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RESEARCH ARTICLE

Longitudinal development of cancer-related fatigue and physical activity in childhood cancer patients

Elisabeth M. Van Dijk-Lokkart[1] | Lindsay M. H. Steur[2] | Katja I. Braam[2,3] | Margreet A. Veening[2,4] | Jaap Huisman[4] | Tim Takken[5] | Marc Bierings[4,6] | Johannes H. Merks[4,7] | Marry M. Van den Heuvel-Eibrink[4,8] | Gertjan J. L. Kaspers[2,4] | Eline Van Dulmen-den Broeder[2] | Raphaële R. L. Van Litsenburg[2,4]

[1]Emma Children's Hospital, Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Medical Psychology, Amsterdam, The Netherlands

[2]Emma Children's Hospital, Amsterdam UMC, Vrije Universiteit Amsterdam, Pediatric Oncology, Cancer Center Amsterdam, Amsterdam, The Netherlands

[3]Faculty of Health, University of Applied Science, Amsterdam, the Netherlands

[4]Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands

[5]Child Development and Exercise Center, Wilhelmina's Children's Hospital, UMC Utrecht, the Netherlands

[6]Department of Pediatric Oncology/Hematology, Wilhelmina Children's Hospital, UMC Utrecht, the Netherlands

[7]Emma Children's Hospital, Amsterdam UMC, Academic Medical Center, Department of Pediatric Oncology, Amsterdam, The Netherlands

[8]Department of Pediatric Oncology/Hematology, Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands

Correspondence
Elisabeth M. van Dijk-Lokkart, Emma Children's Hospital, Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Medical Psychology, P.O. Box 7057, 1007 MB Amsterdam, the Netherlands.
Email: em.vandijk@vumc.nl

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Abstract

Purpose: Cancer-related fatigue is one of the most distressing side effects of childhood cancer treatment. Physical activity can decrease fatigue and has positive effects on other health outcomes. Most research on physical activity pertains to adults, and the few studies that focus on children have limited follow-up time. This study evaluates cancer-related fatigue in children and its association with physical activity over a one-year time period.

Methods: Sixty-eight children with cancer (7–18 years) were recruited during or within the first year after treatment. Physical activity (Actical activity monitor) and cancer-related fatigue (Pediatric Quality-of-Life Questionnaire Multidimensional Fatigue Scale (PedsQL-MFS), self- and parent- reports) were assessed at baseline, 4 months, and 12 months. PedsQL-MFS scores were compared with Dutch norms. Longitudinal association of cancer-related fatigue with physical activity was evaluated (No. NTR 1531).

Results: Generally, PedsQL-MFS scores were worse than norms at baseline and 4 months, and recovered by 12 months except for the parent-proxy scores in adolescents. Younger children (≤12 years) self-reported comparable or better scores than norms. Physical activity generally improved over time, but patients mostly remained sedentary. During follow-up, increased physical activity was associated with less cancer-related fatigue.

Conclusion: Cancer-related fatigue in children improves over time, and increased physical activity is associated with less cancer-related fatigue. Given the sedentary lifestyle of this population, the positive effect of physical activity on cancer-related fatigue, and the many other health benefits of an active lifestyle, it is important to stimulate physical activity in childhood cancer patients and survivors.

KEYWORDS
cancer, children, fatigue, oncology, physical activity

Abbreviations: BMI, body mass index; CPM, count per minute; GEE, generalized estimating equations; PedsQL-MFS, Pediatric Quality-of-Life Questionnaire Multidimensional Fatigue Scale; QLIM, quality-of-life in motion; SD, standard deviation.

E.M. van Dijk-Lokkart and L.M.H. Steur are both first authors and contributed equally.

1 | INTRODUCTION

Cancer-related fatigue is one of the most common and distressing side effects of childhood cancer treatment.[1–3] Cancer-related fatigue is associated with other sequalae that occur in childhood cancer patients, such as depressive symptoms and impaired quality of life.[4–6]

