measures (n=2)[26 33] or a combination (n=2).[27 32] Accelerometer data were reported as minutes/day,[28 34] accelerometer hours,[29] accelerometer counts/hour[27] or pedometer steps.[32] A range of self-report methods were used to measure physical activity, fatigue and quality of life. Online supplemental table S3 shows individual study characteristics.

Meta-analyses of included trials

MVPA (minutes/day)

Based on two studies measuring MVPA,[28 34] there was no difference in MVPA between the intervention and control group from baseline to final follow-up (MD 2.6 min/day, 95% CI −3.67 to 8.89, p=0.42) (figure 2). Heterogeneity, indicated by the I^2 statistic, was 0% (τ^2=0.00, χ^2=0.87, p=0.35).

Total physical activity (all intensities)

Based on five studies,[26–29 33] no significant difference in total physical activity between groups from baseline to follow-up was found (SMD 0.35, 95% CI −0.39 to 1.09, p=0.35 (figure 3). Considerable heterogeneity was evident (I^2=85%, τ^2=0.58, χ^2=26.64, p<0.0001). The trial by Moyer-Mileur *et al*[32] was not included in the meta-analysis due to inadequate data reporting, where graphical data were presented with unlabelled error bars, with no response from the author when contacted. This trial reported that the exercise group completed more pedometer steps than the control group at 12 months, but this result was not significant (p=0.06).[32] Excluding the trial where follow-up was after 6 months[29] did not impact the results (SMD 0.46, 95% CI −0.45 to 1.38, p=0.32).

In the sensitivity analysis omitting the trials with a high RoB (n=2),[27 29] a significant difference between the groups was observed (n=3, SMD 0.87, 95% CI 0.17 to 1.57, p=0.02). When the trial[28] that recruited participants up to 39 years was excluded, no effect on total physical activity was found.

Fatigue

Fatigue was measured in four of the included studies,[26–28 33] and the difference between the trial groups was non-significant, although it approached significance (figure 4) (SMD −0.50, 95% CI −1.03 to 0.02, p=0.06). Heterogeneity was moderate (I^2=57%, τ^2=0.16, χ^2=6.99, p=0.07). The sensitivity analysis excluding the trial with a high RoB (n=1)[27] revealed a significant difference between the groups for fatigue (n=3, SMD 0.74, 95% CI −1.13 to −0.35, p=0.0002). Excluding the trial with older participants[28] did not alter the SMD in fatigue between the trial groups.

Quality of life

Quality of life was measured in four of the included studies,[26 29 33 34] and the difference between trial groups was not significant, although it approached significance (figure 5) (SMD 0.42, 95% CI −0.01 to 0.85, p=0.05). There was evidence of moderate heterogeneity (I^2=55%, τ^2=0.10, χ^2=6.70, p=0.08). In the sensitivity analysis where the trial with a high RoB (n=1)[29] was excluded, a significant difference between the intervention and comparator groups was observed (n=3, SMD 0.62, 95% CI 0.23 to 1.01, p=0.002).

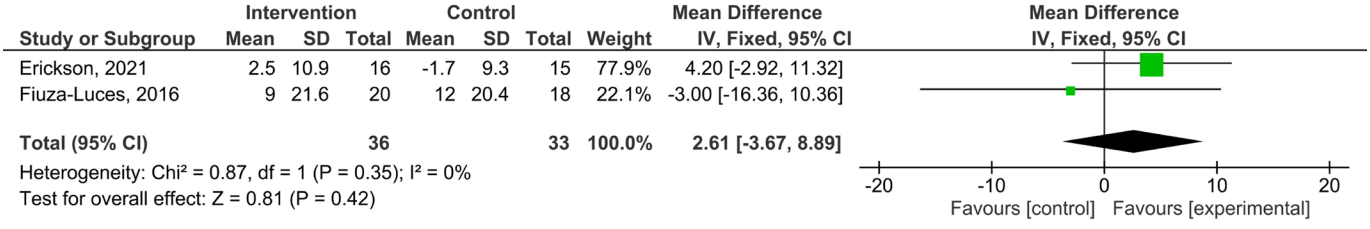

Figure 2 Forest plot of the meta-analysis for change in MVPA (minutes/day) from baseline to final follow-up. MVPA, moderate to vigorous intensity physical activity.

