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Contribution of Sleep Disruption and Physical Inactivity to Fatigue In Survivors of Allogeneic Hematopoietic Cell Transplant

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Contribution of Sleep Disruption and Physical Inactivity to Fatigue In Survivors of Allogeneic

Hematopoietic Cell Transplant

by

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A dissertation submitted in partial fulfillment
of the requirements for the degree of
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Table of Contents

List of Tables

List of Figures

Abstract

Background: Fatigue is a prominent quality of life concern among cancer patients who have undergone allogeneic hematopoietic cell transplantation (HCT). The high percentage of HCT patients reporting fatigue concerns warrants investigation into factors that may contribute to or alleviate fatigue. The present study sought to elucidate relationships among fatigue and behavioral factors including sleep disruption and sedentary activity.

Method: Allogeneic HCT recipients who were one to five years post-transplant were invited to participate in the present study. Participants wore an actigraph assessing sleep efficiency and sedentary behavior for one week, completed daily assessments of fatigue and sleep during the same period, and completed self-report questionnaires of fatigue (summary fatigue), sleep, and sedentary behavior on day seven of the study.

Results: Eighty-two allogeneic HCT recipients (age $M = 56$, 52% female) were enrolled and provided complete data. Forty-five percent of participants met criteria for clinically significant fatigue. Summary fatigue, but not aggregated daily fatigue, predicted sleep efficiency; neither summary nor momentary fatigue predicted sedentary behavior. Sleep disruption during the previous night and sedentary behavior during the day were related to evening reports of daily average fatigue but not daily momentary fatigue.

Conclusion: Results from the present study suggest that nearly half of HCT recipients continue to experience clinically significant fatigue one to five years post-transplant. Results from the daily analysis suggest that patients who sleep better the previous night and are less sedentary that day report less fatigue at the end of the day, which is a finding that warrants replication and

further study. Finally, findings suggest that a daily assessment methodology may be more useful

under circumstances in which there is greater daily variability in fatigue.

Introduction

Cancer-related fatigue has been defined as "a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning" (NCCN Guidelines, 2017). Fatigue is one of the most commonly reported symptoms before, during, and after hematopoietic cell transplant or HCT, an intensive therapy used to treat hematologic malignancies including leukemia, lymphoma, and multiple myeloma (Cohen et al., 2012; Grulke, Albani, & Bailer, 2012; Anderson et al., 2007; Gielissen et al., 2007). This is particularly true for patients undergoing allogeneic HCT (involves receipt of donor cells), who are at risk for a range of side-effects following transplant, including graft-versus-host disease (GVHD) in which grafted donor cells attack host tissue. Chronic GVHD has been shown to moderate fatigue among allogeneic transplant recipients during the first year following transplant (Nelson et al., 2014) and tends to be most prevalent between one to five years post-transplant. Fatigue has been shown to be significantly worse among transplant patients in the post-treatment period compared to non-cancer controls (Hacker et al., 2016; Hann et al., 1998). Previous studies have documented that as many as 81% of transplant recipients report clinically significant fatigue at day 100 post-transplant (Bevans et al., 2008), with between 11 to 31% reporting clinically significant fatigue three or more years after transplant (Jim et al., 2016; Hjermstad et al., 2004). Gielissen and colleagues (2007) investigated the percentage of transplant recipients meeting an established criterion for severe fatigue. They found that 35% of transplant recipients who were 1

to 22 years post-transplant met criteria for severe fatigue and that fatigue severity was not related to time since transplant (Gielissen et al., 2007).

Measurement of Fatigue

Like many symptoms, fatigue is a subjective state and current methods of fatigue measurement rely on patient self-report. Clinicians and researchers most often utilize brief, retrospective, self-report questionnaires to assess fatigue. Unidimensional fatigue scales typically provide data only on the intensity of fatigue, whereas multidimensional scales assess fatigue in a variety of dimensions. For example, the Fatigue Symptom Inventory (FSI) is a commonly used multidimensional fatigue assessment measure that provides data on fatigue severity, interference, and duration (Hann et al., 1998). The majority of what is known about cancer-related fatigue is based on retrospective self-report methodology. That is, respondents are typically asked to provide ratings of their fatigue over a previous period of time, such as the past week. As described next, these retrospective self-report methods have a number of limitations.

Problems with Retrospective Self-Report Methods

Recall is a central component of retrospective self-report methodology. However, cognitive science research suggests that much of lived experience is not retained in memory. In contrast to emotionally salient or unique experiences, mundane states and events are less likely to be encoded, consolidated, stored, and retrieved (Bradburn, Rips, & Shevell, 1987). Therefore, recall may largely represent an individual's attempt to reconstruct experiences through the use of heuristic strategies, which are prone to bias. Adding to this complexity, mental state at the time of information retrieval can also influence memory accessibility. For example, Sprangers and colleagues (1999) demonstrated that the trajectory of pre- to post-radiation fatigue influenced post-radiation recall of pre-radiation fatigue. Specifically, patients who demonstrated a

decreasing trajectory of pre- to post-radiation fatigue reported higher pre-radiation fatigue on a recall assessment than was actually reported at pre-radiation (Sprangers et al., 1999). Findings such as these have been used to argue that autobiographical memory is subject to random error and that systematic bias adversely impacts patient self-report (Shiffman, Stone, & Hufford, 2008).

Another key concern with retrospective self-reported data is that this methodology asks patients to report on experience over some specified period of time. Ideally, patients would recall the particular queried symptom experience during the specified time frame, aggregate and summarize those experiences, and produce an average score representing their experience during that period. However, cognitive science has determined that humans are not well-suited to this highly systematized process. Rather than engage in this process, individuals tend to use short-cuts to arrive at an answer. In one such short-cut, termed the availability heuristic, individuals make judgments about the frequency of experiences based on the availability or ease of retrieval (Tversky & Kahneman, 1973). Those events that are easy to retrieve are deemed more frequent. While heuristics such as these are time and "processing power" savers, the bias inherent in these strategies can have a detrimental impact on the validity of retrospective patient-reported data that is aggregated over time.

While all of these sources of bias should be acknowledged when using traditional retrospective self-report methods, it is important to recognize that these memory processes operate outside of conscious awareness and do not represent deceptive intent. Social desirability bias and deception are additional processes that may influence patient self-report. In summary, autobiographical memory and recall processes are prone to bias, which can adversely impact the validity of retrospective self-report ratings.

3

Alternative Symptom Measurement Strategies

Given the concerns that have been raised about retrospective self-report methods, it is worth considering newer, alternative methods of measuring symptoms such as cancer-related fatigue. These methods are primarily comprised of "real-time" and "near-real-time" data collection. One such method, Ecological Momentary Assessment, also referred to as EMA, represents a potentially valuable alternative approach to symptom data collection. EMA has been defined as a group of "methods using repeated collection of real-time data on subjects' behavior and experience in their natural environments" (Shiffman, Stone, & Hufford, 2008). Core features of EMA include data collection in real-world environments, focus on the current or very recent state of the participant, strategic selection of moments to assess, and repeated sampling over time. While these features are characteristic of EMA studies, implementation is heterogeneous with variations in EMA content, mode of delivery, and schedule.

EMA approaches offer numerous advantages over retrospective self-report methods. Shiffman, Stone, & Hufford (2008) note that EMA approaches produce data that are potentially more reliable than retrospective self-report methods because EMA collects real-time data with repeated sampling over time and does not ask patients to retrospectively aggregate experience. In addition, EMA maximizes ecological validity, meaning that the data collected are more reflective of real-world patient experience. Of particular importance, EMA approaches focus on the current or very recent state of the participant, thus minimizing autobiographical memory processes, which can introduce bias. Therefore, EMA represents methodology that is complementary to retrospective patient self-report and which may be better able to address certain research questions.

EMA With HCT Patients

Surprisingly, HCT is one of the few cancer contexts where electronic EMA methods have been used to measure fatigue (Hacker et al., 2007). Hacker and colleagues (2007) utilized EMA to assess fatigue among 20 HCT recipients for three days before and for three days following transplantation (i.e., receipt of stem cell product). This study obtained impressively high compliance rates, demonstrating that EMA methods are feasible even in the acute period surrounding HCT (Hacker et al., 2007). Unfortunately, this study did not assess fatigue using a retrospective self-report measure, and therefore, does not address questions regarding the comparability of the two assessment methods. Moreover, EMA has yet to be used to address at least one key question in the HCT setting; that is, how do behavioral factors such as sleep disruption and physical activity contribute to fatigue?

Relationship Between Fatigue and Behavior

There are thought to be complex, bidirectional relationships between fatigue and sleep in people with cancer (Minton & Stone, 2012; Rahman, Burton, Galbraith, Lloyd, & Vollmer-Conna, 2011; Alexander, Minton, Andrews, & Stone, 2009). For example, sleep disturbances could cause fatigue during the day, or conversely fatigue during the day could lead to maladaptive sleep behaviors such as daytime napping and difficulties sleeping at night. Similar relationships can be described between fatigue and activity (i.e., physical inactivity could cause fatigue during the day or fatigue could lead to physical inactivity).

Research into the relationships of fatigue with sleep and physical activity in people with cancer has typically relied on retrospective self-report ratings of all three constructs. This literature has consistently demonstrated strong relationships of physical activity and sleep with fatigue (Peters, Goedendorp, Verhagen, Bleijenberg, van der Graaf, 2016; Ratcliff, Lam, Arun,

5

Valero, & Cohen, 2014; Peters, Goedendorp, Verhagen, van der Graaf, & Bleijenberg, 2014; Pertl, Hevey, Collier, Lambe, & O'Dwyer, 2014; Ng et al., 2005; Jacobsen et al., 1999). For example, breast and prostate cancer patients who reported minimal physical activity had greater fatigue than those with high physical activity levels (Humpel & Iverson, 2010). Poor sleep quality was also associated with greater fatigue in this study.