The National Cancer Institute has made high-priority research recommendations for studies on cancer-related fatigue. Among the recommendations is the need for longitudinal research to examine biobehavioral mechanisms (including demographic, biological, medical, functional, and behavioral factors) involved in cancer-related fatigue.[7] A meta-analysis on the effect of exercise on cancer-related fatigue was published in 2014. It showed that exercise has a moderate effect on cancer-related fatigue and additional positive effects on depression and sleep impairments.[8] Physical activity may therefore be one of the biobehavioral mechanisms in cancer-related fatigue. However, only one out of the 72 randomized trials in the meta-analysis included children.[9] This study by Hinds et al did not find an effect of an enhanced physical activity program on cancer-related fatigue. Follow-up was, however, short (up to four days). Since then, four other studies in childhood cancer patients did report a relationship between physical activity and cancer-related fatigue. In a cross-sectional study, greater occurrence and severity of cancer-related fatigue was associated with lower levels of physical activity.[6] One observational study in long-term survivors of childhood leukemia or lymphoma showed that lower levels of physical activity were associated with persistent cancer-related fatigue.[10] The final two studies were intervention studies. The first study used a fitness tracker in children during maintenance treatment for acute lymphoblastic leukemia. Patients who were physically more active reported less cancer-related fatigue after about three weeks.[11] In the second study, the effectiveness of a four-day adventure-based training program was examined in increasing physical activity and reducing fatigue. Higher levels of physical activity and lower levels of cancer-related fatigue were reported in the intervention group.[12]

Given that children with cancer are less physically active,[13–16] it is important to further explore the improvement of cancer-related fatigue through increased physical activity. The end of the treatment and the first period after cessation of therapy may represent a window of opportunity for childhood cancer patients to increase physical activity, as their health is generally improved during this time. Increasing levels of physical activity in this time frame could provide an opportunity to improve cancer-related fatigue in these children. However, long-term effects on cancer-related fatigue have not been previously evaluated. Therefore, this study aims to evaluate cancer-related fatigue in children with cancer during the final stages of treatment and the first period after cessation of therapy, and its association with physical activity over a one-year time period. This information is valuable to better understand the biobehavioral mechanisms of persistent cancer-related fatigue in children.

2 | METHODS

2.1 | Procedure

For the present study, data collected as part of a randomized controlled trial on the effectiveness of a combined physical exercise and psychosocial training program to improve physical fitness ('Quality of Life in Motion' (QLIM) study) were used. Details of the design of this study are reported elsewhere.[17] Briefly, the QLIM intervention consisted of a 12-week physical intervention including cardiorespiratory and muscle strength training twice a week at a physical therapy sports center near the child's home. The psychosocial intervention was specifically developed for the QLIM study and consisted of six child sessions of 60 minutes every two weeks, and two parent sessions. The QLIM intervention was compared with care as usual.

2.2 | Study population

Patients were identified through the Dutch Childhood Oncology Group registry, which includes all children with a diagnosis of cancer or a low-grade malignancy. Eligible patients were aged between 7 and 18 years, diagnosed with any type of childhood cancer, treated with chemotherapy and/or radiotherapy, and they were still receiving treatment or were within the first year after cessation of treatment. Patients on treatment were included only if their clinical condition enabled them to participate in and to complete the intervention program. Exclusion criteria were stem cell transplantation, growth hormone therapy, wheelchair dependency, inability to ride a bike, learning difficulties, and a lack of informed consent from the parent and/or the child (aged ≥12 years). Recruitment took place between March 2009 and July 2013 in four out of six pediatric oncology centers in the Netherlands: VU University Medical Center (Amsterdam), Wilhelmina's Children's Hospital UMC (Utrecht), Emma Children's Hospital/Academic Medical Center (Amsterdam), and Erasmus Medical Center/Sophia Children's Hospital (Rotterdam). Informed consent was provided by all parents and participating children aged 12 years and older. The Medical Ethics Committee of the VU University Medical Center (No 2008/208) has approved the study protocol, and the study is registered at the Dutch Trial Register (No. NTR 1531).

2.3 | Data collection and instruments

At three time points (baseline, after 4 months, and after 12 months) data collection took place for the same outcome measures. Timing of baseline assessment differed between patients, depending on their start in the QLIM study: during treatment or within the first year after the end of the latest treatment. The two follow-up measurements were collected 4 and 12 months after baseline. Questionnaires were filled out at the hospital, and the process was supervised by a member of the research staff. Measurements with an accelerometer took place shortly after questionnaire assessment and registered activities of the included patients at home.

