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# The Moderated Mediating Effects of Nutrition and Physical Activity Between Fatigue and Quality of Life in Childhood Cancer Survivors

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ABSTRACT

*Purpose:* The aim of this study was to investigate the associations between nutrition, physical activity, fatigue, and quality of life (QoL) among childhood cancer survivors. The specific purpose was to examine whether nutrition mediated and physical activity moderated the relationship between fatigue and QoL in this population.

*Methods:* A pooled sample of 120 childhood cancer survivors was recruited at pediatric oncology wards and ambulatory settings between August 2020 and May 2021. We collected data on participants' demographic characteristics, fatigue, nutritional status, physical activity, and QoL. We then adapted Hayes Process Macro to examine the mediating and moderating effects of nutrition and physical activity on the relationship between fatigue and QoL.

*Results:* In models adjusted for age and sex, (1) the simple mediation analysis identified the mediating effect of nutrition on the relationship between fatigue and QoL; and (2) the mediation and moderation analysis identified that the direct effect of nutrition between fatigue and QoL was significant when adding (a) physical activity and (b) fatigue × physical activity. There were significantly decreasing trends in physical activity at 1 standard deviation below the mean and at the mean, but not at 1 standard deviation above the mean.

*Conclusions:* Our findings demonstrate that nutrition mediated and physical activity moderated the relationship between fatigue and QoL. This highlights an opportunity to enhance QoL among childhood cancer survivors through healthy lifestyle interventions. To ensure that future interventions address children's needs and promote the greatest impact, such interventions should include nutrition and physical activity components that involve nurses, pediatric oncology physicians, nutritionists, and physical therapists.



## Introduction

For children aged 1 through 14 years in high-income countries such as Taiwan and the United States, cancer is the second leading cause of death [1,2]. Due to advances in cancer treatment, the 5-year survival rate has dramatically improved over the past 60 years, from less than 25% to more than 80% [3]. The term "childhood cancer survivors" indicates people who were first diagnosed with cancer under the age of 18. A children diagnosed with cancer is considered to be a childhood cancer survivor from the time of diagnosis until the end of life [4]. However, despite treatment advances, childhood cancer survivors continue to experience short- and long-term adverse effects [5]. This has turned research attention from "how to survive" to "how to live with cancer well."

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For childhood cancer survivors, cancer-related fatigue (CRF) is one of the most distressing adverse effects [6]. CRF is both more severe than fatigue in healthy people and less likely to be relieved by sleep or rest [7]. While CRF typically improves after treatment is completed, it continues to affect long-term survivors [6]. Persistent CRF not only negatively correlates with nutritional status [8,9] and physical activity [10], it also negatively interferes with quality of life (QoL) [11]. These findings support that fatigue causes these declines, but these associations have not been examined by a single study. Because CRF negatively correlates with nutritional status [8,9] in childhood cancer survivors, and nutritional status positively affects QoL [12,13], we hypothesize that nutrition mediates the relationship between CRF and QoL. In addition, we hypothesize that physical activity moderates the relationship between CRF and QoL, given that physical activity significantly reduces CRF in childhood cancer survivors [14] and significantly enhances QoL in healthy children [15], while fatigue also significantly affects QoL in childhood cancer survivors [11].

Systemic inflammation may be one explanation for these associations. Both CRF [16] and malnutrition [17] are known to activate pro-inflammatory cytokines. This results in systemic inflammation, which creates a catabolic situation and leads to worse QoL in people with cancer [18,19]. Physical activity plays a significant role in reducing the inflammatory protein at sites of inflammation [20]. Thus, proper nutrition and physical activity may have the potential to inhibit the systemic inflammation reaction [21–23].

Evidence has shown that a healthy lifestyle, consisting of proper nutrition and physical activity, improves the relationship between fatigue and QoL [24,25]. However, research into optimizing childhood cancer survivors' QoL through healthy lifestyle has been limited. The prior research evaluating QoL in association with lifestyle factors has focused primarily on physical activity [24]. Research studies that integrate nutrition, within a single study, to examine the associations between nutrition, physical activity, fatigue, and QoL for childhood cancer survivors are extremely limited. In view of the potential manageability of nutrition and physical activity behaviors, such a study could be important to facilitating timely development of healthy lifestyle interventions for this population.