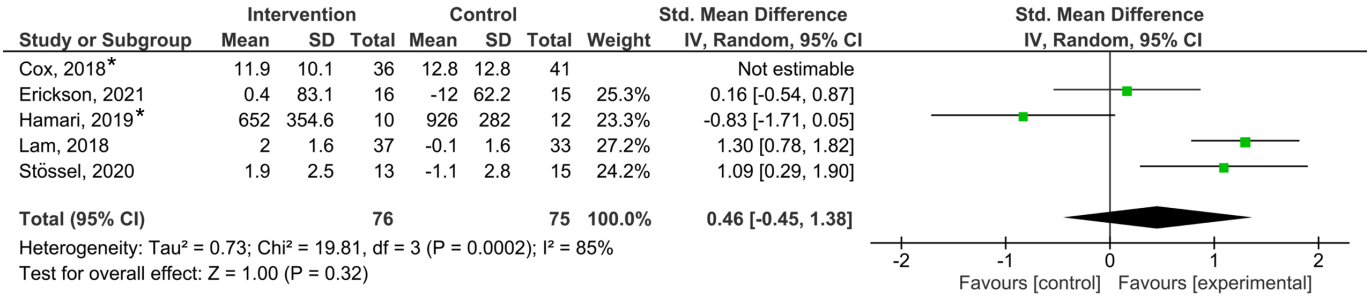

Figure 3 Forest plot of the meta-analysis for total physical activity at final follow-up (all trials). *Follow-up data used directly as baseline data unavailable.

Sedentary behaviour (minutes/day)

It was not possible to conduct a meta-analysis to assess the impact of physical activity interventions on sedentary behaviour, as only one study reported data.[34] There was no significant difference between the trial groups in this trial, with a decrease of 18 and 27 min observed by the intervention and control groups, respectively.[34]

Risk of bias

Of the seven studies, only one had a low RoB, four had some concerns, and two had a high RoB (online supplemental figure S1). Trials were deemed to have some concerns for RoB due to a lack of information on the allocation process, and/or no previous publication of a specified analysis plan. For trials categorised as having a high RoB, this was typically due to a lack of blinding and potential bias because a self-report method was used to assess the primary trial outcome.

DISCUSSION

Young people receiving cancer treatment engage in less physical activity and experience substantial side effects compared with children without cancer.[35] In our analyses, participation in a physical activity intervention did not significantly increase physical activity. Analyses showed no significant improvements in fatigue and quality of life scores, although in both cases significance was approached (p=0.06 and p=0.05, respectively). Furthermore, in sensitivity analyses based on trials of high methodological quality only, physical activity interventions during cancer treatment for young people significantly increased participation in physical activity (total), reduced feelings of fatigue and improved quality of life. These sensitivity analyses, however, were based on only a small number of randomised participants. This review has highlighted that there is a lack of research investigating the effects of physical activity interventions for young people during cancer treatment, with the greatest research gap evident in adolescents and young adults.

Comparisons with previous literature

The findings of this review are in line with previous reviews outlined below, where mixed findings have been reported. Caution should be applied when making comparisons with previous reviews, however, because they included trials of physical activity interventions that had taken place both during and after the completion of cancer treatment. Ito *et al* found that exercise interventions had a positive effect on fatigue in both young patients with cancer and survivors.[36] Likewise, Munsie *et al* reported that young people randomised to a physical activity intervention during and after cancer treatment reported improvements in quality of life but not in cancer-related fatigue.[37] A Cochrane Library review by Braam *et al* that reviewed exercise interventions for children and young adults during and after treatment for childhood cancer reported no changes in participation in daily physical activity despite improvements in health-related quality of life scores.[38] However, unlike these previous reviews, our review focused solely on physical activity interventions for young people during cancer treatment. Young people receiving treatment for cancer face different challenges and circumstances compared with young people who have finished treatment, which need to be considered when designing physical activity interventions for this population. For example, young people receiving cancer treatment must manage their day-to-day life around hospital appointments and treatment-related