2.4 | Cancer-related fatigue

Cancer-related fatigue was assessed by the self-report and parent-proxy report version of the PedsQL Multidimensional Fatigue Scale Acute Version (PedsQL-MFS). This instrument measures both the child's and his/her parent's perception of fatigue in pediatric patients.[18] It has often been used in childhood cancer patients.[1,19,20] This 18-item questionnaire has three subscales: general fatigue (six items), sleep/rest fatigue (six items), and cognitive fatigue (six items). A total fatigue score can also be derived. The participants indicated on a 5-point Likert scale to what extent the child had difficulties with the stated problem in the past month: never (0), almost never (1), sometimes (2), often (3), and almost always (4). Each answer was reversed, scored, and rescaled to a 0 to 100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, and 4 = 0). The items on each subscale were summarized and divided by the number of items in the subscale to get a total score between 0 and 100 for each subscale, with higher scores indicating higher levels of functioning or less cancer-related fatigue. Scale scores were calculated in case at least half of the items on a subscale were filled out by participants. The Dutch version has adequate psychometric properties and normative scores of the Dutch population are available.[21] Based on the available Dutch norm data, two age groups were identified for comparison: school-aged children aged 7 to 12 years and adolescents aged 13 to 18 years.

2.5 | Physical activity

Participants wore an accelerometer (Actical activity monitor; B series, Philips Respironics Actical Mini Mitter, Co Inc., USA) on the left hip in an elastic waist belt during daytime at waking hours (between 6:00 am and 11:59 pm) on four consecutive days (Wednesday–Saturday). Accelerometer measurements had previously been validated in healthy children aged 7 to 18 years.[22] Data were collected with a 15-second epoch interval.[23] Valid measurements required a wear time of at least 500 min/day. When data showed 60 minutes of consecutive zeros on the readout, these data were coded as non-wear time and excluded from the analyses. Physical activity was expressed as mean counts per minutes (CPM). According to previously described thresholds, physical activity of < 100 CPM was considered sedentary, < 900 CPM as light activity, < 2200 CPM as moderate activity, and ≥ 2200 CPM as vigorous activity.[24] Children who were moderately to vigorously active for a mean of ≥ 60 minutes per day during the four-day measurement period were considered to comply with the Dutch healthy exercise norm.[25]

2.6 | General and medical characteristics

Information on sex, age, diagnosis, treatment, and time since diagnosis was obtained from the patients' medical records.

2.7 | Statistical analysis

There were no significant beneficial effects of the QLIM intervention on physical fitness, physical and psychosocial function at 4 and 12 months, except for a larger improvement in lower body muscle strength at 12 months in the intervention group.[26–28] Therefore, patients were evaluated together for the purpose of the present study, irrespective of the QLIM study group they were originally assigned to. As the results presented here are a post hoc analysis of the QLIM study data, a power calculation based on the primary outcome of the present study was not established.

Population characteristics were presented in means with standard deviation (SD) and frequencies. Mean scores and SD were calculated for all (sub)scales of the PedsQoL MFS at each time point and were compared with Dutch norms using independent samples *t* tests. In addition, Cohen effect sizes were calculated to compare cancer-related fatigue between the childhood cancer patients and the Dutch norm population, and to represent the meaning and magnitude of the differences. Cohen effect sizes were calculated by subtracting the mean score of the norm population from the mean score of the study population and dividing it by the largest SD of both populations. Effect sizes between 0.2 and 0.5 were considered small, effect sizes between 0.5 and 0.8 moderate, and effect sizes ≥ 0.8 large.[29]

In order to describe physical activity, mean CPM were calculated. In addition, mean minutes of sedentary, light, moderate, and vigorous activity per day were calculated. Generalized estimating equations (GEE) analyses were used to determine the longitudinal development of mean CPM and mean minutes of activity. Missing data were considered to be completely at random, and all available longitudinal data were included in the analyses. Percentages of children who complied with the Dutch healthy exercise norm were presented.

GEE analysis was used to determine the longitudinal development of the association between cancer-related fatigue and physical activity over time.

Age, sex, and intervention group (intervention vs care as usual) were always included in the GEE analysis. Diagnosis, type of treatment, time since diagnoses, body fat percentage, and the body mass index (BMI) z-score at baseline were examined as variables for a possible effect on the development of physical activity and the association between cancer-related fatigue and physical activity over time. The final model was adjusted for factors that appeared to modify the model in order to represent the most accurate development of physical activity and the association between cancer-related fatigue and physical activity over time.

IBM Statistics SPSS version 20 was used for statistical analyses. Significance level was set at a two-sided *P* value of 0.05 for all analyses.

