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

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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-proxy 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
1 | INTRODUCTION

Cancer-related fatigue is one of the most common and distressing side effects of childhood cancer treatment. Cancer-related fatigue is associated with other sequelae that occur in childhood cancer patients, such as depressive symptoms and impaired quality of life.

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.

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. 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. 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 physical activity levels were associated with lower levels of physical activity. 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. 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.

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.

Given that children with cancer are less physically active, 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. 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. It has often been used in childhood cancer patients. 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 ($O = 100, 1 = 75, 2 = 50, 3 = 25,$ 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 the child. The Dutch version has adequate psychometric properties (0.5 and 0.8 moderate, and 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).

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.

### 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. Data were collected with a 15-second epoch interval. 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. Physical activity was assessed 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. 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.

### 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. 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.

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.

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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. 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...
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 | 13–18 years Baseline | Follow-up 4 months | Follow-up 12 months | Healthy children |
|---------------------------------------|--------------------|--------------------|--------------------|-----------------|---------------------|--------------------|--------------------|-----------------|
| Self-report                           |                    |                    |                    |                 |                     |                    |                    |                 |
| General fatigue                       | 80.14 (14.04)      | 84.17 (15.02)      | 86.04 (16.90)      | 82.40 (13.93)   | 61.93 (22.57)      | 69.60 (22.86)      | 76.75 (22.94)      | 76.72 (14.31)   |
| Sleep-rest fatigue                    | 77.04 (16.28)      | 78.00 (14.60)      | 87.08 (10.63)      | 77.64 (15.52)   | 66.33 (16.65)      | 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)      | 75.60 (19.46)   | 65.99 (21.69)      | 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)      | 78.58 (13.04)   | 64.75 (18.00)      | 69.72 (19.32)      | 75.31 (20.09)      | 75.24 (11.95)   |
| Parent report                         |                    |                    |                    |                 |                     |                    |                    |                 |
| General fatigue                       | 65.32 (21.57)      | 72.04 (20.22)      | 76.53 (17.59)      | 82.65 (13.36)   | 48.73 (28.41)      | 63.17 (27.44)      | 65.41 (26.24)      | 77.71 (15.93)   |
| Sleep-rest fatigue                    | 77.24 (19.37)      | 80.17 (18.45)      | 81.80 (16.40)      | 85.94 (12.92)   | 60.37 (21.45)      | 68.47 (25.40)      | 70.97 (26.93)      | 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)      | 72.85 (23.44)      | 73.88 (24.20)      | 78.93 (17.99)   |
| Total fatigue                         | 71.79 (16.80)      | 75.11 (16.60)      | 78.43 (13.28)      | 81.45 (12.27)   | 58.14 (21.93)      | 68.16 (23.15)      | 69.64 (23.82)      | 79.17 (13.99)   |

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.

aP < 0.05; bP < 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.

4 | DISCUSSION

Cancer-related fatigue is a common complaint in pediatric patients, and physical activity may be a tool to address this complaint. 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%). 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. 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. 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. This may hamper the correct identification of patients with important cancer-related fatigue. The somewhat conflicting results between the self-reports and the parent-proxy scores that were found in...
this study, is a phenomenon that is often encountered in pediatric psychosocial research. There is often lower agreement on subjective outcomes, such as cancer-related fatigue, compared with more objective outcomes. Parental worries may exaggerate their perception of child functioning and response shift may reflect the patients’ adaptive style. 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.

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. 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.

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.