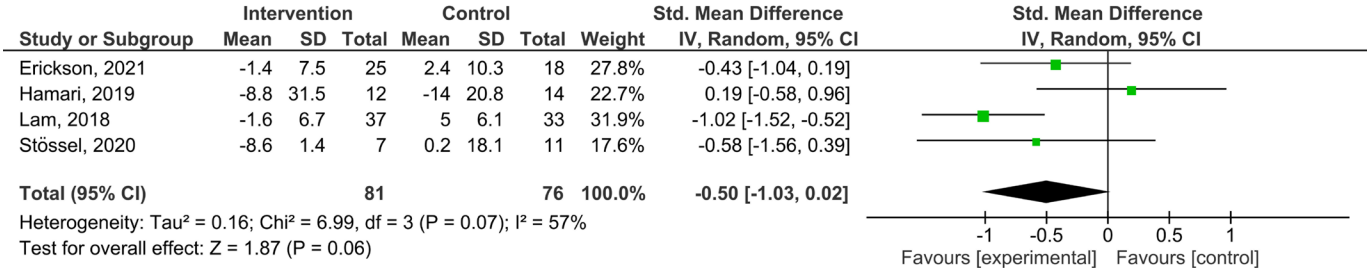

Figure 4 Forest plot of the meta-analysis for fatigue from baseline to final follow-up.

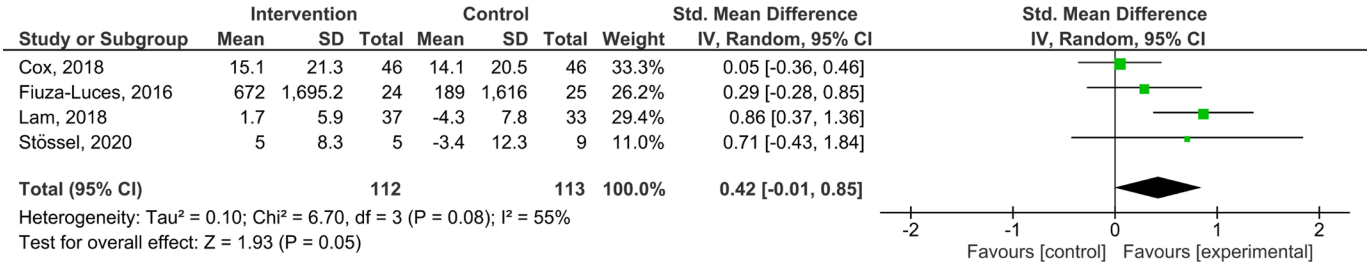

Figure 5 Forest plot of the meta-analysis for quality of life from baseline to final follow-up.

side effects, which will impact the amount of physical activity they can achieve.

Impact on physical activity

There are some plausible explanations as to why some trials in this review found no difference in physical activity levels between trial groups. The interventions evaluated may have been unsuccessful at increasing physical activity because of difficulties with adherence to interventions. Participants may have missed physical activity sessions due to medical problems related to cancer and cancer treatment, such as infections, extreme fatigue and severe nausea.[26 28 34] In trials involving hospital-based programmes, adherence was reduced by parents being unavailable to take their children to the hospital to participate in physical activity sessions, or because sessions coincided with chemotherapy and lack of time/staff/space.[26 34] Overcoming barriers that this population face when seeking to be physically active is critical for the success of physical activity interventions for young people with cancer. To highlight this point further, one review reported that supervised exercise interventions, where adherence was 87%, led to significant improvements in daily physical activity and quality of life in children who had received treatment for cancer.[39] This point is evident in the trial by Lam *et al*,[33] where 86% of children randomised to the physical activity group received all coaching sessions, and reported higher levels of physical activity than the control group.[33] Studies in this review suggest that providing support to overcome barriers to physical activity and providing appropriate physical activity challenges are important to facilitate adherence.[28 29] These strategies should be considered when designing future physical activity programmes for young people with cancer. Importantly, previous reviews agree that physical activity interventions in this population are feasible, safe and typically have no adverse effects.[39 40]