### *Aim*

The aim of this study was to investigate the associations between nutrition, physical activity, fatigue, and QoL among childhood cancer survivors. Specifically, our purpose was to examine whether (a) nutrition mediated and (b) physical activity moderated the relationship between fatigue and QoL for childhood cancer survivors.

## Methods

### *Design, setting, and sample*

This correlational study was conducted in accordance with the STROBE guidelines. A pooled sample of 120 childhood cancer survivors were recruited at pediatric oncology wards and ambulatory settings in a university-based hospital in Taiwan that is well-known for pediatric oncology care. Participants were recruited between August 2020 and May 2021, using the following inclusion criteria: (1) age between 3 and 18 years; (2) inpatient receiving active treatment in pediatric oncology/hematology wards, outpatient receiving active treatment in ambulatory settings, or survivor (having completed cancer treatment) now receiving care in ambulatory settings; and (3) ability to understand the study information. We used G-Power version 3.1.9 (Franz Faul, Universität Kiel, Germany) to compute sample size a priori. Although a generally accepted power is .80 [26], higher power is more desirable if it is practically feasible [27]. A minimum of 108 participants would be needed to reach a sufficient power (90.0%), alpha error (.05), and effect size (0.15).

### *Ethical considerations*

This study was approved by the institutional review board of the National Taiwan University Hospital (Approval no. 202001RINA). Upon agreeing to participate, the child participants provided informed assent and their parents provided informed consent. Once the formal consents were received from the participants and their parents (guardians), all of the measures would be collected. All participants were also informed they had the right to withdraw from the study at any time for any reason.

### *Procedure*

A research assistant approached participants who met the inclusion criteria, along with their parents (guardians), and explained the research aims and procedures. Those who agreed to participate were given a set of questionnaires that included a demographic survey, the Pediatric Quality of Life Inventory Multidimensional Fatigue scale (PedsQL-MFS), the Exercise Involvement Scale, and the Pediatric Quality of Life Inventory 3.0 Cancer Module (PedsQL-C). Both a parent and a research assistant were present when children answered the study questionnaires in case assistance was needed. After completing questionnaires, they were brought to the examination room for evaluating the nutritional status (phase angle) measured by a bioelectrical impedance analysis (BIA) device (InbodyS10, Biospace Co., Seoul, Korea).

### *Measures*

***Demographics.*** Survey items collected demographic data on participants' age, sex, cancer diagnosis, treatment status, years in current treatment status, and body mass index (BMI). The survey also collected data on the child's, father's, and mother's education level.

***Fatigue.*** We used the Mandarin version of the PedsQL-MFS to measure fatigue. This scale was developed to assess fatigue among children with cancer aged 2 to 18 years [28]. It is an 18-item 5-point Likert scale from 0 (never) to 4 (almost always). There are three dimensions: general fatigue (6 items), sleep/rest fatigue (6 items), and cognitive fatigue (6 items). In this study, children 7 years and younger used the proxy-reported versions of the scale for their age group (2–4 years and 5–7 years), and those aged 8 to 18 years used the self-report version. Total scores were transformed on a scale from 0 to 100. Based on the PedsQL-MFS manual, higher scores indicate less fatigue, but we reversed the direction so that higher scores indicated greater fatigue, which seemed more intuitive. Studies have demonstrated the PedsQL-MFS's excellent reliability and validity among children with cancer [28–31]. The Cronbach $\alpha$s in the current study were between .72 and .93 across the three age groups.

***Nutritional status.*** BIA is a method for acquiring body composition parameters (e.g., phase angle, body fat, muscle mass) that has the advantages of being noninvasive, safe, easy to use, and offering immediate results [32]. Phase angle represents cellular integrity, inflammation, nutritional status, and immune status [33] and has been recommended as a prognostic tool for nutritional screening of children [34–36]. To complete the phase angle measures with the InbodyS10 device, participants had to fast for at least 2 hours, empty their bladder, measure their height and body weight with



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minimal clothing, and rest for at least 10 minutes before the BIA measurement. During measurement, eight electrodes were attached to hands and feet (this process took around 2 minutes).