While a large literature has demonstrated links between self-reported physical activity and fatigue and between self-reported sleep and fatigue, this literature is not without drawbacks. For instance and as already noted, a host of factors contribute to bias in retrospective self-reports. A review of self-reported physical activity in particular found that measurement methods have considerable impact on the observed level of activity, with self-report measures yielding levels that are both higher and lower than levels obtained with objective methods of measurement (Prince et al., 2008). Similarly, the lack of a relationship between self-reported and objectively measured sleep is one of the most published findings in sleep medicine (Buysse et al., 2008). These issues lead to questions about the validity and precision of self-reported behavior.

Many of these problems can be overcome through direct observation of behavior. Advances in technology have produced options for aiding scientists and clinicians in "observing" behavior. For instance, actigraphy involves the objective measurement of activity by means of an accelerometer that records and averages physical movement (Ancoli-Israel et al., 2003). It has been successfully used to measure sleep/wake patterns in breast and gynecologic cancer patients (Liu et al., 2013; Ancoli-Israel et al., 2006; Jim et al., 2011), patients with advanced cancer (Ma, Chang, & Lin, 2014), and autologous HCT patients (Nelson et al., 2017). It has also been used successfully to measure activity and sedentary behavior among cancer patients (Broderick, Ryan, O'Donnell, Hussey, 2014; Maddocks & Wilcock, 2012; Jim et al., 2011).

Actigraphy to Measure Sleep Disruption and Sedentary Behavior

Research investigating links between objectively measured behavior and self-reported fatigue has produced conflicting results. Several studies that have investigated these relationships do not support a link between objectively measured behavior (e.g., mean daytime activity) and fatigue as measured by retrospective self-reports (Yennurajalingam et al., 2016; Servaes, Verhagen, & Bleijenberg, 2002; Fernandes et al, 2006). For example, Fernandes and colleagues (2006) determined that fatigue severity rated for the past week was not related to actigraphy measured activity, sleep, or circadian rhythm impairments among female inpatients with cancer. Other studies have yielded mixed findings (Miaskowski et. al., 2011; Minton & Stone, 2012; Berger et al., 2007). For example, fatigue severity over the current day was related to acrophase, a circadian rhythm variable that measures the time of day of the peak of the rhythm, but not to other sleep, activity, or circadian rhythm measures among women prior to adjuvant breast cancer chemotherapy (Berger et al., 2007). Minton & Stone (2012) examined self-reported and objective measures of sleep and activity among survivors of breast cancer who were split into two groups, women who met criteria for cancer-related fatigue syndrome in the past month and those who did not. These authors found differences between groups on self-reported sleep, as well as differences in objectively measured daytime activity; however, no differences were observed with objective measures of sleep.

A third set of studies yielded more supportive evidence regarding links between objectively measured behavior and self-reported fatigue among cancer populations (Berger et al., 2010; Winters-Stone, Bennett, Nail, & Schwartz, 2008; Mallinson, Cella, Cashy, & Holzner, 2006; Ancoli-Israel, Moore, & Jones, 2001; Berger & Higginbotham, 2000). Liu and colleagues (2012) found that fatigue severity over the past week was positively associated with subjective

sleep scores and actigraphy measured total naptime and was negatively associated with total wake time during the day among newly diagnosed women with stage I-III breast cancer. Similarly, at the level of daily experience, it has been demonstrated that actigraphy measured sleep disturbance during chemotherapy can initiate a symptom cascade leading to increased fatigue as measured by daily ratings and increased depressive symptoms (Jim et al., 2013). In addition, a recent study found a positive relationship between cancer-related fatigue and sleep time and a strong inverse relationship between cancer-related fatigue and physical performance as measured by smart-bracelet devices among patients with metastatic pancreatic cancer (Shen et al., 2016). Moreover, objectively measured increases in physical activity have been associated with decreases in self-reported fatigue among patients receiving radiation treatment (Sarna & Conde, 2001).

While accumulating evidence linking behavioral factors to fatigue appears promising, it is unclear why evidence has been so mixed. Differences in cancer type, treatment received, time of assessment (e.g., before, during, or after treatment), method of sleep and activity assessment (i.e., objective vs. self-report), and methods of fatigue measurement (i.e., daily vs. retrospective) are likely important and may partially account for varying evidence. Moreover, objective indices are capable of producing a diverse array of sleep and activity variables. Therefore, it is important that researchers carefully choose sleep and activity variables apriori based on theory and a close review of previous literature.

As already discussed, processes such as memory bias and heuristics influence reports of symptoms such as fatigue. It may be that these processes, in combination with the temporal gap, which occurs between objectively recording behavior and assessing symptoms with summary measures, could partially account for the observed mixed evidence. If this is the case, then EMA

symptom assessment offers a temporal advantage of less time between measurement and the objectively assessed behavior, as well as the benefit of a reduced bias of confounding memory, heuristic, or other processes. In this way, an EMA approach to assessing fatigue may yield more consistent evidence for relationships of self-reported fatigue with objective measures of sleep disturbance and sedentary activity. The implications of this are likely multifactorial and may include provision of a more sophisticated understanding of the contribution of behavioral factors to cancer-related fatigue as well as improved identification of intervention targets for addressing cancer-related fatigue.

Considerations for Research Within the Setting of HCT

While relationships between self-reports of sleep, activity, and fatigue are well characterized, relationships between objectively measured sleep and activity with self-reported fatigue are not well understood. Moreover, even less is known about the impact of daily sleep and activity on daily fatigue. Given these key unanswered questions, the present study characterized fatigue among allogeneic HCT patients and investigated relationships of sleep and sedentary behavior with fatigue. Fatigue was assessed in two ways. First, patients were asked to provide "daily fatigue" ratings, which were collected using an EMA approach every day for the seven-day study period. For select statistical analyses, these daily fatigue ratings were averaged across the seven-day study period to create an "aggregated daily fatigue" variable. Second, patients provided "summary fatigue" ratings, which were collected using a validated retrospective self-report questionnaire completed at the end of the seven-day study period. During this seven-day study period, sleep disruption and sedentary behavior were assessed primarily by actigraphy and used to create aggregated seven-day measures of sleep disruption and sedentary behavior. These data were used to conduct between-persons analyses to examine

the extent to which aggregated daily fatigue accounts for additional variance in aggregated sleep disruption and sedentary behavior beyond summary fatigue, as well as the extent to which summary fatigue accounts for additional variance in aggregated sleep disruption and sedentary behavior beyond aggregated daily fatigue.

In addition to the approaches described above, exploratory analyses were conducted that take a within-persons perspective to the interrelationships between sleep disruption, sedentary behavior, and fatigue. The advantage of the within-persons approach is that unlike the between-persons approach that compares a person to others, a within-person approach evaluates outcomes or predictors in relation to themselves (Curran & Bauer, 2011). Thus, using this method, we were able to evaluate whether a person is likely to rate themselves as more fatigued after nights with greater sleep disruption, as compared to nights when their sleep is less disrupted. To begin to disentangle the complex relationships between sleep disruption, sedentary behavior, and fatigue, the intraindividual variation in the association between these variables over the seven-day study period was explored. The data collected were used to address the following aims and hypotheses.

Aims & Hypotheses

Aim 1: To characterize the prevalence and daily variability of fatigue among allogeneic HCT survivors. Univariate relationships between all fatigue variables, sleep disruption, and sedentary behavior were also characterized.

Aim 2: To investigate the relative contribution of aggregated daily fatigue and summary fatigue to aggregated sleep disruption.

Hypothesis 2a: Aggregated daily fatigue was expected to account for additional variance in sleep disruption above and beyond the influence of summary fatigue.

Hypothesis 2b: Summary fatigue was expected to account for additional variance in sleep disruption above and beyond the influence of aggregated daily fatigue.

Aim 3: To investigate the relative contribution of aggregated daily fatigue and summary fatigue to aggregated sedentary behavior.

Hypothesis 3a: Aggregated daily fatigue was expected to account for additional variance in sedentary behavior above and beyond the influence of summary fatigue.

Hypothesis 3b: Summary fatigue was expected to account for additional variance in sedentary behavior above and beyond the influence of aggregated daily fatigue.

While positive relationships were expected between both daily fatigue and summary fatigue with objectively measured sleep disruption and sedentary behavior consistent with review of the literature, daily fatigue was expected to demonstrate a more consistent pattern of significant relationships with sleep disruption and sedentary behavior than summary fatigue.

Aim 4: To explore whether sleep disruption during the previous night and sedentary behavior during the day were related to evening reports of fatigue.

Method

Participants

The study sample included adults who underwent an allogeneic HCT at Moffitt Cancer Center for treatment of a hematologic disease. Eligible participants: 1) were diagnosed with a hematologic malignancy, 2) underwent an allogeneic HCT approximately 1 to 5 years prior to study enrollment, 3) were ≥18 years of age, 4) had no history of other cancers other than non-melanoma skin cancer, 5) had no evidence of disease progression at the time of study enrollment, 6) had ambulatory patient status at the time of study enrollment, 7) had internet access, 8) were able to speak and read English, and 9) were able to provide informed consent.

Procedures

Study eligibility was determined through consultation with physicians, clinical staff, medical record and registry data review. Eligible patients returning to clinic for an appointment were approached during their clinic visit and had the study protocol explained to them. Those who agreed to participate signed an informed consent form. They were then given an actigraph, instructions for completing an electronic web-based daily log and study questionnaire, and a postage-paid envelope. Participants wore the actigraph for seven consecutive 24-hour periods and completed a daily log of their sleep and fatigue during that time. Access to the electronic web-based daily log was texted to participants at 6 pm each evening and they were informed that they had until 9 pm each evening to complete the log. Participants completed the electronic study questionnaire on day 7 of the study. Participants returned all study materials in the postage-paid

envelope. Relevant clinical information was collected with the assistance of the Moffitt Bone

Marrow Transplant Registry and medical record review.

