Dynamic Monitoring and Risk Assessment of Fatigue in Survivors of Childhood Cancer

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Abstract
Background
Persistent fatigue is one of the most common and burdensome late effects in childhood cancer survivors (CCS), yet its mechanisms remain poorly understood.

Methods
This PhD combined longitudinal surveys, physical fitness testing, blood biomarkers, and real-time ecological momentary assessment with wearable monitoring in adolescent and young adult CCS, with comparisons to healthy controls.

Results
Fatigue was highly prevalent, multidimensional, and fluctuated markedly over time. Psychological distress, poor sleep, and reduced physical fitness were key modifiable contributors. Biomarker analyses revealed biological alterations and two distinct subgroups, underscoring fatigue heterogeneity.

Conclusion
Fatigue in CCS is a dynamic, multifactorial condition requiring systematic screening and personalized, multidisciplinary care.

Introduction: fatigue as a key survivorship issue

Thanks to major advances in pediatric oncology, survival rates for childhood cancer now exceed 80%. As a result, increasing attention is being paid to the long-term consequences of cancer and its treatment. Many survivors experience late effects that persist well into adolescence and adulthood, affecting daily functioning and quality of life (1). Among these late effects, fatigue stands out as one of the most common and burdensome, yet it often remains underrecognized in clinical practice.

Fatigue in childhood cancer survivors (CCS) is not simply a transient or benign symptom. It can persist for years after treatment completion, interfere with school participation, social engagement, emotional well-being, and cognitive functioning, and significantly reduce overall quality of life (2). Importantly, fatigue may occur even in survivors without active disease, clear medical complications, or abnormal routine clinical findings. This makes fatigue challenging to recognize, explain, and manage in routine follow-up care.

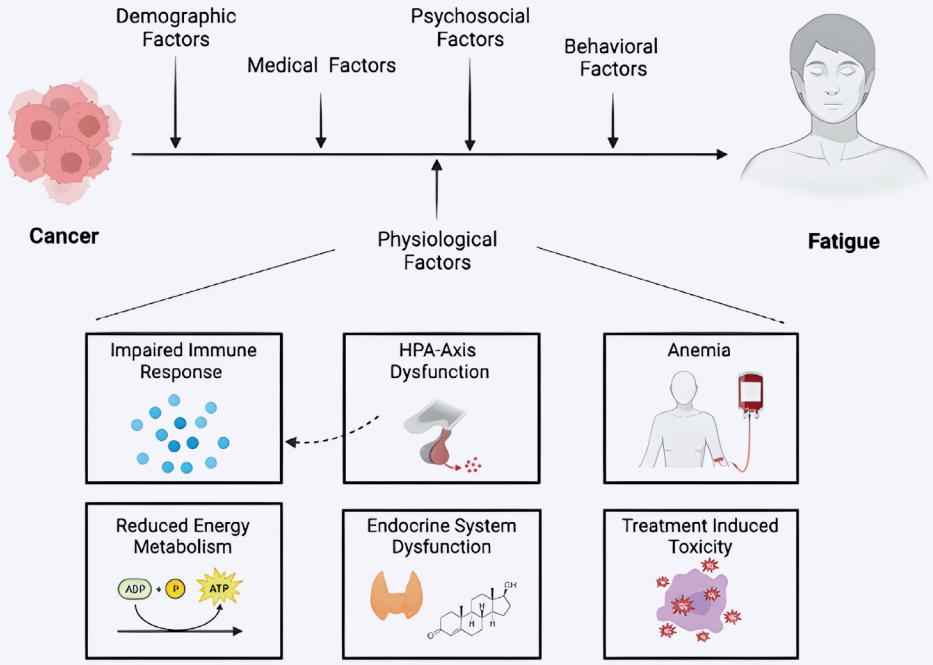
The etiology of fatigue in CCS is complex and multifactorial. Psychological, behavioral factors and biological alterations all appear to contribute. Moreover, fatigue is not static: it fluctuates over time and across contexts. This PhD dissertation aimed to advance understanding of fatigue in CCS by investigating its psychological, behavioral, biological, and momentary contributors, using a combination of longitudinal surveys, physical fitness testing, biomarker analyses, and real-time monitoring with ecological momentary assessment (EMA) and wearable devices.