Phase angle values have a pattern that holds regardless of gender: values increase progressively from the first years of life until 18 years of age, stabilize from age 19 until 48 years of age, and then decrease progressively thereafter [37]. The phase angle reference values for boys are 5.60° for 3- to 5-year-olds, 6.00° for 6- to 12-year-olds, 6.40° for 13- to 15-year-olds, and 7.30° for 16- to 18-year-olds. Reference values for girls are 5.40° for 3- to 5-year-olds, 5.90° for 6- to 12-year-olds, 6.30° for 13- to 15-year-olds, and 6.40° for 16-to 18-year-olds [37]. Higher scores within the relevant age strata indicate better nutritional status [36]. We set a cutoff point for poor nutritional status at less than 4.00°, which is the same cutoff used for adults with cancer [38].

***Physical activity.*** We used a three-item Exercise Involvement Scale to evaluate participants' degree of physical activity in the prior week [39]. The item regarding exercise frequency ("During the last week, how many times did you engage in exercise?") has six graded response options ranging from 1 (zero) to 6 (5 or more times a week); higher scores indicate more frequent exercise. The item regarding exercise intensity ("During the past week, how much effort did you put into exercising each time?") also has six graded responses: 1 (extremely easy), 2 (very easy), 3 (easy), 4 (a little hard), 5 (very hard), and 6 (extremely hard); higher scores indicate greater amount of effort invested in exercise. The item regarding exercise duration ("During the past week, how much time did you spend exercising per time?") again has six graded responses, starting at 1 (0–10 minutes) and increasing in 10-minute intervals to 6 (51–60 minutes); higher scores indicate longer average duration. The equation is as follows: exercise involvement = exercise frequency × (exercise intensity + exercise duration). Again, higher scores indicate higher levels of physical activity.

***Quality of life.*** QoL was measured using the Mandarin version of the PedsQL-C. This scale was developed to assess the QoL of children with cancer aged 2 to 18 years [40]. There are eight dimensions: pain and hurt, nausea, procedural anxiety, treatment anxiety, worry, cognitive problems, perceived physical appearance, and communication. Scale items use a 5-point Likert scale from 0 (never) to 4 (almost always). PedsQL-C has 25 items for children aged 2 to 4 years, 26 items for those aged 5 to 7 years, and 27 items for those aged 8 to 18 years. Total scores were transformed on a scale from 0 to 100, with higher scores indicating better QoL. Studies have demonstrated the PedsQL-C's excellent reliability and validity among children with cancer [11]. The Cronbach αs in the current study were between .75 and .91 across the three age groups.

### *Statistical analysis*

All statistical analyses were performed using SPSS 20.0 (SPSS Inc., Chicago, IL). We used frequency and percentage to analyze participants' categorical demographic characteristics; we used mean and standard deviation to characterize the interval/ratio demographic characteristics and main variables. Pearson correlation analysis was used to examine the bivariate correlations between fatigue, nutrition, physical activity, and QoL.

Hayes Process Macro with SPSS was used for the analysis [41]. First, to identify the simple mediation, we examined whether nutrition mediated the relationship between fatigue and QoL [41]. Once the simple mediation was identified, we identified the mediation and moderation in Model 5 by examining whether both nutrition mediated and physical activity moderated the relationship between fatigue and QoL [41]. Because previous studies have pointed out gender and age differences in phase angle [37,42], we controlled for covariates (age and sex) in all model analyses. Finally, we plotted the conditional effects of physical activity at low (1 standard deviation below the mean value of physical activity), moderate (mean value of physical activity), and high (1 standard deviation above the mean value of physical activity) levels.

## Results

### *Descriptive analysis*

Of the 124 participants who agreed to participate and completed all measures, 4 were excluded due to poor-quality BIA measurements. This resulted in 120 included participants (96.8%; 77 boys and 43 girls). The descriptive analyses of participants' age, sex, diagnosis, BMI status, and child's, father's, and mother's education levels are summarized in Table 1.