Measures (see Appendix).

    Demographic characteristics. Participants completed a standardized self-report form

assessing demographics including age, gender, race, ethnicity, education, income, marital status,

and employment status, as well as height and weight as part of the study questionnaire.

Participants also completed a self-report version of the ECOG performance status scale (Oken et

al., 1982).

    Summary fatigue. Participants completed the Fatigue Symptom Inventory (FSI) on the

final day of the study. The FSI is a 14-item self-report measure of fatigue during the past week

assessing three domains of fatigue: severity, interference, and duration (Hann et al., 1998).

Fatigue severity is a composite of the average of four items assessing the most, least, and average

in the past week, and current level of fatigue experienced. The fatigue interference subscale

consists of the average of seven items assessing fatigue interference in the past week with

general level of activity, ability to bathe and dress, normal work activity, ability to concentrate,

relations with other people, and enjoyment of life. Fatigue duration consists of the number of

days fatigued and the amount of time fatigued per day in the past week. Each item is rated on an

11-point Likert scale from 0 to 10 with higher scores indicating greater fatigue. Analyses focused

on the composite fatigue severity score. Scores of ≥ 4 on the average of the fatigue severity items

are indicative of clinically meaningful fatigue according to National Comprehensive Cancer

Network guidelines (NCCN Guidelines, 2017). The FSI is a valid and reliable measure among

cancer populations (Donovan & Jacobsen, 2010; Hann et al., 1998) with a reliability coefficient

of α = .91 for the severity subscale, α = .93 for the interference subscale, and α = .77 for the duration subscale in the present study.

Daily fatigue. Participants provided daily fatigue ratings at the end of the day for 7 days through the use of an electronic diary. Questions were adapted from the FSI and participants were asked to rate: their level of fatigue right now (momentary fatigue), their peak fatigue during the day (most fatigue), their average fatigue during the day (average fatigue), and how much fatigue interfered with their activities during the day (fatigue interference). Of these items, analyses focused on participant ratings of "level of fatigue right now" as the primary daily fatigue outcome of interest. Each item was rated on an 11-point Likert scale from 0 to 10 with higher scores indicating greater fatigue or greater interference from fatigue. Participants were asked to record their daily fatigue ratings each evening between 6 and 9 pm. Participants received daily standard text messages granting access to the log and reminding them to complete their fatigue ratings. Aggregated scores were created by averaging scores for each item over the seven-day study period.

Sleep disruption. Sleep disruption was measured objectively using the ActiGraph GT9X Link (Pensacola, FL) and was used to objectively quantify sleep patterns. Participants were asked to wear the actigraph on their non-dominant wrist continuously for a seven-day period. Data from the actigraph was downloaded and analyzed using ActiLife v6.13.3 (ActiGraph, LLC, Pensacola, Florida). All downloaded data first underwent Wear Time Validation, which is a tool in ActiLife that flags periods of non-wear for further analysis. These periods were reviewed and scored as wear or non-wear time according to a pre-determined set of rules and accepted standards. Sleep indices were calculated using the Cole-Kripke algorithm in combination with daily patient sleep logs of bed and wake times. The primary sleep variable of interest for the

analyses was sleep efficiency (i.e., the percentage of time spent sleeping in relation to time spent in bed). Other variables that were explored included: sleep onset latency (SOL, i.e., the amount of time taken to fall asleep), wake after sleep onset (WASO, i.e., minutes awake after an extended period of sleep), and total sleep time (TST, i.e., the time spent asleep at night) (Berger et al., 2008). Aggregated sleep efficiency, which was created by averaging daily sleep efficiency over the seven-day study period, was used as an outcome for Aims 2 and 3 of the study. Daily sleep efficiency was used as a predictor for Aim 4 of the study.

Sleep disruption was also measured subjectively using the Pittsburgh Sleep Quality Inventory (PSQI). Participants completed the PSQI on the final day of the study. The PSQI is a 19-item self-report measure of sleep disruption during the past week assessing seven domains and providing a global score. Higher scores indicate greater sleep disruption. Analyses focused on the global score. Scores of ≥ 5 on the global sleep scale are indicative of clinically meaningful sleep disturbance (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). The PSQI is a valid and reliable measure among cancer populations (Beck, Schwartz, Towsley, Dudley, & Barsevick, 2004) with an overall reliability coefficient of $\alpha = .87$ for the global sleep scale in the present study.

Sedentary behavior. The ActiGraph GT9X Link (Pensacola, FL) was also used to objectively quantify sedentary behavior. Data from the actigraph was downloaded and analyzed using ActiLife v6.13.3 (ActiGraph, LLC, Pensacola, Florida). All data first underwent Wear Time Validation, described above. Sedentary behavior indices were then calculated using the Freedson Adult (1998) algorithm which compares actigraph-derived activity values to the following cut points for activity classification: Sedentary 0 – 99, Light 100 – 1951, Moderate 1952 – 5724, Vigorous 5725 – 9498, and Very Vigorous 9499 and above. The primary sedentary

behavior measure of interest was sedentary time or the percentage of time spent engaging in sedentary activity. Aggregated sedentary behavior, which was created by averaging daily sedentary time over the seven-day study period, was used as an outcome for Aims 2 and 3 of the study. Daily sedentary time was used as a predictor for Aim 4 of the study.

Subjective reports of sedentary behavior were also assessed using the Marshall Sitting Questionnaire (MSQ). Participants completed the MSQ on the final day of the study. The MSQ is a 5-item self-report measure of sitting during the past week and patients are asked to estimate how much time they spend sitting on an average weekday and on an average weekend day. Higher scores indicate greater time spent sitting. Calculation of a summary score was planned for the purposes of this project. The MSQ is a valid and reliable measure and has been used to assess sedentary behavior among cancer populations (Boyle, Lynch, Courneya, & Vallance, 2015).

Patients also completed an activity report on the last day of the study to aid in understanding of the types of activities patients generally engaged in. This activity questionnaire included seven questions, one for each day of the study, about the main type of activity participated in each day. Participants could choose one of five options including: working outside the home, working within the home (at home job), leisure activities outside the home, leisure activities within the home, or other: please describe. For the purposes of the present study, frequencies were tabulated to determine the primary types of activities participants were engaged in throughout the study period.

Symptoms. Given the relationship between cGVHD and fatigue among allogeneic HCT recipients, participants completed the Lee Symptom Scale on the final day of the study. The Lee Symptom Scale is a 30-item scale assessing cGVHD symptom burden in seven areas (e.g., eyes and mouth, skin). For the purposes of this study, the scale was keyed to the past week. Each item

is rated on a 5-point Likert scale from 0 to 4 with higher scores indicating greater symptom burden. The Lee Symptom Scale is a valid and reliable measure among allogeneic HCT populations (Lee, Cook, Soiffer, & Antin, 2002) with a reliability coefficient of $\alpha = .85$ in the current study.

Participants also completed the Functional Assessment of Cancer Therapy Bone Marrow Transplant specific subscale (FACT-BMT) on the final day of the study. The FACT-BMT is a 23-item scale assessing symptoms and concerns common to transplantation. The FACT-BMT was used for descriptive purposes. The FACT-BMT is valid and reliable among allogeneic transplant patients (McQuellon et al., 1997) with a reliability coefficient of $\alpha = .78$ in the current study.

Medical characteristics. Medical characteristics were collected with the aid of the Moffitt Bone Marrow Transplant Registry and abstracted via medical record review (e.g., cancer diagnosis, donor type, ablation, time since transplant, etc).

Statistical Analyses

Descriptive statistics (means, standard deviations, ranges, frequencies) were used to characterize the sample. In those cases where participants missed $\leq 20\%$ of items on an individual scale, the participant's available data was used to calculate an item-level mean value for imputation. Distribution normality of scaled scores was evaluated (skew and kurtosis value +/- 2). Scaled scores for the present study's main predictor variables and outcomes met criteria for normal distribution. To address Aim 1, descriptive statistics (e.g., means, standard deviations, and frequencies) were used to characterize the prevalence and daily variability of fatigue. Levels of clinically significant fatigue were also examined using frequencies with the cut-offs previously specified. Finally, Pearson correlation coefficients were examined to determine

relationships among aggregated daily fatigue, summary fatigue, sleep disruption, and sedentary behavior.

In addition, and prior to performing the primary analyses, Pearson correlations were used to confirm relationships between subjective sleep disruption as measured by the PSQI global sleep score and aggregated daily and summary fatigue. Pearson correlations were also planned to confirm relationships between self-reported sedentary behavior as measured by the MSQ and aggregated daily and summary fatigue. These analyses were planned to confirm expected relationships and aid in explaining the pattern of observed findings.

To address Aim 2, hierarchical multiple regression analyses were planned to explore the incremental and combined variance accounted for by aggregated daily fatigue versus summary fatigue in predicting sleep disruption. To accomplish this, two models were planned. In the first model, all significant demographic and clinical factors would be entered on the first step, summary fatigue would be entered on the second step, and aggregated daily fatigue would be entered on the third and final step. This set of analyses was planned to determine whether aggregated daily fatigue as measured by EMA contributes any additional variance above and beyond the influence of summary fatigue. In the second model, all significant demographic and clinical factors would be entered on the first step, aggregated daily fatigue would be entered on the second step, and summary fatigue would be entered on the third and final step. This set of analyses was planned to determine whether summary fatigue accounts for unique variance above and beyond the influence of aggregated daily fatigue in predicting sleep disruption.