Fatigue is more than “being tired”

Fatigue in CCS is best understood as a multidimensional symptom. Survivors may experience physical fatigue, characterized by reduced endurance and rapid exhaustion, as well as cognitive fatigue, manifesting as concentration difficulties, mental slowness, or “brain fog.” Emotional exhaustion and reduced motivation are also commonly reported. These dimensions often co-occur but do not necessarily evolve in parallel.

FIGURE: Overview of hypothesized mechanisms involved in fatigue.

Note. The origin, duration and severity of fatigue is an interplay of physiological factors, demographic factors (e.g. sex and age at diagnosis,…), medical factors (e.g. type of diagnosis and treatment, pre-existing health conditions,…), psychosocial factors (e.g. anxiety, depression, stress, social isolation and support,…) and behavioral factors (e.g. physical activity, sleep patterns,…). This figure was created with BioRender.



In pediatric survivorship research and clinical care, fatigue is typically assessed using questionnaires that capture both a global fatigue score and domain-specific subscales. For example, the PedsQL Multidimensional Fatigue Scale distinguishes between general fatigue, sleep/rest fatigue, and cognitive fatigue (3). Such multidimensional assessment is crucial, as different fatigue domains may have different contributors and clinical implications.

An additional challenge is that fatigue fluctuates markedly over time (4). Survivors frequently report variations within a single day, influenced by sleep, activity, emotional stress, and situational demands. A survivor may therefore appear relatively well during a clinic visit, while experiencing substantial fatigue-related impairment in daily life. Recognizing fatigue as a dynamic symptom rather than a stable trait is essential for adequate assessment and care.

Psychological distress as a long-term contributor

Psychological factors play an important role in fatigue among CCS. Cancer diagnosis and treatment represent potentially traumatic experiences, and a substantial proportion of survivors report ongoing cancer-related distress years after treatment completion. This includes fear of cancer recurrence and post-traumatic stress symptoms.

In our longitudinal study of adolescent and young adult CCS, fear of cancer recurrence and post-traumatic stress symptoms were found to predict higher fatigue levels one year later (5). These associations persisted even after accounting for baseline fatigue, highlighting distress as a genuine risk factor rather than a mere consequence of fatigue. Survivors who worried more about their health or experienced intrusive memories related to cancer were more likely to report persistent fatigue over time.

Resilience, defined as the ability to recover from stress, was associated with lower concurrent fatigue levels. However, resilience did not buffer the impact of cancer-related distress on future fatigue. This suggests that while resilience is beneficial, it may not be sufficient to offset the effects of ongoing psychological distress.

For pediatricians, these findings underscore the importance of considering psychological well-being when survivors present with fatigue. Persistent fatigue should prompt questions about health-related worries, traumatic stress, and emotional burden, even years after treatment.

Modifiable behavioral and physical contributors

Beyond psychological distress, several modifiable behavioral and physical factors contribute to fatigue in CCS. Among these, sleep quality and physical fitness emerged as particularly important (6).

Compared to healthy peers, CCS reported significantly higher levels of fatigue across all domains (general (44.7% vs. 23%), sleep/rest (55.3% vs. 30.8%), cognitive (64.7% vs. 29.3%) and total (56.5% vs. 25%) fatigue). Poor sleep quality was strongly associated with higher fatigue, especially sleep/rest fatigue and general fatigue. Disturbed or insufficient sleep can exacerbate daytime tiredness, impair emotional regulation, and reduce cognitive functioning, creating a vicious cycle that maintains fatigue.

Physical fitness also played a key role. Lower cardiorespiratory fitness, assessed using cardiopulmonary exercise testing (VO_2 peak), was associated with higher fatigue levels. Survivors with reduced endurance reported more fatigue, even when accounting for other factors. Importantly, fatigue was closely linked to broader outcomes, including reduced quality of life, emotional difficulties, and cognitive complaints.

These findings highlight that fatigue should not be viewed in isolation. Instead, it often reflects a broader pattern of reduced physical reserve and impaired recovery. From a clinical perspective, this supports the integration of sleep assessment, physical activity promotion, and rehabilitation strategies into survivorship care.