The mean (*SD*) scores in fatigue, nutrition, physical activity, and QoL were 22.48 (15.51), 4.32 (0.75), 28.65 (13.75), and 79.14 (14.29), respectively (see Table 2). We calculated the percentage of participants with a phase angle less than 4.00° to obtain a 38.3% prevalence of poor nutrition.

### *Bivariate analysis*

Each pair among the four variables was significantly correlated (*r* range, −.60 to .38), except for the pair of nutrition with physical activity ($r = .16$; see Table 2). This indicated that although the two modifiable factors (nutrition and physical activity) were not

**Table 1** *Demographic Characteristics of Participants.*

| Variables | *Mean (SD) or n (%)* | |
|---|---|---|
| **Age** | 8.01 | (3.93) |
| **Sex** | | |
| Male | 77 | (64.2) |
| Female | 43 | (35.8) |
| **Diagnosis** | | |
| ALL | 65 | (54.2) |
| AML | 11 | (9.2) |
| NHL | 7 | (5.8) |
| HL | 4 | (3.3) |
| Neuroblastoma | 12 | (10.0) |
| Brain tumor | 4 | (3.3) |
| Others[a] | 17 | (14.2) |
| **BMI status** | | |
| Underweight | 13 | (10.8) |
| Healthy weight | 69 | (57.5) |
| Overweight or obesity | 38 | (31.7) |
| **Child's education** | | |
| Below elementary | 42 | (35.0) |
| Elementary | 57 | (47.5) |
| Junior high | 12 | (10.0) |
| Senior high or above | 9 | (7.5) |
| **Father's education** | | |
| Junior high | 7 | (5.8) |
| Senior high | 31 | (25.8) |
| Associate or bachelor's degree | 59 | (49.2) |
| Master's degree or PhD | 22 | (18.3) |
| Missing | 1 | (0.8) |
| **Mother's education** | | |
| Junior high | 6 | (5.00) |
| Senior high | 26 | (21.7) |
| Associate or bachelor's degree | 66 | (55.0) |
| Master's degree or PhD | 20 | (16.7) |
| Missing | 2 | (1.7) |

*Note*. [a]Others included bladder cancer, hepatoblastoma, kidney cancer, and retinoblastoma; ALL = acute lymphocytic leukemia; AML = acute myeloid leukemia; BMI = body mass index; NHL = non-Hodgkin's lymphoma; HL = Hodgkin's lymphoma; SD = standard deviation.



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**Table 2** *Variable Descriptions and Pearson Correlations.*

| Variables | Range | Mean | *SD* | Fatigue | Nutrition | Physical activity | QoL |
|---|---|---|---|---|---|---|---|
| 1. Fatigue | 0.00-69.44 | 22.48 | (15.51) | $r = 1.00$ | $r = -.19$* | $r = -.34$** | $r = -.60$** |
| 2. Nutrition | 2.60-6.50 | 4.32 | (0.75) | | $r = 1.00$ | $r = .16$ | $r = .29$** |
| 3. Physical activity | 2.00-60.00 | 28.65 | (13.75) | | | $r = 1.00$ | $r = .38$** |
| 4. QoL | 37.96-100.00 | 79.14 | (14.29) | | | | $r = 1.00$ |

*Note.* QoL = quality of life; SD = standard deviation.
*$p < .05$, **$p < .01$.

correlated with each other, each was individually correlated with both fatigue and QoL.

*Simple mediation analysis*

After adjusting for age and sex, simple mediation analysis found both a significant total effect (β = −.55, 95% confidence interval [CI] −.69 to −.42) and a significant direct effect (β = −.52, 95% CI −.66 to −.39) of nutrition on the relationship between fatigue and QoL. We further examined the indirect effect and found that the 95% CI (−.08 to −.00) did not include zero. This indicated that after adjusting for age and sex, nutrition partially mediated the adverse effect of fatigue on QoL (see Figure 1).

*Mediation and moderation analysis (Model 5)*

In the mediation and moderation analysis, after adjusting for age and sex, the direct effect of nutrition on the relationship between fatigue and QoL was significant (β = −.39, 95% CI −.55 to −.24) when adding physical activity (β = .21, 95% CI .05 to .37) and fatigue × physical activity (β = .01, 95% CI .00 to .02). This indicates that all paths in Model 5 were significant ($p < .050$) and that suggests that physical activity qualified as a moderator between fatigue and QoL when controlling for nutrition (see Figure 2).