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

| Table 4 | Participants, N (%) | Follow-up 4 months | Follow-up 12 months | Generalized estimating equations |
|---------|----------------------|-------------------|-------------------|---------------------------------|
|         | Baseline               |                   |                   | Crude model $\beta$ (95% CI) |
| P value | Adjusted model $\beta$ (95% CI) | P value | Parent report Crude model $\beta$ (95% CI) |
| P value | Adjusted model $\beta$ (95% CI) | P value | Adjusted model $\beta$ (95% CI) |
|         | Mean (standard deviation) unless otherwise specified. | Adjusted for age, sex, intervention group. | Adjusted for age, sex, intervention group, body fat %. | Adjusted for age, sex, intervention group, body fat %, BMI Z-score, time since diagnosis, treatment type, and diagnosis. | None of the variables additionally modified the crude model. |

| Minutes of sedentary behavior | 851.34 (92.99) | 863.27 (73.60) | 831.18 (85.26) | $-6.87 (19.58 - 5.84)$ | 0.29 | $-3.98 (-17.22 - 9.26)$ | 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 | $0.22 (-13.17 - 13.60)$ | 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 | $1.16 (-2.63 - 4.95)$ | 0.55 |
| Minutes of vigorous activity | 1.84 (4.50) | 2.08 (3.61) | 4.52 (7.04) | $1.36 (0.39 - 2.34)$ | $<0.01$ | $<0.01$ | $<0.01$ |
| $\geq$ 60 minutes moderate/vigorous active, N (%) | 9 (14.8) | 1 (2.6) | 4 (13.8) | $<0.01$ | $<0.01$ | $<0.01$ | $<0.01$ |

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

| Table 5 | Self-report Crude model $\beta$ (95% CI) | P value | Adjusted model $\beta$ (95% CI) | P value | Parent report Crude model $\beta$ (95% CI) | P value | Adjusted model $\beta$ (95% CI) | P value |
|---------|-----------------|--------|-----------------|--------|-----------------|--------|-----------------|--------|
| PedsQL Multidimensional Fatigue Scale | | | | | | | | |
| General fatigue | 0.09 (0.06 - 0.13) | $<0.01$ | $<0.01$ | 0.09 (0.05 - 0.14) | $<0.01$ | 0.07 (0.03 - 0.12) | $<0.01$ |
| Sleep-rest fatigue | 0.07 (0.03 - 0.12) | $<0.01$ | $<0.01$ | 0.07 (0.04 - 0.11) | $<0.01$ | 0.06 (0.03 - 0.10) | $<0.01$ |
| Cognitive fatigue | 0.07 (0.04 - 0.10) | $<0.01$ | $<0.01$ | 0.03 (-0.01 - 0.07) | 0.11 | 0.01 (-0.03 - 0.04) | 0.62 |
| Total fatigue | 0.08 (0.05 - 0.11) | $<0.01$ | $<0.01$ | 0.06 (0.03 - 0.09) | $<0.01$ | 0.05 (0.02 - 0.08) | $<0.01$ |

This study provides evidence that increased physical activity is longitudinally associated with lower cancer-related fatigue in this subgroup of childhood cancer survivors that experience persistent fatigue. 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.

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.

This study is, a phenomenon that is often encountered in pediatric psychosocial research. There is often lower agreement on subjective outcomes, such as cancer-related fatigue, compared with more objective outcomes. Parental worries may exaggerate their perception of child functioning and response shift may reflect the patients’ adaptive style. 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.
ruled out. 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, 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.

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REFERENCES

1. Daniel LC, Brumley LD, Schwartz LA. Fatigue in adolescents with cancer compared to healthy adolescents. Pediatr Blood Cancer. 2013;60:1902-1907.

2. Tomlinson D, Zupanec S, Jones H, O’Sullivan C, Hesser T, Sung L. The lived experience of fatigue in children and adolescents with cancer: a systematic review. Support Care Cancer. 2016;24:3623-3631.

3. Hinds P, Hockenberry-Eaton M, Quargenti A, et al. Fatigue in 7- to 12-year-old patients with cancer from the staff perspective: an exploratory study. Oncol Nurs Forum. 1999;26:37-45.

4. Meeske KA, Siegel SE, Globe DR, Mack WJ, Bernstein L. Prevalence and correlates of fatigue in long-term survivors of childhood leukemia. J Clin Oncol. 2005;23:5510-5515.