Fatigue in daily life: insights from ecological momentary assessments and wearables

Traditional questionnaires provide valuable information about overall fatigue levels but fail to capture short-term fluctuations and contextual influences. To address this limitation, this PhD used ecological momentary assessments (EMA) combined with wearable monitoring to study fatigue as it unfolds in daily life.

Using a smartphone app, CCS reported their fatigue multiple times per day, while a wearable device continuously tracked sleep, heart rate, and physical activity. These intensive measurements revealed pronounced within-day and day-to-day variability in fatigue, demonstrating that fatigue is not simply a stable background characteristic but a dynamic experience.

Importantly, most variability in fatigue reflected within-person fluctuations rather than stable differences between survivors. For general fatigue, 71% of the variability occurred within individuals over time (and 29% reflected between-person differences). For cognitive fatigue, 69% of the variability occurred within individuals over time (and 31% reflected between-person differences). In other words, fatigue is not only about who is more fatigued on average, but also very much about when a survivor is more fatigued.

Within-person analyses showed that sleeping longer than usual predicted lower next-day fatigue for both general and cognitive fatigue, while higher prior tension predicted higher subsequent fatigue in both domains. Importantly, recent physical activity showed opposite associations depending on the fatigue domain: taking more steps in the preceding two hours was associated with higher momentary general fatigue, but lower momentary cognitive fatigue. In addition, general fatigue increased across the day with a nonlinear late-day acceleration, whereas this diurnal pattern was not observed for cognitive fatigue.

For clinicians, these results emphasize that timing and context matter. Because a large part of fatigue reflects short-term fluctuations, a single fatigue score may miss clinically relevant patterns. Fatigue complaints may depend on recent sleep, activity, and stress, which are not always apparent during clinic visits. Although EMA and wearables are not yet standard tools in clinical practice, they illustrate how fatigue monitoring could evolve toward more personalized and timely assessment.

Biological alterations and fatigue heterogeneity

Biological mechanisms are increasingly recognized as contributors to fatigue in cancer survivors. Our systematic review of the literature identified consistent associations between fatigue and inflammatory cytokines, hypothalamic–pituitary–adrenal axis dysregulation, oxidative stress, and neurotrophic alterations, although pediatric data remain limited (7).

In our biomarker analyses comparing CCS to healthy controls, Gfap, total tau and MCP-1 differed between groups. Furthermore, clustering analyses revealed two biologically distinct subgroups among CCS: an inflammatory-dominant subgroup and a glial-associated subgroup. Despite these biological differences, fatigue severity did not differ between the subgroups.

This finding highlights the heterogeneity of fatigue. Similar levels of fatigue may arise from different underlying biological pathways, underscoring why no single biomarker can fully explain or predict fatigue (8). Clinically, this reinforces the need for multifactorial assessment and cautions against overly reductionist explanations.

Clinical implications for pediatric practice

Fatigue should be considered a core outcome in survivorship care. Pediatricians play a key role in recognizing and addressing fatigue, particularly as survivors transition from oncology-centered care to general follow-up.

Several practical implications emerge from this work: (a) fatigue should be systematically screened, even in survivors who appear medically stable, (b) persistent fatigue warrants assessment of psychological distress, sleep quality, and physical functioning, (c) because fatigue fluctuates over time, clinicians should explore patterns and triggers (e.g., time of day, recent sleep, activity, or stress) rather than relying on a single global fatigue score, (d) normalizing severe fatigue as "part of survivorship" may delay appropriate support, (e) multidisciplinary approaches, including psychological support, sleep interventions, physical rehabilitation, and guidance on activity pacing, are likely to be most effective.

Addressing fatigue early and in a time-sensitive manner may help prevent secondary consequences such as school difficulties, social withdrawal, and reduced participation in physical activity.

Future perspectives

Looking ahead, digital tools such as smartphone apps and wearable devices offer promising opportunities for real-time fatigue monitoring and personalized intervention. Combined with biomarker-informed phenotyping, such approaches could enable earlier identification of high-risk survivors and more tailored support. Ultimately, improving fatigue management is essential for preserving quality of life and long-term functioning in this growing survivor population.

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