*Conditional moderating effect on the direct effect of fatigue on QoL*

Figure 3 demonstrates how the conditional moderating effect of physical activity affected the relationship between fatigue and QoL after controlling for nutrition. There were significantly decreasing trends in the coefficients of conditions of physical activity at 1 standard deviation below the mean (low physical activity) (β = −.56, 95% CI −.72 to −.40) and at the mean (moderate physical activity) (β = −.39, 95% CI −.55 to −.24). There was no significantly decreasing trend in condition of physical activity at 1 standard deviation above the mean (high physical activity) (β = −.23, 95% CI −.47 to .01). These results indicate that fatigue was negatively and significantly correlated with QoL among children with low and moderate levels of physical activity.

## Discussion

Our study identified the associations between nutrition, physical activity, fatigue, and QoL among childhood cancer survivors. Responding to the specific purpose, our finding identified the mediating role of nutrition between fatigue and QoL, which indicates that enhancing children's nutrition could reduce the adverse effect of fatigue on QoL. This is supported by prior studies [13,43].

When we compare the mean phase angle of our study sample with the estimated reference values for healthy children's phase angles in Germany [37], it appears likely that our participants had worse nutritional status. In addition, our use of the cutoff point for poor nutritional status in adults with cancer [38] resulted in more than one-third of study participants categorized as in poor nutritional status. This is a high proportion of malnutrition among children with cancer and is similar to prior findings [44]. Altogether, these findings highlight the importance of routinely assessing nutritional status for childhood cancer survivors. The goal would be to detect malnutrition early and thus provide timely nutrition interventions to prevent poor nutrition hindering their growth and development [45].

However, there is currently no standardized nutrition assessment in clinical practice for children with cancer [46]. Using a BIA device to acquire phase angle would be a good start. There may be differences in phase angle between populations, and population-specific reference values may be required [42]. As of now, though, published reference values of phase angle for children are lacking. Establishing reference values for healthy children in Taiwan or in other countries with similar ethnic and cultural backgrounds is needed. These reference values can then serve as a basis for phase angle evaluations in the clinical setting to identify childhood cancer survivors—or children with other diseases—whose nutritional status should be closely watched.

Responding to the specific purpose, our finding identified the moderating role of physical activity between fatigue and QoL. This indicates that physical activity may be the variable that affects the strength of the relation between fatigue and QoL. We found that fatigue has an adverse effect on QoL among children who engaged in low and moderate levels of physical activity. In contrast, fatigue had no adverse effect on QoL among those who engaged in a high level of physical activity. These findings indicated that physical activity might protect childhood cancer survivors from the adverse effect of fatigue and lead to a good and stable QoL. This inference is supported by prior findings that physical activity has a positive effect on QoL in childhood cancer survivors [24,47]. However, an opposite finding was reported by a systematic review and meta-analysis: that physical activity did not moderate QoL [48]. That finding could be associated with participants not following the instructions of physical activity programs due to lack of time, motivation, exercise skills, exercise partners, poor health status, or reluctance to sweat [49,50]. For example, Kim's study found that only 5.0% of participating childhood cancer survivors met physical activity guidelines [49]; Sims's study reported that average increases in participants' activity levels post-intervention only reached 4.47 minutes per day [50]; and Wu's study indicated that children undergoing cancer treatment do not achieve the recommended level of physical activity suggested by the Children's Oncology Group [51,52]. In addition, children entering adulthood are known to follow a natural behavioral pattern of gradually becoming more physically inactive [53]. We conclude that childhood cancer survivors need additional assistance to be physically active.