To address Aim 3, hierarchical multiple regression analyses were planned to explore the incremental and combined variance accounted for by aggregated daily fatigue versus summary fatigue in predicting sedentary behavior. These analyses parallel the structure of those described

18

in Aim 2. In the first model, all significant demographic and clinical factors would be entered on the first step, summary fatigue would be entered on the second step, and aggregated daily fatigue would be entered on the third and final step. This set of analyses was planned to determine whether aggregated daily fatigue as measured by EMA contributes any additional variance above and beyond the influence of summary fatigue. In the second model, all significant demographic and clinical factors would be entered on the first step, aggregated daily fatigue would be entered on the second step, and summary fatigue would be entered on the third and final step. This set of analyses was planned to determine whether summary fatigue accounts for unique variance above and beyond the influence of aggregated daily fatigue in predicting sedentary behavior.

To address Aim 4, multi-level models using SAS PROC MIXED were created to address the hypothesis that daily sleep disruption or sedentary behavior as measured by actigraphy would be related to daily fatigue. These analyses use a time-lagged approach. In the case of sleep disruption, this approach allows investigation into whether sleep disruption as measured by actigraphy during the previous night predicts daily fatigue ratings obtained the following evening. In the case of sedentary behavior, this approach allows investigation of whether daily sedentary behavior as measured by actigraphy predicts daily fatigue ratings obtained that evening. An advantage of these models is the ability to include all participants regardless of whether complete data are available. Therefore, these analyses included all participants who contributed at least three days of daily fatigue and actigraphy data. Models 1 – 4 were "empty models" that included one of the following: daily outcome (momentary fatigue or average fatigue) or daily predictor (sedentary behavior or sleep efficiency). Model 5 included either sedentary behavior or sleep efficiency, each centered at the sample mean, as predictors of daily fatigue. These models allow investigation into whether sedentary behavior during the day and

sleep efficiency the previous evening predicts daily fatigue at the group level. Model 6 included either sedentary behavior or sleep efficiency, each centered at the person mean, as predictors of daily fatigue. These models were the focus of Aim 4 and allow investigation into whether sedentary behavior during the day and sleep efficiency the previous evening predicts daily fatigue at the level of the individual.

Data analyses were performed using SAS Version 9.4 (Cary, NC). A p value < .05 (two-tailed) was considered statistically significant. Based on previous research (Jim et al., 2011; Rumble et al., 2010), effect sizes for relationships of interest in the present study were expected to be medium (i.e., r = 0.30). A power analysis using G*Power 3.1 indicated that a sample of 84 patients would be needed to detect significance of a medium effect (r = 0.30) with a Type I error rate of 0.05 (two-tailed) and power of 0.80. For the regression analyses, a sample size of 84 participants would allow for an effect size of $f^2 = 0.12$ to be detected with 80% power and an alpha of .05. Assuming an approximate 15% correction for missing data and objective data recording failure, the present study proposed recruiting 96 participants with 84 providing complete data. Complete data was defined as data collected from at least two weekdays and a weekend day for a total of at least three out of seven days of data. Based on higher than anticipated rates of non-compliance to study design, a total of 117 participants were recruited.

Results

Recruitment and Patient Characteristics

Figure 1 depicts patient flow through the study. Overall, 513 patients were screened for eligibility between June 2017 and January 2018. Of these, 335 were excluded from the study due to: receiving a transplant other than allogeneic HCT (n=95), being less than one year post-transplant (n=88), being greater than five years post-transplant (n=86), having a history of other malignancy (other than non-melanoma skin cancer, n=25), having recurrence/progression of disease (n=19), not being proficient in English (n=16), having non-ambulatory status (n=3), not having cellphone or internet access (n=2), or being deceased (n=1). Of the original 513 patients screened, 178 patients were deemed eligible and 133 of these patients were invited to participate in the study.

Of the 133 patients approached, 117 patients consented to the study (88% of eligible patients). Patients who agreed to participate did not differ from those who declined participation on the basis of age, gender, ethnicity, or race (all p values > .05). Three patients were deemed ineligible after consent due to disease progression, three were lost to follow-up, and one discontinued participation due to feeling too ill to participate. Of the 110 patients who completed the study, nine did not complete the study questionnaire, while nine did not complete the study questionnaire on day seven of the study. Six patients failed to provide at least three days of EMA including at least two weekdays and one weekend day, three patients did not provide at least 72 hours of usable actigraphy data, and one patient never received the text messages, which delivered the EMA component of the study. The final sample for analytic purposes consisted of

82 patients. Participants who were included in the final sample (n = 82) were compared to those who were not (n = 35). Participants who were included in the final sample were older (t = -2.37, $p < .05$); the groups did not differ on the basis of gender, ethnicity, or race (all p values > .05).

Demographic characteristics of the sample are presented in Table 1. The majority of participants were female, non-Hispanic White, and married or living with a partner. The sample was highly educated with the majority having at least some college. Medical characteristics of the sample are presented in Table 2. At the time of study entry, participants were an average of 2.5 years post-transplant. The majority was diagnosed with leukemia (56%) and received transplanted cells from a matched unrelated donor (66%). Half the participants received a myeloablative regimen and half did not. Sixty percent of participants had been diagnosed with stage I or II acute GVHD, and a majority of participants were diagnosed with mild (22%) or moderate (39%) chronic GVHD.

Table 3 presents descriptive statistics including means and standard deviations for participant self-reported sleep disruption (PSQI), symptoms (Lee cGVHD Scale), and quality of life (FACT-BMT). On average, participants reported relatively high levels of sleep disruption as measured by the PSQI global sleep score (M = 8.15, SD = 4.32). Seventy-eight percent of participants scored a 5 or greater indicating clinically significant sleep disruption.

Data from the MSQ were dropped from the present study due to the large percentage of missing responses. Missing data on the five MSQ items ranged from 46% to 65%. Specifically, the minimum percentage of missing data (46% of responses) occurred on item 1 (time spent sitting while traveling to and from places) on a weekday. The maximum percentage of missing data (65% of responses) occurred on item 2 (time spent sitting while at work) on a weekend day. Participant-reported activities from the categories on the activities questionnaire were as follows:

leisure activities within the home (38%), leisure activities outside the home (21%), working outside the home (17%), other (14%), working within the home (10%).

Table 4 presents descriptive statistics including means and standard deviations for sleep disruption and activity variables obtained via actigraphy. On average, participants demonstrated poor sleep efficiency ($M = 78.93$, $SD = 8.88$). While participants on average were able to fall asleep within at least 10 minutes ($M = 8.61$, $SD = 6.83$) and slept for 6.7 hours ($M = 399.64$ minutes, $SD = 63.64$), they were awake after initially falling asleep for an average of 99.29 minutes ($SD = 50.41$) during the night. On average, participants spent a considerable percentage of their time engaged in sedentary activity ($M = 55.41\%$, $SD = 10.19$), light activity ($M = 35.86\%$, $SD = 8.58$), or moderate activity ($M = 8.73\%$, $SD = 4.37$), but not vigorous activity or very vigorous activity.

Aim 1: Prevalence and Daily Variability of Fatigue Among HCT Recipients

Figure 2 depicts the daily fatigue means for ratings of momentary fatigue, fatigue interference, most fatigue, and average fatigue. Table 5 presents descriptive statistics including means and standard deviations for aggregated daily fatigue and summary fatigue variables. Aggregated daily fatigue mean scores were as follows: 3.57 ($SD = 1.91$) for momentary fatigue, 4.69 ($SD = 2.05$) for fatigue interference, 3.25 ($SD = 1.71$) for most fatigue, and 2.51 ($SD = 2.01$) for average fatigue. Summary fatigue mean scores as measured by the FSI were as follows: 3.54 ($SD = 1.97$) on fatigue severity, 2.47 ($SD = 2.06$) on fatigue interference, 5.26 ($SD = 2.22$) on number of days fatigued, and 3.73 ($SD = 2.38$) on fatigue per day. Forty-five percent of participants met or exceeded the clinically significant cut point of 4 on the FSI severity subscale.

Table 6 presents univariate relationships between all fatigue variables and objectively assessed sleep disruption and sedentary behavior as well as self-reported sleep disruption,

symptoms, and quality of life. Consistently strong relationships were evident between self-report measures of sleep disruption, quality of life, and GVH symptoms and measures of aggregated daily fatigue and summary fatigue (all *p* values < .001). Similarly, significant relationships were observed between sleep efficiency and measures of aggregated daily fatigue and summary fatigue (all *p* values < .05) except for momentary fatigue and FSI duration (# of days) (*p* values > .05). Less consistent relationships were evident between actigraphy-assessed activity indices and fatigue. Sedentary time was associated with average fatigue (*p* < .05) and FSI interference (*p* < .01), but no other fatigue indices (*p* values > .05).

Actigraphy-assessed sleep efficiency was correlated with PSQI-assessed global sleep (r = -0.32, *p* < .01). Corresponding relationships between self-reported sedentary behavior, as measured by the MSQ, and actigraphy-assessed sedentary behavior could not be determined due to the extent of missing MSQ data.

Aim 2: Relative Contribution of Aggregated Daily Fatigue and Summary Fatigue to Aggregated Sleep Disruption

Relationships of actigraphy-assessed sleep efficiency with sociodemographic and medical characteristics are presented in Table 7. Participants who were married or partnered, were white, and had at least some college education scored higher on sleep efficiency as assessed by actigraphy (all *p* values < .10). Therefore, these demographic factors were controlled for in subsequent analyses with sleep efficiency as the outcome.

Relationships among aggregated daily fatigue variables and summary fatigue variables were preliminarily examined and are presented in Table 8. The relationship between aggregated momentary fatigue and FSI-measured summary fatigue severity was unexpectedly strong (r = .90, *p* < .001). Corresponding relationships among other aggregated daily fatigue variables and

other summary fatigue variables were similarly high (see Table 8). The high degree of collinearity among these variables precluded conducting the original planned analyses for Aim 2 and, therefore, an alternate strategy was developed.