3 | RESULTS

Out of 174 eligible patients, 68 (39.1%) agreed to participate in the QLIM study. General and medical characteristics were not found to be different between the participants and the nonparticipants. Perceived burden of the intervention and increased travel distance to the hospital were related to nonparticipation.[30] Between baseline and the first follow-up assessment at four months, nine (13.2%) participants dropped out, mainly due to the recurrence of disease or

TABLE 1 Population characteristics

	Baseline[a] ($n = 68$)	Follow-up 4 months[a] ($n = 59$)	Follow-up 12 months[a] ($n = 53$)
Age in years, mean (SD)	13.2 (3.1)	13.5 (3.1)	14.0 (3.2)
Age			
7–12 years	30 (44.1)	25 (42.4)	20 (37.7)
13–18 years	38 (55.9)	35 (57.6)	33 (62.3)
Time since diagnose in months, mean (SD)	12.6 (7.2)	17.2 (7.3)	25.0 (7.2)
Sex			
Female	32 (47.1)	28 (47.5)	26 (49.1)
Male	36 (52.9)	31 (52.5)	29 (50.9)
Diagnosis			
Hematologic malignancy	46 (67.6)	38 (64.4)	36 (67.9)
Brain tumor	7 (10.3)	6 (10.2)	5 (9.4)
Solid tumor	15 (22.1)	15 (25.4)	12 (22.6)
Treatment			
CT[b]	42 (61.8)	23 (59.3)	33 (62.3)
CT+[c]	26 (38.2)	35 (40.7)	20 (37.7)
Body fat percentage, mean (SD)	31.3 (7.5)	29.9 (7.7)	30.2 (7.8)
BMI Z-score, mean (SD)	0.6 (1.1)	-	-

SD, standard deviation.
[a]*n* (%), unless otherwise specified; [b]CT, chemotherapy only; [c]CT+, chemotherapy combined with radiotherapy or surgery.

medical complications (7/9). An additional 6 (8.8%) participants dropped out between 4 and 12 months after baseline for the same medical reasons. General and medical characteristics of the study group at all three time points are summarized in Table 1.

3.1 | Cancer-related fatigue

Most PedsQL-MFS scores in both age groups increased over time, reflecting an improvement in cancer-related fatigue (Table 2). Cohen effect sizes for the magnitude and meaning of the differences in fatigue scores between the study population and the norm population are shown in Table 3.

3.2 | School-aged children 7–12 years

Self-reported PedsQL-MFS scores were not statistically different between the study population and the norm population at baseline and after four months. Effect sizes were small. Children with cancer reported significantly less fatigue than the norm population at 12 months after baseline on the sleep-rest and cognitive fatigue subscales, and on the total fatigue scale. The effect sizes were moderate (0.51 to 0.63).

Parents reported significantly higher general and total PedsQL-MFS scores, indicating more fatigue in their children at baseline and after four months compared with the norm population. In addition, they reported more sleep-rest fatigue at baseline. However, most effect sizes were small. Moderate effect sizes were reported for general fatigue (baseline and four months) and total fatigue (baseline). Twelve months after diagnosis, PedsQL-MFS scores were not statistically different between childhood cancer patients and the norm population, and effect sizes were small.

3.3 | Adolescents 13–18 years

Self-reported PedsQL-MFS scores were significantly lower (i.e., more fatigue) compared with the norm population on all subscales at baseline and this remained for general fatigue at four months. Furthermore, at four months, more total cancer-related fatigue was reported compared with the norm population. Effect sizes were small to moderate (−0.66 to −0.29). Twelve months after baseline, there were no statistically significant differences in self-reported fatigue between the study population and the norm population, and effect sizes were small.

Parents reported more fatigue in their adolescents on all subscales compared with the norm at baseline, and effect sizes were moderate to strong (−1.02 to −0.58). After 4 and 12 months, parents reported significantly more cancer-related fatigue on all (sub)scales with the exception of cognitive fatigue. Effect sizes were small to moderate (−0.53 to −0.37).

3.4 | Physical activity

Results for physical activity are presented in Table 4. CPM significantly increased over time and was adjusted for age, sex, intervention group, and percentage of fat mass ($P = 0.04$). Minutes of sedentary behavior per day slightly decreased, and activity levels slightly increased during the one-year follow-up. However, except for the development in minutes of vigorous activity (adjusted for age, sex, and intervention group) ($P < 0.01$), changes in activity levels were not significant. Only a small subgroup of children (2.6%–14.8%) complied with the Dutch healthy exercise norm.