Evidence indicates that among children undergoing cancer treatment in hospitals, personalized physical activity programs are associated with better QoL, in both physical and psychological dimensions [47]. A similar finding in adult cancer survivors indicates that supervised physical activity has significantly greater effects on QoL than unsupervised activity [54]. Based on these findings, we infer that personalized and supervised physical activity programs



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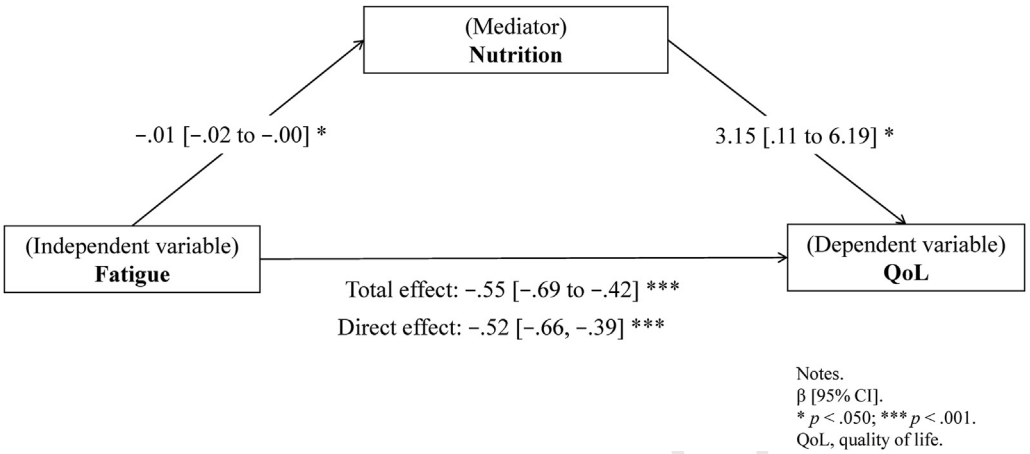


*Figure 1.* Simple mediation analysis after controlling for the covariates of sex and age.

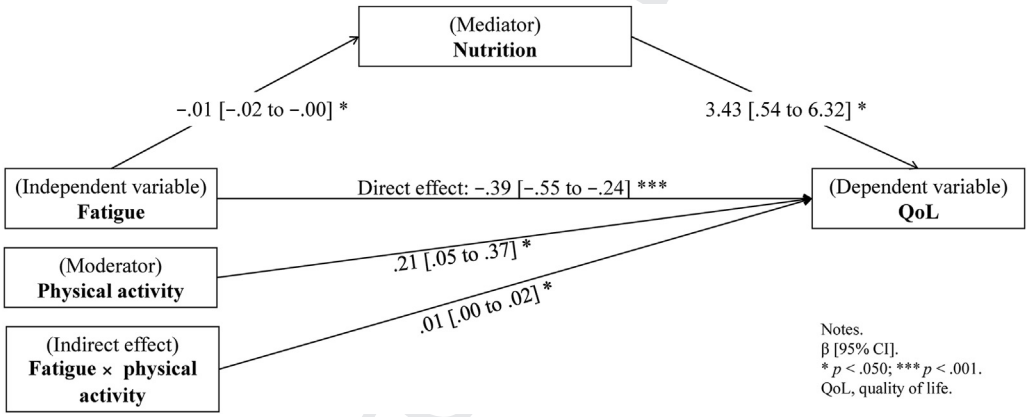


*Figure 2.* Mediation and moderation analysis for conditional direct effect after controlling for the covariates of sex and age (Model 5).