Other reasons why trials may not have found differences in physical activity levels between trial groups relate to study methodology, particularly concerning the measurement of physical activity, study sample size and study design. The measurements of physical activity within the trials may have failed. For example, the studies included in this review that used accelerometers reported high amounts of missing physical activity data.[28] Related to the issue of missing data, poor compliance to wearing and returning the accelerometers in young people with or recovering from cancer has also been noted in studies and may be due to the added burden this places on child patients with cancer and their families, at a time where they are already feeling overwhelmed. Some studies in this review used self-report measurements.[26 27 32 33] Although this approach may reduce participant burden, research has consistently demonstrated that self-reported physical activity is less accurate than when measured using accelerometers.[35] Measuring light physical activity is important in this population as this is likely to be the intensity of exercise patients with cancer engage in. However, some trials only measured moderate and vigorous-intensity physical activity.

Each trial was small (the largest randomised 107 participants(17)) and may not have been adequately statistically powered to detect differences in outcomes. Lack of blinding and using self-report measures to assess physical activity resulted in two trials being assessed as having a high RoB, further highlighting the need for high-quality trials with sufficient sample sizes in this field.

Strengths

This review has a number of important strengths. This review contributes robust evidence to limited knowledge on the role of physical activity interventions for young people with cancer. Several methodological procedures were included in the review to reduce the probability of bias influencing the findings; not limiting the search to studies written in English, searching for studies from inception across a range of databases, the inclusion of sensitivity analyses, and the use of two independent reviewers to conduct the screening process, collect outcome data and assess the RoB in trials.

Limitations

This review has some methodological weaknesses that should be considered when interpreting the findings. The small sample sizes in the included studies were small, which may have introduced bias to the findings. Due to the limited number of published physical activity trials in this population, only seven eligible studies were included, each with variability in patient characteristics, interventions and outcome assessment methods, which may not support the use of meta-analyses and mean that subgroup analyses were not appropriate. This review did not investigate the effects of variables such as body mass index and muscle strength, which are important

outcomes associated with participation in physical activity and are important questions for future research.

Clinical implications

Physical activity interventions may be beneficial for young people with cancer during cancer treatment. As engaging in physical activity is considered safe and feasible and may have positive benefits on outcomes such as fatigue and quality of life, supporting young patients with cancer to engage in physical activity during their treatment may be valuable. However, more research is warranted to establish the benefits of physical activity in this population, along with further research on how to effectively prescribe physical activity.

Future directions

To draw firm conclusions about the benefits of physical activity during cancer treatment for young people, interventions that seek to increase adherence to physical activity are required. For young people undergoing cancer treatment, adhering to hospital-based exercise programmes is challenging and is affected by barriers such as time and transport restrictions. Better adherence may therefore be seen in flexible, home-based interventions that encourage participants to self-monitor and regulate their physical activity behaviour. To capture all of the physical activity that young people with cancer may achieve, the measurement tool used must be able to assess and capture light-intensity physical activity accurately, particularly given public health guidelines in many countries now emphasise that all physical activity is good for health, regardless of its intensity.[40] Future interventions should consider incentivising participants to wear and also return their accelerometer devices to reduce the probability of missing outcome data undermining the quality of such trials.

CONCLUSIONS

Evidence regarding the effects of physical activity interventions on participation in physical activity and other health outcomes in young people undergoing treatment for cancer is mixed, based on limited evidence and contingent on study quality. Adequately powered high-quality trials that focus on promoting adherence to the intervention in this population of young people are required.

Contributors The guarantor, EL, drafted the manuscript which was reviewed and edited by the coauthors AJD, KG and VEK. EL, AJD, KG and VEK all contributed to the screening process. EL and VEK completed data extraction with KG consulted to resolve conflicts between EL and VEK. EL, VEK and KG completed the quality of evidence assessment. The final version of the manuscript was approved by all authors.

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ORCID iD

Ellie Langworthy http://orcid.org/0000-0001-9432-9242

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