The revised analyses included two sets of models with summary fatigue and aggregated daily fatigue predicting aggregated sleep disruption, respectively. Results are presented in Table 9. In the first set of models in which summary fatigue was used to predict sleep disruption, all demographic and clinical variables significantly ($p < .10$) related to aggregated sleep efficiency were first entered. Summary fatigue was then entered to determine the variance in sleep efficiency accounted for by summary fatigue above and beyond these demographic and clinical variables. Specifically, in the first step, dichotomized versions of marital status, race, and educational status were entered and were found to account for 13% of the variance in sleep efficiency, $F(3, 78) = 5.17$, $p < .01$. In the second step, summary fatigue accounted for an additional 9% of the variance in sleep efficiency ($\beta = -0.30$, $p < .01$).

In the second set of models in which aggregated daily fatigue was used to predict aggregated sleep efficiency, all demographic and clinical factors significantly ($p < .10$) related to aggregated sleep disruption were first entered. Aggregated daily fatigue was then entered to determine the variance in aggregated sleep efficiency accounted for by aggregated daily fatigue above and beyond these demographic and clinical variables. Once again, dichotomized versions of marital status, race, and educational status were found to account for 13% of the variance in sleep efficiency, $F(3, 78) = 5.17$, p < .01. In the second step, aggregated daily fatigue accounted for an additional 1% of the variance in sleep efficiency ($\beta = -0.13$, $p > .05$).

Aim 3: Relative Contribution of Aggregated Daily Fatigue and Summary Fatigue to Aggregated

Sedentary Behavior

Relationships of aggregated sedentary behavior with sociodemographic and medical characteristics are presented in Table 7. No significant relationships were observed between aggregated sedentary behavior and sociodemographic or medical factors (all p values > .18). Therefore, no covariates were included in the Aim 3 analyses. Like Aim 2, the high degree of collinearity among aggregated daily fatigue and summary fatigue precluded conducting the original planned analyses for Aim 3 and, therefore, an alternate strategy was developed. Univariate correlations are presented in Table 6. Here, we present similar analyses using regression.

The refined analyses included two models, results for which are presented in Table 10. In the first model, summary fatigue was entered as the only predictor to determine the variance in aggregated sedentary behavior accounted for by summary fatigue. Summary fatigue accounted for 1% of the variance in sedentary behavior, $F(1, 80) = 2.02$, $p = .16$.

In the second model, aggregated daily fatigue was entered as the only predictor to determine the variance in aggregated sedentary behavior accounted for by aggregated daily fatigue. Aggregated daily fatigue accounted for no measurable variance in aggregated sedentary behavior, $F(1, 80) = 0.75$, $p = .39$.

Aim 4: Association of Sleep Disruption and Sedentary Behavior with Evening Reports of Fatigue

These analyses investigated the hypothesis that daily sleep disruption or sedentary behavior as measured by actigraphy would be related to daily reports of fatigue. These analyses were carried out using multi-level modeling, a statistical approach to longitudinal data analyses. Using these models, we are able to distinguish between-person variance (differences in average

scores) from within-person variance (fluctuations in scores from a person's average). The analyses focused on one set of same-day relationships (i.e., the relationship between sedentary behavior and daily fatigue) and one set of lagged relationships (i.e., how sleep efficiency predicts the next evening's daily fatigue) with two outcome variables of interest (i.e., daily momentary fatigue and daily average fatigue) for each set. Lagging was achieved through study design and database set-up, which coded the first night of sleep as a day 1 variable. Therefore, no statistical lagging had to be done. In these analyses, the Aim 4 predictors were separately grand-mean centered at the sample mean and person-centered at the person-level mean (a person's usual level of daily sleep efficiency or sedentary behavior, as represented by each person's mean across all seven days of the study).

Variability in daily measures (results from models 1 – 4). Models 1 through 4 provide information on the total variance in daily actigraphy measures (i.e., sleep efficiency and sedentary behavior) as well as daily assessments of fatigue (i.e., momentary fatigue and average fatigue). The total variance is composed of differences between persons in average scores and differences within persons in the fluctuation of these scores. Table 11 lists the percentages of between- and within-person relative contribution to the total variance of scores. Results suggested that the majority of the variance in all variables was driven by between-person differences in average scores; however, there was sufficient within-person variation to proceed with planned analyses.

Concurrent analyses with sedentary behavior predicting daily fatigue (results from models 5 – 6). Results from these analyses are displayed in Table 12. Results from model 5, which focused on between-person differences in average scores, revealed that participants who on average were more sedentary during the day had higher evening reports of average daily

27

fatigue ($\beta = 4.44$, $p < .05$) but not momentary fatigue ($\beta = 1.56$, $p > .05$). Results from model 6, which focused on adding in the within-person fluctuation in scores, revealed that at times when sedentary behavior was higher than usual for individuals, evening reports of average daily fatigue were also higher than usual ($\beta = 3.92$, $p < .01$). This finding did not extend to results with momentary fatigue ($\beta = -0.58$, $p > .05$).

      Time-lagged analyses with sleep efficiency predicting daily fatigue (results from models 5 – 6). Results from these analyses are displayed in Table 12. Results from model 5, which focused on between-person differences in average scores, revealed that participants who on average experienced less efficient sleep had higher reports of average daily fatigue ($\beta = -0.09$, $p < .001$) but not momentary fatigue ($\beta = -0.04$, $p > .05$) the next evening. Results from model 6, which focused on adding in the within-person fluctuation in scores, revealed that at times when sleep efficiency was lower than usual for individuals, reports of average daily fatigue were higher than usual the next evening ($\beta = -0.02$, $p < .05$). This finding did not extend to results with momentary fatigue ($\beta = -0.02$, $p > .05$).

Discussion

The present study sought to characterize daily fatigue and the relationships of objectively-assessed sleep disruption and sedentary behavior with patient-reported fatigue among allogeneic HCT recipients who were one to five years post-transplant. Results demonstrated that allogeneic HCT recipients continue to struggle with fatigue in the post-treatment period. Forty-five percent of participants met criteria for clinically significant fatigue on a retrospective fatigue measure. Of note, fatigue severity was unrelated to time since transplant. This estimate exceeds reports from previous studies that between 11 to 35% of HCT recipients meet criteria for clinically significant fatigue three or more years after transplant (Jim et al., 2016; Gielissen et al., 2007; Hjermstad et al., 2004). In the present study, daily assessments of fatigue using an EMA-like approach were similarly high. The only other study to our knowledge to use an EMA approach for fatigue assessment among transplant recipients assessed fatigue prior to transplant and, again, in the acute period after transplant (Hacker et al., 2007). That study reported that a minority of patients reported clinically significant fatigue prior to transplant; however, a large majority met criteria after transplant.

A major focus of the present study was examination of relationships of aggregated daily and summary fatigue with actigraphy-assessed sleep disruption and sedentary behavior. It was hypothesized that aggregated daily fatigue would predict aggregated actigraphy-assessed sleep disruption and sedentary behavior over and above summary fatigue. However, the unexpectedly high multicollinearity among the aggregated daily and summary fatigue variables precluded our ability to carry out planned analyses. While relationships among the fatigue variables were

29

expected to be strong, relationships at times exceeded $r = .90$. There are several possible explanations. First, the strength of these relationships may simply be reflective of the phenomenological experience and pattern of fatigue for allogeneic transplant recipients beyond one year post-transplant. Second, wording for the daily assessments of fatigue borrowed heavily from the summary fatigue measure. This feature may have increased participants' awareness of their daily fatigue thereby impacting their summary fatigue scores on the FSI. Third, participants were one to five years post-HCT and were not undergoing active treatment. This feature may, in part, account for the lack of variability in daily ratings of fatigue, resulting in greater correspondence between daily and summary ratings of fatigue.

Though not ideal, revised analyses focused on developing separate models of the ability of aggregated daily fatigue and summary fatigue in predicting actigraphy-assessed sleep disruption and sedentary behavior. Summary fatigue, but not aggregated daily fatigue, was found to be predictive of aggregated sleep efficiency. In contrast, neither aggregated daily fatigue nor summary fatigue was found to be predictive of aggregated sedentary behavior.

The original hypotheses with regard to this aspect of the study were based on work suggesting that autobiographical memory and recall processes are prone to bias, which can adversely impact the validity of retrospective self-report ratings (Shiffman, Stone, & Hufford, 2008). Despite the large body of evidence supporting these underlying processes, these sources of bias within retrospective measures, if present, did not hold in the present study. To our knowledge, there are no studies with transplant recipients or cancer patients with which to directly compare these results, making interpretation within a larger literature difficult. It is possible that sources of bias may be more influential when measuring symptomatology during times within which there is more variability in daily fatigue and other symptoms (e.g., while

30

undergoing active treatment). As already mentioned, it is also possible that underlying sources of bias were minimized in the present study because participants were asked to provide daily assessments of symptom experience thereby making their daily experience of symptoms more salient in recall. While there are a number of factors specific to the present study's design that could influence results, these findings preliminarily suggest that an EMA methodology does not present an advantage over traditional retrospective measures in cases where symptoms assessed daily are aggregated over time.

As part of the current study, it was theorized that memory bias and heuristics in combination with the temporal gap which occurs between objectively recording behavior and assessing symptoms with summary measures, could partially account for the mixed evidence in relationships between self-reported symptoms and objectively-assessed behavior. The present study sought to evaluate whether EMA-based symptom assessment, in offering an advantage of a closer temporal measurement to objectively assessed behavior, would yield more consistent relationships than summary measures between self-reported symptoms and objectively assessed behaviors. Findings suggest that the temporal gap may not explain mixed results and that future research should investigate other factors (e.g., population and treatment factors) that may account for the difference in relationships. Despite lack of evidence for advantages of an EMA-based assessment approach, these findings are encouraging in that they provide support for the existing body of work that has relied on traditional retrospective measures of symptom experience. This is potentially important information for researchers designing studies of symptoms in cancer patients and good news for patients in terms of maintaining low participant burden.