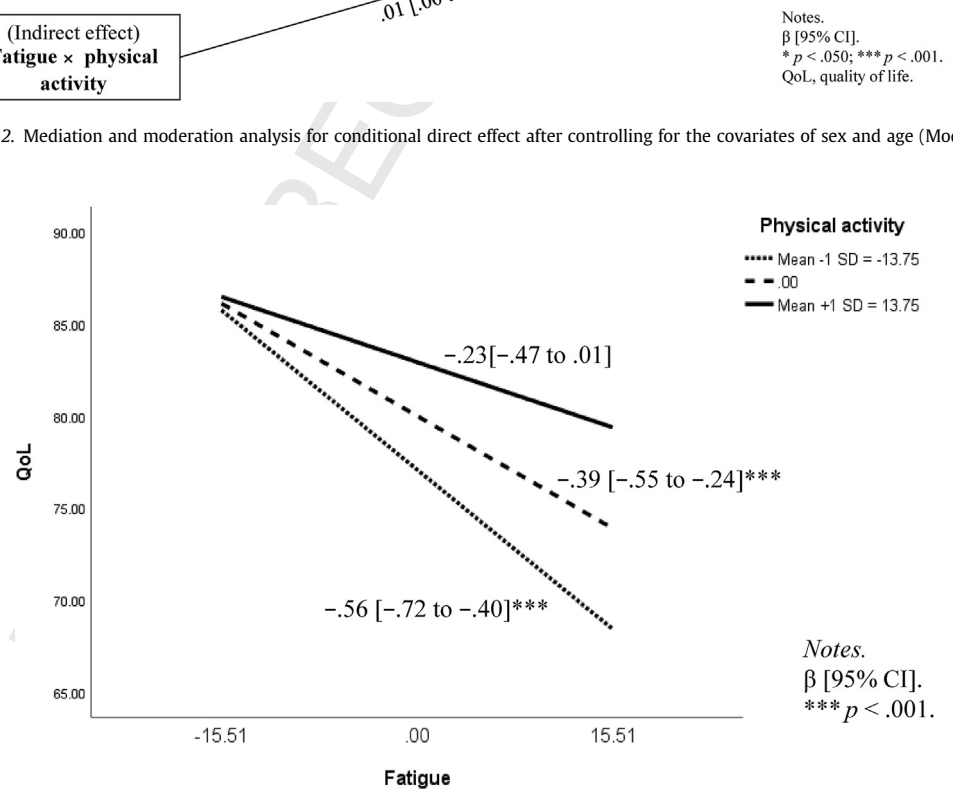


*Figure 3.* Conditional moderating effects of physical activity on the effects of fatigue on quality of life after controlling for the covariates of sex and age.

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can help childhood cancer survivors reach the minimum intensity, frequency, and duration of activity suitable for improving QoL.

In summary, our study clearly addresses the importance of healthy lifestyle behaviors. A healthy lifestyle consists of proper nutrition and adequate physical activity, both of which are essential to reduce fatigue and enhance QoL for childhood cancer survivors. Yet cancer treatment and its effects directly limit children's opportunities to engage in healthy nutrition and physical activity. Children are known to be at a developmental stage of adopting and consolidating health behaviors [55]. Long-term cancer treatment at a young age may lead these children to get used to an unhealthy lifestyle during critical stages of developing behavioral patterns [56]. Evidence indicates that small and optimal changes in children's lifestyle behaviors can result in obvious improvements to children's health outcomes [47]. Thus, timely correction of such behaviors is important. Such intervention can help these children continue a healthy lifestyle into adulthood.

### *Limitations*

Our use of a convenience sample from one medical center may limit this study's generalizability. Also, we used a standard value to identify malnutrition that is based on an adult population [38]; further research to identify appropriate phase angle reference values and cutoff points for malnutrition among children is needed.

### *Implications*

We observed a high prevalence of malnutrition in our study participants. Clinical practice for childhood cancer survivors should include regular screening of phase angle: at diagnosis, throughout therapy, and into survivorship. A phase angle cutoff point for malnutrition among children needs to be established. In addition, future research is needed to identify unhealthy lifestyle factors and then to develop healthy lifestyle interventions. Such interventions must include adequate frequency, intensity, and duration of physical activity as well as sufficient nutrition to facilitate meaningful changes in lifestyle factors. Clinical dietitians, physical therapists, and pediatric oncology nurses should work as a team to promote healthy nutrition and physical activity among children with cancer.

## Conclusion

Our study demonstrates the importance of both nutrition and physical activity in reducing the adverse effect of fatigue on QoL. This highlights an opportunity to enhance QoL among children with cancer through healthy lifestyle interventions. Healthy lifestyle behaviors need to be promoted throughout children's entire treatment trajectory and in survivorship. Future interventions should include nutrition and physical activity components and should involve nurses, pediatric oncology physicians, nutritionists, and physical therapists to ensure that the interventions address children's needs and promote the greatest impact.

## Conflict of interest

The authors have no conflicts of interest relevant to this article to disclose.

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