3.5 | Longitudinal development of the association between cancer-related fatigue and physical activity

Adjusted for age, sex, and intervention group, a statistically significant positive association between cancer-related fatigue and physical activity was found during the one-year follow-up, with the exception of parent reported cognitive cancer-related fatigue (Table 5). These results indicate that during the one-year period, more physically active children experience less cancer-related fatigue. The associations between self-reported cancer-related fatigue and physical activity were not influenced by diagnosis, type of treatment, time since diagnosis, percentage of body fat, or BMI *z*-score at baseline. The association between all parent reported cancer-related fatigue (sub)scales and physical activity over time was influenced by the percentage of body fat. Furthermore, the association between parent-reported cognitive cancer-related fatigue and physical activity over time was influenced by diagnosis and type of treatment. The associations

TABLE 2 PedsQL Multidimensional Fatigue Scale scores and comparison with the norm population

PedsQL Multidimensional Fatigue Scale	7–12 years Baseline	Follow-up 4 months	Follow-up 12 months	Healthy children[21]	13–18 years Baseline	Follow-up 4 months	Follow-up 12 months	Healthy children[21]
Self-report	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
General fatigue	80.14 (14.04)	84.17 (15.02)	86.04 (16.90)	82.40 (13.93)	**61.93 (22.57)**[b]	**69.60 (22.86)**[a]	76.75 (22.94)	76.72 (14.31)
Sleep-rest fatigue	77.04 (16.28)	78.00 (14.60)	**87.08 (10.63)**[b]	77.64 (15.52)	**66.33 (16.65)**[a]	67.49 (22.47)	73.25 (22.23)	71.88 (14.17)
Cognitive fatigue	81.75 (18.49)	80.58 (16.83)	**86.04 (20.34)**[a]	75.60 (19.46)	**65.99 (21.69)**[b]	72.06 (22.92)	75.93 (21.51)	77.15 (15.30)
Total fatigue	79.87 (13.74)	80.92 (11.80)	**86.39 (13.56)**[a]	78.58 (13.04)	64.75 (18.00)	**69.72 (19.32)**[a]	75.31 (20.09)	75.24 (11.95)
Parent report								
General fatigue	**65.32 (21.57)**[b]	**72.04 (20.22)**[b]	76.53 (17.59)	82.65 (13.36)	**48.73 (28.41)**[b]	**63.17 (27.44)**[b]	**65.41 (26.24)**[b]	77.71 (15.93)
Sleep-rest fatigue	**77.24 (19.37)**[b]	80.17 (18.45)	81.80 (16.40)	85.94 (12.92)	**60.37 (21.45)**[b]	**68.47 (25.40)**[b]	**70.97 (26.93)**[b]	80.87 (15.06)
Cognitive fatigue	75.15 (20.06)	73.17 (19.36)	76.97 (17.03)	75.78 (19.40)	**66.44 (24.19)**[b]	72.85 (23.44)	73.88 (24.20)	78.93 (17.99)
Total fatigue	**71.79 (16.80)**[b]	**75.11 (16.60)**[a]	78.43 (13.28)	81.45 (12.27)	58.14 (21.93)	**68.16 (23.15)**[b]	**69.64 (23.82)**[b]	79.17 (13.99)

[a] $P < 0.05$; [b] $P < 0.01$. P values for the difference between study population and norm population. Significant differences are shown in bold.

TABLE 3 Meaning and magnitude of the differences between the study population and the norm population: Cohen effect sizes

PedsQL Multidimensional Fatigue Scale	7–12 years Baseline	Follow-up 4 months	Follow-up 12 months	13–18 years Baseline	Follow-up 4 months	Follow-up 12 months
Self-report						
General fatigue	−0.18	0.10	0.20	**−0.66**	**−0.31**	0.00
Sleep-rest fatigue	−0.03	0.03	**0.63**	**−0.33**	−0.19	0.06
Cognitive fatigue	0.31	0.25	**0.51**	**−0.51**	−0.22	−0.06
Total fatigue	0.09	0.13	**0.57**	−0.58	**−0.29**	0.00
Parent report						
General fatigue	**−0.78**	**−0.51**	−0.33	**−1.02**	**−0.53**	**−0.47**
Sleep-rest fatigue	**−0.43**	−0.29	−0.22	**−0.96**	**−0.49**	**−0.37**
Cognitive fatigue	−0.14	−0.14	0.05	**−0.58**	−0.30	−0.14
Total fatigue	**−0.56**	**−0.37**	−0.21	−0.96	**−0.48**	**−0.40**