An exploratory aim of the present study was to evaluate whether an individual would be likely to rate themselves as more fatigued after nights with greater sleep disruption or days with greater sedentary behavior, as compared to times when their sleep was less disrupted and they were more active. To answer this question, sources of variability in study predictors and outcomes were first explored. These analyses revealed that the daily fatigue measures showed significant variability, with persons varying from one another and across days over the seven-day study period. Relationships between sedentary behavior, sleep efficiency, and fatigue at the group level were then assessed and showed that individuals who were more sedentary and had less efficient sleep were more likely to rate themselves as more fatigued on average. Finally, at times when persons were more sedentary than usual or had less efficient sleep than usual, they were more likely to rate their average level of fatigue as greater than usual. The literature is mixed with regard to associations between objectively measured behavior and self-reported symptoms. Although some studies have found no relationships (e.g., Fernandes et al., 2006), findings from the present study are in line with a growing number of studies demonstrating links between objectively measured behavior and self-reported fatigue among cancer patients using a daily analysis approach (Jim et al., 2013; Jim et al., 2011) and more traditional summary approaches (Shen et al., 2016; Liu et al., 2012; Berger et al., 2010; Berger et al., 2007; Sarna & Conde, 2001). Results from the present study were obtained through the use of sophisticated modeling techniques capable of identifying and elucidating relationships at the group-level as well as at the person-level. These findings represent an important addition to previous literature and warrant replication and further study.

These observed relationships were demonstrated with average fatigue as the outcome; corresponding relationships with momentary fatigue as the outcome were not significant. This

pattern of results suggests that patients' summaries of fatigue for the day may be more meaningful than a single, momentary rating when conducting a daily analysis of relationships with actigraphy-assessed behavior. Moreover, these findings highlight the need for researchers to carefully choose variables apriori based on theory and a close review of previous literature. Although this methodology does not overcome the problem of examination of cross-sectional relationships, this approach begins to untangle these relationships by modeling temporal relations between how sedentary people are and how well they sleep and their related experience of fatigue.

It was originally theorized that aggregated daily assessments of fatigue would explain additional variability in objectively-assessed sleep and sedentary behavior beyond that accounted for summary measures of fatigue. As noted previously, this expectation was based on EMA approaches collecting real-time data with repeated sampling over time and not asking patients to retrospectively aggregate experience. Although these hypotheses could not be tested due to the high collinearity between aggregated daily and summary measures of fatigue, results from the present study suggest that EMA assessments of symptoms may still be valuable in select circumstances. Findings from the present study suggest that an EMA approach to measurement is useful in studies assessing day-to-day fluctuation in symptoms and daily analysis of relationships among fluctuating symptoms. Results suggest that interindividual differences, at the group level, and intraindividual differences, at the person level, in the relationship between sleep efficiency or sedentary behavior and daily fatigue are both important for understanding how these factors relate to one another. Use of EMA assessments of symptoms under these conditions allows for a more sophisticated understanding of the contribution of behavioral factors to cancer-related fatigue. This approach may also aid in improved identification of intervention targets for

33

addressing cancer-related fatigue. Therefore, EMA represents methodology that is complementary to retrospective patient self-report and which may be better able to address certain research questions.

The present study had several limitations. First, the study was slightly underpowered with a final sample of 82 participants instead of 84 as indicated by power analyses. Second, and as already discussed, the high collinearity among fatigue indices led to changes in planned analyses. Third, the large amount of missing MSQ data precluded our ability to assess relationships between objectively-assessed and self-reported sedentary behavior. Finally, it is possible that daily assessments of fatigue may have influenced participants' responses on the summary fatigue measure. Despite these limitations, the present study adds to existing literature characterizing fatigue among patients who have received allogeneic HCT. In addition to collecting retrospective reports of fatigue, the current study examined daily reports of fatigue using an EMA-based measurement approach. Moreover, the study characterized sleep and activity behavioral patterns using actigraphy, a methodology that complements use of self-report measures in providing a more complete picture of these behaviors in real time.

Results from this study suggest several future directions. First, further exploration into daily relationships among sleep, activity, and fatigue is needed. To date, most studies that have looked at these relationships have done so at the group level; results from the present study suggest that interindividual and intraindividual variation are both important for gaining a richer understanding of the complexity of these factors and how they relate. Second, results support conducting research investigating the efficacy of interventions focused on ameliorating sleep disruption and reducing sedentary activity as means for lessening the severity and impact of fatigue on daily life in patients who have undergone HCT. While a majority of participants in the

present study did not meet criteria for clinically significant fatigue, a large minority continued to struggle with fatigue. Moreover, results from the present study suggest that many patients were sedentary for considerable periods of time and were experiencing disrupted sleep. Both of these behaviors should be targeted for intervention. Results from the present study further suggest that accelerometers represent a valuable methodology for measurement of behaviors alongside traditional self-report methods and should be incorporated into intervention research.

In conclusion, the present study adds to previous literature examining fatigue and its relationship with sleep and activity in a cancer population. Additionally, the study evaluates the relative merits of retrospective versus daily approaches to assessing fatigue. Major findings were that: nearly half of patients one to five years post-transplant experience clinically significant fatigue; retrospective measures continue to be valuable tools for assessing relationships of fatigue with actigraphy-assessed behavior; daily assessments of patient symptoms represent a valuable tool for exploring person-level relationships between fatigue and actigraphy-assessed behaviors. In addition to providing support for both retrospective and daily approaches to assessing fatigue, findings identify behavior targets (i.e., sedentary behavior and sleep disruption) for interventions designed to address cancer-related fatigue.

Table 1. *Demographic Characteristics (N = 82)*

Characteristic	n (%)
Age, years	
M (SD)	56 (11.7)
Range	25 - 74
Gender, No. (%)	
Male	39 (47.6)
Female	43 (52.4)
Ethnicity, No. (%)	
Not Hispanic	75 (91.5)
Hispanic	7 (8.5)
Race, No. (%)	
White	75 (91.5)
Nonwhite	7 (8.5)
Marital Status, No. (%)	
Married or living with partner	60 (73.2)
Not married	22 (26.8)
Education, No. (%)	
High school or less	14 (13.4)
College or more	68 (86.6)
Employment, No. (%)	
Work full-time or part-time	26 (31.7)
Retired	26 (31.7)
Disabled	23 (28.1)
Other	7 (8.5)
Income, No. (%)	
< 40K	24 (29.3)
$\geq$ 40K	58 (70.7)
Functional Status, No. (%)	
0	32 (39.1)
1	42 (51.2)
2	7 (8.5)
3	1 (1.2)
4	0 (0.0)

Table 2. *Medical Characteristics (N = 82)*

Characteristic	n (%)
Cancer type, No. (%)	
Leukemia	46 (56.1)
Non-Hodgkin lymphoma	14 (17.1)
Myelodysplastic Syndrome	7 (8.5)
Multiple Myeloma	6 (7.3)
Myeloproliferative Syndrome	5 (6.1)
Other	4 (4.9)
Ablation, No. (%)	
Myeloablative	41 (50.0)
Non-myeloablative	41 (50.0)
Donor type, No. (%)	
Related	28 (34.1)
Matched Unrelated	54 (65.9)
Time since transplant, days	
M (SD)	942 (449.3)
Range	370 - 1889
aGVHD grade, No. (%)	
0	26 (31.7)
I – II	49 (59.8)
III – IV	4 (4.9)
Unknown	3 (3.6)
cGVHD grade, No. (%)	
None	24 (29.3)
Mild	18 (22.0)
Moderate	32 (39.0)
Severe	7 (8.5)
Unknown	1 (1.2)

Note. aGVHD = acute graft-versus-host disease, cGVHD = chronic graft-versus-host disease.

Table 3. *Descriptive Statistics for Sleep Disruption and Symptoms*

Variables	n	Score range possible	*M (SD)*	Min	Max
Sleep Disruption					
Global sleep	82	0 – 10	8.15 (4.02)	1	18
Sleep duration	81	0 – 3	0.42 (0.70)	0	3
Nighttime disturbance	77	0 – 3	1.82 (0.76)	0	3
Sleep latency	76	0 – 3	1.38 (1.03)	0	3
Daytime dysfunction	82	0 – 3	1.22 (0.80)	0	3
Sleep efficiency	81	0 – 3	0.99 (1.08)	0	3
Sleep quality	82	0 – 3	1.26 (0.68)	0	3
Sleep medication use	82	0 – 3	1.10 (1.35)	0	3
Symptoms					
cGVHD	81	0 – 120	18.30 (11.65)	0	68
FACT-BMT	81	0 – 92	67.88 (11.07)	23	89

Note. All sleep disruption items derived from the PSQI. cGVHD = chronic graft-versus-host disease. FACT-BMT = functional assessment of cancer therapy-BMT specific subscale.

Table 4. *Actigraphy Descriptive Statistics (N = 82)*

Variables	*M (SD)*	Min	Max
Sleep disruption			
Sleep efficiency, %	78.93 (8.88)	51.79	93.19
SOL, min	8.61 (6.83)	0.43	28.57
WASO, min	99.29 (50.41)	24.86	288.86
TST, min	399.64 (63.64)	252.57	541.43
Sedentary behavior			
Sedentary time, %	55.41 (10.19)	36.22	77.45
Light time, %	35.86 (8.58)	15.24	53.84
Moderate time, %	8.73 (4.37)	0.50	24.90
Vigorous time, %	0.00 (0.00)	0.00	0.00
Very vigorous time, %	0.00 (0.00)	0.00	0.00

Note. All variables listed were aggregated across the 7 study days. SOL = Sleep onset latency which is represented in minutes, WASO = wake after sleep onset which is represented in minutes, TST = total sleep time which is represented in minutes, Sedentary time = percent spent in sedentary activity, Light time = percent spent in light activity, Moderate time = percent spent in moderate activity, Vigorous time = percent spent in vigorous activity, Very vigorous time = percent spent in very vigorous activity.