5. Mulrooney D, Ness K, Neglia J, et al. Fatigue and sleep disturbance in adult survivors of childhood cancer: a report from the childhood cancer survivor study (CCSS). Sleep. 2008;31:271-281.

6. Ho KY, Li WHC, Lam KKW, et al. Relationships among fatigue, physical activity, depressive symptoms, and quality of life in Chinese children and adolescents surviving cancer. Eur J Oncol Nurs. 2019;38:21-27.

7. Barsevick AM, Irwin MR, Hinds P, et al. Recommendations for high-priority research on cancer-related fatigue in children and adults. J Natl Cancer Inst. 2013;105:1432-1440.

8. Tomlinson D, Diorio C, Beyene J, Sung L. Effect of exercise on cancer-related fatigue. Am J Phys Med Rehabil. 2014;93:675-686.

9. Hinds PS, Hockenberry M, Rai SN, et al. Clinical field testing of an enhanced-activity intervention in hospitalized children with cancer. J Pain Symptom Manag. 2007;33:686-697.

10. Zeller B, Loge JH, Kanellopoulos A, Hamre H, Wyller VB, Ruud E. Chronic fatigue in long-term survivors of childhood lymphomas and leukemia: persistence and associated clinical factors. J Pediatr Hematol Oncol. 2014;36:438-444.

11. Hooke MC, Gilchrist L, Tanner L, Hart N, Withycombe JS. Use of a fitness tracker to promote physical activity in children with acute lymphoblastic leukemia. Pediatr Blood Cancer. 2016;63:684-689.

12. Li WHC, Ho KY, Lam KKW, et al. Adventure-based training to promote physical activity and reduce fatigue among childhood cancer survivors: a randomized controlled trial. Int J Nurs Stud. 2018;83:65-74.

13. Winter C, Muller C, Brandes M, et al. Level of activity in children undergoing cancer treatment. Pediatr Blood Cancer. 2009;53:438-443.

14. Winter C, Muller C, Hoffmann C, Boos J, Rosenbaum D. Physical activity and childhood cancer. Pediatr Blood Cancer. 2010;54:501-510.

15. Braam K, Dijk-Lokkart E, Kaspers G, et al. Cardiorespiratory fitness and physical activity in children with cancer. Support Care Cancer. 2016;24:2259-2268.

16. Fisher RS, Rausch JR, Ferrante AC, et al. Trajectories of health behaviors across early childhood cancer survivorship. Psychooncology. 2019;28:68-75.

17. Braam KI, van Dijk EM, Veening MA, et al. Design of the Quality of Life in Motion (QLIM) study: a randomized controlled trial to evaluate the effectiveness and cost-effectiveness of a combined physical exercise and psychosocial training program to improve physical fitness in children with cancer. BMC Cancer. 2010;10:624.

18. Varni JW, Burwinkle TM, Katz ER, Meeske K, Dickinson P. The PedsQL in pediatric cancer: reliability and validity of the pediatric quality of life inventory generic core scales, multidimensional fatigue scale, and cancer module. Cancer. 2002;94:2090-2106.

19. Gordijn MS, van Litsenburg RR, Gemke RJ, et al. Sleep, fatigue, depression, and quality of life in survivors of childhood acute lymphoblastic leukemia. Pediatr Blood Cancer. 2013;60:479-485.

20. Mört S, Lähteenmäki PM, Matomäki J, Salmi TT SS. Fatigue in young survivors of extracranial childhood cancer: a Finnish nationwide survey. Oncol Nurs Forum. 2011;38:445-454.