Note: Cohen effect sizes were calculated as follows: [(mean score population – mean score norm population) /largest standard deviation]. A negative effect size indicates more fatigue compared with norm population, and a positive effect size indicates less fatigue compared with norm population. Significant differences are shown in bold.

remained significant after adjustment for these factors in the final models.

4 | DISCUSSION

Cancer-related fatigue is a common complaint in pediatric patients, and physical activity may be a tool to address this complaint.[8] This longitudinal study describes cancer-related fatigue and its relation to physical activity over time in childhood cancer patients aged 7 to 18 years. Cancer-related fatigue was not a disturbing factor for most children; scores were somewhat lower or comparable with the norm. Over the year, both children/adolescents and their parents reported improved fatigue scores. Activity levels positively changed during the study period, albeit nonsignificantly for the most part probably due to the small sample size. Only 2.6% to 14.8% of the children complied with the Dutch healthy exercise norm, although this is not drastically lower than that for healthy Dutch children (15%–21%).[31] During the one-year follow-up, increased physical activity was associated with less general, sleep/rest, and total cancer-related fatigue, regardless of age, sex, intervention group, diagnosis, type of treatment, time since diagnosis, body fat percentage and BMI at baseline.

Reports on previous childhood cancer cohorts have also shown similar self-reported cancer-related fatigue in survivors compared with norms.[19,32,33] One explanation could be that data on childhood cancer survivors are compared with data on healthy pediatric populations, in which the prevalence of fatigue is also high. ter Wolbeek et al described a severe fatigue prevalence of 20.5% in a large population of Dutch adolescent females.[34] A second explanation could be the use of the PedsQL-MFS for assessing cancer-related fatigue. Although the PedsQL-MFS has acceptable psychometric properties, including content validity and internal consistency and responsiveness, there are inconsistent reports regarding known group validity in pediatric cancer.[35,36] This may hamper the correct identification of patients with important cancer-related fatigue. The somewhat conflicting results between the self-reports and the parent-proxies that were found in

TABLE 4 Physical activity outcomes at each measurement and development of physical activity over time (generalized estimating equations)

	Baseline[a]	Follow-up 4 months[a]	Follow-up 12 months[a]	Generalized estimating equations Crude model β (95% CI)[b]	P value	Adjusted model β (95% CI)	P value
Participants, N (%)	61 (90)	38 (64)	29 (55)	—	—	—	—
Counts per minute	161.92 (107.74)	157.06 (77.93)	199.14 (117.39)	17.59 (4.22– 30.97)	0.01	14.81 (0.53– 29.09)[c]	0.04
Minutes of sedentary behavior	851.34 (92.99)	863.27 (73.60)	831.18 (85.26)	−6.87 (19.58– 5.84)	0.29	−3.98 (−17.22– 9.26)[c]	0.56
Minutes of light activity	201.96 (76.89)	191.24 (64.76)	212.92 (78.10)	2.75 (−9.80– 15.30)	0.67	0.22 (−13.17– 13.60)[d]	0.98
Minutes of moderate activity	24.89 (23.70)	23.70 (17.11)	29.20 (25.11)	1.87 (−1.76– 5.50)	0.31	1.16 (−2.63– 4.95)[c]	0.55
Minutes of vigorous activity	1.84 (4.50)	2.08 (3.61)	4.52 (7.04)	1.36 (0.39– 2.34)	<0.01	—[e]	—
≥ 60 minutes moderate/vigorous active, N (%)	9 (14.8)	1 (2.6)	4 (13.8)	—	—	—	—

[a]Mean (standard deviation) unless otherwise specified.
[b]Adjusted for age, sex, intervention group.
[c]Adjusted for age, sex, intervention group, and body fat %.
[d]Adjusted for age, sex, intervention group, body fat %, BMI Z-score, time since diagnosis, treatment type, and diagnosis.
[e]None of the variables additionally modified the crude model.