Table 5. *Fatigue Descriptive Statistics (N = 82)*

Variables	Score range possible	*M (SD)*	Min	Max
Aggregated daily fatigue				
Momentary fatigue	0 – 10	3.57 (1.91)	0	7.6
Fatigue interference	0 – 10	4.69 (2.05)	0	8.5
Most fatigue	0 – 10	3.25 (1.71)	0	7.75
Average fatigue	0 – 10	2.51 (2.01)	0	7.83
Summary fatigue				
FSI severity	0 – 10	3.54 (1.97)	0	8.5
FSI interference	0 – 10	2.47 (2.06)	0	8.0
FSI duration (# of days)	0 – 7	5.26 (2.22)	0	7.0
FSI duration (per day)	0 – 10	3.73 (2.38)	0	10.0

Note. Aggregated daily fatigue items were assessed as follows: (1) Momentary fatigue was assessed by asking patients, "Rate your level of fatigue right now," (2) Fatigue interference was assessed by asking patients, "Rate how much did fatigue interfere with your general level of activity today," (3) Most fatigue was assessed by asking patients, "Rate your level of fatigue at the time you felt most fatigued today," and (4) Average fatigue was assessed by asking patients, "Rate your average level of fatigue today." FSI = Fatigue Symptom Inventory.

Table 6. *Pearson Correlation Coefficients of Fatigue Variables with Sedentary Behavior, Sleep, and Symptom Variables*

Variables	Momentary fatigue	Fatigue interference	Most fatigue	Average fatigue	FSI severity	FSI interference	FSI duration (# of days)	FSI duration (per day)
Sedentary time	0.10	0.11	0.15	**0.23***	0.16	**0.26****	0.01	0.16
Light time	-0.08	-0.06	-0.14	**-0.23***	-0.14	**-0.22***	0.08	-0.12
Moderate time	-0.06	-0.13	-0.09	-0.08	-0.10	-0.17	-0.18	-0.13
Sleep efficiency	-0.17	**-0.24***	**-0.35****	**-0.37*****	**-0.37*****	**-0.29****	-0.17	**-0.31****
SOL	-0.07	0.02	-0.00	0.11	0.06	0.05	0.12	0.14
WASO	**0.26***	**0.32****	**0.42*****	**0.44*****	**0.43*****	**0.33****	0.17	**0.34****
TST	0.10	0.05	-0.03	0.00	0.00	0.03	-0.07	-0.04
PSQI Global	**0.40*****	**0.40*****	**0.49*****	**0.57*****	**0.50*****	**0.52*****	**0.29****	**0.52*****
cGVHD	**0.47*****	**0.45*****	**0.44*****	**0.54*****	**0.56*****	**0.59*****	**0.41*****	**0.56*****
FACT-BMT	**-0.49*****	**-0.44*****	**-0.47*****	**-0.54*****	**-0.56*****	**-0.61*****	**-0.38*****	**-0.49*****

Note. $* p < .05$, $** p <.01$, $*** p < .001$. Sedentary time = percent spent in sedentary activity, Light time = percent spent in light activity, Moderate time = percent spent in moderate activity, SOL = Sleep onset latency, WASO = wake after sleep onset, TST = total sleep time. PSQI = Pittsburgh sleep quality inventory. cGVHD = chronic graft-versus-host disease. FACT-BMT = functional assessment of cancer therapy-BMT specific subscale

Table 7. *Point Biserial Correlations Between Study Outcomes and Sociodemographic and Medical Variables*

Sociodemographic Variables	Aggregated sleep efficiency		Aggregated sedentary time	
	r_{pb}	p	r_{pb}	p
Gender (Female)	0.05	.68	-0.04	.73
Ethnicity (Hispanic)	-0.04	.72	0.13	.23
Race (White)	**0.19**	**.09**	0.04	.75
Marital Status (Married)	**0.31**	**.004**	-0.05	.67
Education (Some College)	**0.29**	**.008**	0.15	.18
Employment (Working)	0.08	.49	-0.14	.22
Age	0.14	.20	0.14	.22
Days Post Transplant	-0.13	.25	-0.15	.19

Note. Significant relationships ($p < .10$) are bolded and were controlled for in hierarchical regression models. Aggregated sleep efficiency and aggregated sedentary time were both derived from actigraphy.

Table 8. *Pearson Correlation Coefficients Among Fatigue Indices*

Variables	FSI severity	FSI interference	FSI duration (# of days)	FSI duration (per day)
Momentary fatigue	**0.90**	**0.76**	**0.57**	**0.74**
Fatigue interference	**0.90**	**0.74**	**0.66**	**0.73**
Most fatigue	**0.90**	**0.76**	**0.66**	**0.73**
Average fatigue	**0.85**	**0.84**	**0.54**	**0.77**

Note. All bolded items indicate *p* < .001.

Table 9. *Aim 2 Multivariable Hierarchical Regression Models with Sleep Efficiency as an Outcome*

	Predictors	R^2	β	*p*
Model 1	Step 1	0.13	-	-
	White	-	0.14	.17
	Married	**-**	**0.24**	**.03**
	College educated	**-**	**0.22**	**.04**
	Step 2	0.22	-	-
	White	-	0.13	.20
	Married	**-**	**0.21**	**.05**
	College educated	-	0.19	.07
	FSI severity	**-**	**-0.30**	**.003**
Model 2	Step 1	0.13	-	-
	White	-	0.14	.17
	Married	**-**	**0.24**	**.03**
	College educated	**-**	**0.22**	**.04**
	Step 2	0.14	-	-
	White	-	0.15	.17
	Married	**-**	**0.23**	**.03**
	College educated	**-**	**0.21**	**.05**
	Momentary fatigue	-	-0.13	0.22

Note. All bolded items indicate *p* < .05. FSI severity = summary fatigue, Momentary fatigue = aggregated daily fatigue.

Table 10. *Aim 3 Multivariable Hierarchical Regression Models with Sedentary Time as an Outcome*

		Predictors	R^2	β	*p*
Model 1	Step 1		0.01	-	-
		FSI severity	-	0.16	.16
Model 2	Step 1		-0.00	-	-
		Momentary fatigue	-	0.10	.39

Note. All bolded items indicate *p* < .05. FSI severity = summary fatigue, Momentary fatigue = aggregated daily fatigue.

Table 11. *Aim 4 Models 1 through 4 - Variability*

Daily Variables	Percent of Total Between-Person Variance (ICC)	Percent of Total Within-Person Variance
Momentary fatigue	56%	44%
Average fatigue	57%	43%
Sedentary time	71%	29%
Sleep efficiency	60%	40%

Table 12. *Aim 4 Models 5 and 6 - Predictors*

Models	Predictors	Momentary fatigue		Average fatigue	
		β	*p*	β	*p*
Model 5	Sedentary time	1.56	.45	**4.44**	**.04**
Model 6	Sedentary time	-0.58	.63	**3.92**	**.002**
Model 5	Sleep efficiency	-0.04	.07	**-0.09**	**<.001**
Model 6	Sleep efficiency	-0.02	.17	**-0.02**	**.04**

Note. All bolded items indicate *p* < .05.

```
Enrollment          Screened (n=513)

                    Excluded  (n=335)
                        • HCT other than allogeneic (n=95)
                        • <1 year post-HCT (n=88)
                        • >5 years post-HCT (n=86)
                        • History of other malignancies
                          (n=25)
                        • Recurrence/Progression (n=19)
                        • Non-English speaking (n=16)
                        • Non-ambulatory status (n=3)
                        • No cellphone/internet access (n=2)

                    Eligible (n=178)

                    Eligible/Pending at time of study close
                       (n=34)
                    Could not be reached / No appointment
                       (n=11)

Study Period        Consented (n=117)

                    Ineligible after consent (disease progression;
                    n=3)
                    Lost to follow-up (n=3)
                    Discontinued participation (n=1)

                    Completed Study (n=110)

                    Excluded from analysis (n=28)
                        • Did not complete questionnaire
                          (n=9)
                        • Completed questionnaire day other
                          than day 7 (n=9)
Analysis                • EMA criteria not met (n=6)
                        • No actigraphy data (actigraph
                          recording failure, actigraph never
                    Included in Analysis (n=82)   returned, n=3)
```