21. Gordijn MS, Suzanne Gordijn M, Cremers EMP, Kaspers GJL, Gemke RJBJ. Fatigue in children: reliability and validity of the Dutch PedsQL Multidimensional Fatigue Scale. Qual Life Res. 2011;20:1103-1108.
23. Janssen X, Cliff D, Reilly J, et al. Evaluation of Actical equations and thresholds to predict physical activity intensity in young children. J Sport Sci. 2015;33:498-506.
24. Puyau MR, Adolph AL, Vohra FA, Butte NF. Validation and calibration of physical activity monitors in children. Obes Res. 2002;10:150-157.
25. Health Council of the Netherlands. Physical activity guidelines 2017. The Hague: Health Council of the Netherlands, 2017; publication no. 2017/08e.
26. van Dijk-Lokkart EM, Braam KI, van Dulmen-den Broeder E, et al. Effects of a combined physical and psychosocial intervention program for childhood cancer patients on quality of life and psychosocial functioning: results of the QLIM randomized clinical trial. Psychooncology. 2015;24:815-822.
27. Braam KI, van Dijk-Lokkart EM, van Dongen JM, et al. Cost-effectiveness of a combined physical exercise and psychosocial training intervention for children with cancer: results from the quality of life in motion study. Eur J Cancer Care (Engl). 2017;26.
28. Braam KI, van Dijk-Lokkart EM, Kaspers GJL, et al. Effects of a combined physical and psychosocial training for children with cancer: a randomized controlled trial. BMC Cancer. 2018;18:1289.
29. Cohen J. Statistical Power Analysis for Behavioral Sciences. New York: Academic Press; 1977.
30. van Dijk-Lokkart EM, Braam KI, Huisman J, et al. Factors influencing childhood cancer patients to participate in a combined physical and psychosocial intervention program: quality of life in motion. Psychooncology. 2015;24:465-471.
31. Netherlands Organisation for applied scientific research. Trendrapport Bewegen en Gezondheid 2000/2014. 2015.
32. Mort S, Lahteenmaki PM, Matomaki J, Salmi TT, Salantera S. Fatigue in young survivors of extracranial childhood cancer: a Finnish nationwide survey. Oncol Nurs Forum. 2011;38:E445-54.
33. Meeske KA, SE Siegel, Globe DR, Mack WJ, Bernstein L. Prevalence and correlates of fatigue in long-term survivors of childhood leukemia. J Clin Oncol. 2005;23:5501-5510.
34. ter Wolbeek M, Van Doornen LJP, Kavelaars A, Heijnen CJ. Severe fatigue in adolescents: a common phenomenon? Pediatrics. 2006;117:e1078-1086.
35. Tomlinson D, Hindes PS, Ether M-C, Ness KK, Zupanec S, Sung L. Psychometric properties of instruments used to measure fatigue in children and adolescents with cancer: a systematic review. J Pain Symptom Manage. 2012;45:83-91.
36. Crichton A, Knight S, Oakley E, Babi FE, Anderson V. Fatigue in child chronic health conditions: a systematic review of assessment instruments. Pediatrics. 2015;135:e1015-e1031.
37. Fakhry H, Goldenberg M, Sayer G, et al. Health-related quality of life in childhood cancer. J Dev Behav Pediatr. 2013;34:419-440.
38. Eiser C, Morse R. Can parents rate their child’s health related quality of life? Results of a systematic review. Qual Life Res. 2001;10:347-357.
39. Eiser C, Eiser JR, Stride CB. Quality of life in children newly diagnosed with cancer and their mothers. Health Qual Life Outcomes. 2005;3:29.
40. Visser MRM, Smets EMA, Sprangers MAG, De Haes HJCJM. How response shift may affect the measurement of change in fatigue. J Pain Symptom Manage. 2000;20:12-18.
41. Zhang FF, Hudson MM, Huang I-C, et al. Lifestyle factors and health-related quality of life in adult survivors of childhood cancer: a report from the St. Jude Lifetime Cohort Study Cancer. 2018;124:3918-3923.
42. Scott JM, Li N, Liu Q, et al. Association of exercise with mortality in adult survivors of childhood cancer. JAMA Oncol. 2018;4:1352-1358.

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