TABLE 5 Longitudinal development of the relation between fatigue and physical activity

	Self-report Crude model β (95% CI)[a]	P value	Adjusted model β (95% CI)[b]	P value	Parent report Crude model β (95% CI)[a]	P value	Adjusted model β (95% CI)	P value
PedsQL Multidimensional Fatigue Scale								
General fatigue	0.09 (0.06–0.13)	<0.01	—	—	0.09 (0.05–0.14)	<0.01	0.07 (0.03– 0.12)[c]	<0.01
Sleep-rest fatigue	0.07 (0.03–0.12)	<0.01	—	—	0.07 (0.04–0.11)	<0.01	0.06 (0.03– 0.10)[c]	<0.01
Cognitive fatigue	0.07 (0.04–0.10)	<0.01	—	—	0.03 (−0.01–0.07)	0.11	0.01 (−0.03– 0.04)[d]	0.62
Total fatigue	0.08 (0.05–0.11)	<0.01	–	—	0.06 (0.03– 0.09)	<0.01	0.05 (0.02– 0.08)[c]	<0.01

[a]β adjusted for age, sex, intervention group.
[b]None of the variables additionally modified the crude model.
[c]β adjusted for age, sex, intervention group, body fat %.
[d]β adjusted for age, sex, intervention group, body fat %, type of treatment, diagnosis.

this study, is a phenomenon that is often encountered in pediatric psychosocial research.[37] There is often lower agreement on subjective outcomes, such as cancer-related fatigue, compared with more objective outcomes.[38] Parental worries may exaggerate their perception of child functioning and response shift may reflect the patients' adaptive style.[39,40] It is generally agreed that it is useful to gather information from the child as well as the parents, in order to evaluate cancer-related fatigue from all viewpoints.[38]

It is, however, important to notice that several studies have shown that despite the normal prevalence of fatigue in this population, there is a subgroup of childhood cancer survivors that experience (persistent) cancer-related fatigue and that these patients are at increased risk for adverse outcomes, such as depressive symptoms, anxiety, impaired quality of life, insomnia, and pain.[10,32,33] This subgroup could benefit from interventions that ameliorate cancer-related fatigue.

This study provides evidence that increased physical activity is longitudinally associated with lower cancer-related fatigue in childhood cancer patients. Considering the many other health benefits of an active lifestyle, promoting physical activity during and after treatment may benefit childhood cancer survivors in many ways. For example, higher levels of physical activity have been associated with an improvement in health-related quality of life and a lower mortality risk.[41,42]

To our knowledge, this is the first longitudinal association study of physical activity and fatigue in childhood cancer. This study, however, has some limitations. The study group is relatively small and heterogeneous (e.g., diagnosis, time since diagnosis, on or off treatment), which leads to less possibility for analyses of potential modifiers of the found association. Also, only 39% of the eligible patients participated in the study leading to questions regarding generalizability. As reported previously, the nonparticipants perceived their physical fitness higher compared with participants. However, cancer-related fatigue was not assessed in the nonparticipants. Therefore, participation bias based on levels of cancer-related fatigue could not completely be ruled out.[30] Furthermore, not all patients completed the physical activity follow-up assessments. Physical activity outcomes at baseline were not statistically different between patients who completed the 12-month follow-up assessment and patients who did not. However, patterns of physical activity development might still be different between both groups. Another limitation is that we did not take other causes of possible fatigue into our analyses such as sleep problems, depression, anxiety, and physical morbidities associated with fatigue and reduced physical activity. Finally, this was a post hoc analysis of the QLIM study in which no distinction was made between the intervention and the control group. Even though no significant effect of the combined physical exercise and psychosocial training program on physical fitness was found,[26,27] there may have been some beneficial effects of participating in the QLIM study on an individual level that may have influenced our results.

In conclusion, the prevalence of self-reported cancer-related fatigue of children and adolescents in the final stages of cancer treatment and the first period after the end of treatment is similar to fatigue levels in the general population. Parents, however, reported more cancer-related fatigue in children and adolescents. Increased physical activity is longitudinally associated with less cancer-related fatigue. Given the largely sedentary lifestyle of this population, the positive association of physical activity on cancer-related fatigue, and the many other health benefits of an active lifestyle, it is important to stimulate physical activity in childhood cancer survivors.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONFLICTS OF INTEREST

The authors have indicated no conflicts of interest related to this article.

ORCID

Raphaële R. L. Van Litsenburg
https://orcid.org/0000-0003-3441-5135

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