Figure 1. Flow Diagram

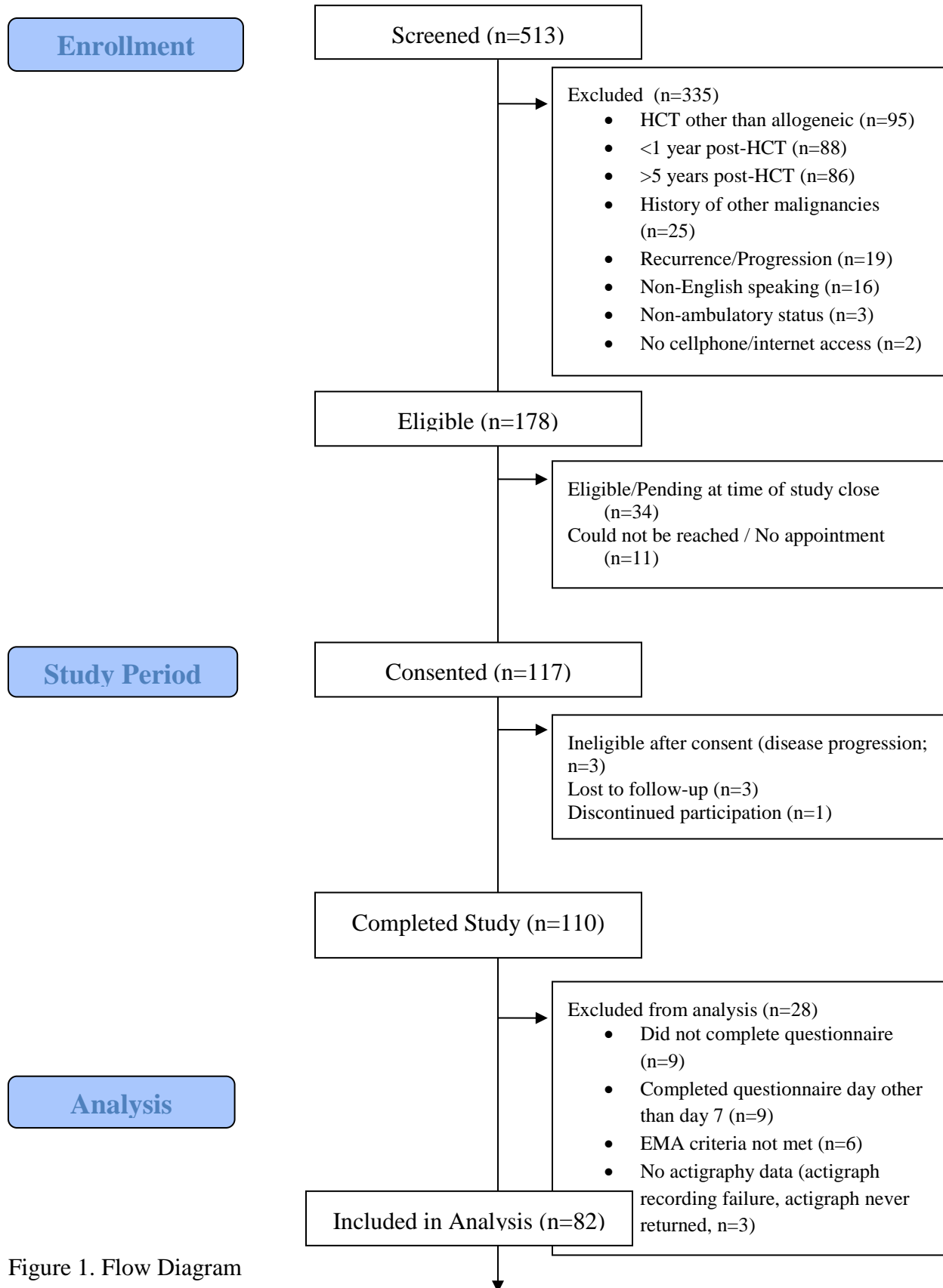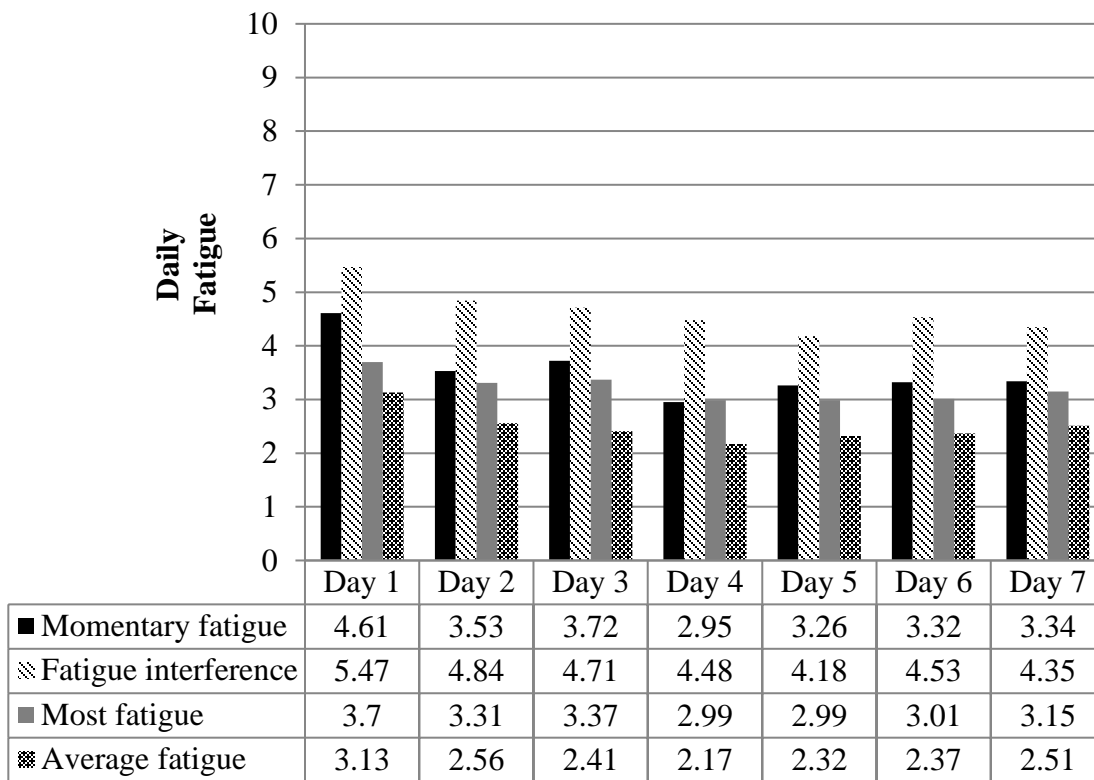|	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
■ Momentary fatigue	4.61	3.53	3.72	2.95	3.26	3.32	3.34
＼ Fatigue interference	5.47	4.84	4.71	4.48	4.18	4.53	4.35
■ Most fatigue	3.7	3.31	3.37	2.99	2.99	3.01	3.15
▨ Average fatigue	3.13	2.56	2.41	2.17	2.32	2.37	2.51

Figure 2. Daily Fatigue Means

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Appendices

Appendix A

May 22, 2017

Heather Jim, Ph.D.
H Lee Moffitt Cancer Center
12902 Magnolia Drive
MRC-PSY
Tampa, FL 33612

RE: **Expedited Approval for Initial Review**
IRB#: Pro00030395
Title: Contribution of Sleep Disruption and Physical Inactivity to Fatigue In Survivors of
  Allogeneic Hematopoietic Cell Transplant

Study Approval Period: 5/22/2017 to 5/22/2018

Dear Dr. Jim:

On 5/22/2017, the Institutional Review Board (IRB) reviewed and **APPROVED** the above
application and all documents contained within, including those outlined below.

Approved Item(s):
Protocol Document(s):
Protocol V1 2017.03.06.docx

Consent/Assent Document(s)*:
Informed Consent v1.doc.pdf

*Please use only the official IRB stamped informed consent/assent document(s) found under the
"Attachments" tab. Please note, these consent/assent documents are valid until the consent
document is amended and approved.

It was the determination of the IRB that your study qualified for expedited review which
includes activities that (1) present no more than minimal risk to human subjects, and (2) involve
only procedures listed in one or more of the categories outlined below. The IRB may review

research through the expedited review procedure authorized by 45CFR46.110. The research proposed in this study is categorized under the following expedited review category:

(5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).

(6) Collection of data from voice, video, digital, or image recordings made for research purposes.

(7) Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

As the principal investigator of this study, it is your responsibility to conduct this study in accordance with IRB policies and procedures and as approved by the IRB. Any changes to the approved research must be submitted to the IRB for review and approval via an amendment. Additionally, all unanticipated problems must be reported to the USF IRB within five (5) calendar days.

We appreciate your dedication to the ethical conduct of human subject research at the University of South Florida and your continued commitment to human research protections. If you have any questions regarding this matter, please call 813-974-5638.

Sincerely,

John A. Schinka, Ph.D.

John Schinka, Ph.D., Chairperson
USF Institutional Review Board

Contribution of Sleep Disruption and Physical Inactivity to Fatigue In Survivors of Allogeneic Hematopoietic Cell Transplant

Patient Questionnaire

Study ID#: ☐☐☐

Date Completed: ☐☐ / ☐☐ / ☐☐☐☐

For questions or comments, please contact:

Ashley Nelson, M.A.
Research Coordinator
Health Outcomes and Behavior, MRC-PSY
Moffitt Cancer Center
12902 Magnolia Drive
Tampa, FL 33612
Telephone #: 1-800-456-3434 ext. 4606
Ashley.Nelson@moffitt.org

GBI

1. Today's Date: ☐☐ / ☐☐ / ☐☐☐☐ (MM/DD/YYYY)

2. Date of Birth: ☐☐ / ☐☐ / ☐☐☐☐ (MM/DD/YYYY)

3. Age: ☐☐

4. Gender: ☐ Male ☐ Female

5. Ethnic Group: ☐ Hispanic/Spanish/Latino ☐ Not Hispanic/Spanish/Latino

6. Racial Background (check one):

☐ Black/African American American ☐ Indian or Alaskan Native

☐ White/Caucasian ☐ Native Hawaiian/Pacific Islander

☐ Asian ☐ More than one race (specify):_____

7. Marital status:

☐ Married or living with partner ☐ Divorced ☐ Widowed

☐ Single ☐ Separated

8. Completed Education:

☐ Less than 12 years ☐ Trade school ☐ College graduate

☐ High school graduate ☐ Some college ☐ Post-graduate degree

9. Current Employment Situation (check the one box that applies the most):

☐ Working full time ☐ Working part time ☐ Seeking work

☐ On leave with pay ☐ On leave without pay ☐ Disabled

☐ Student ☐ Homemaker ☐ Retired

10. What is your approximate annual gross income:

☐ Less than $10,000 ☐ $20,000 - $39,999 ☐ $60,000 - $100,000

☐ $10,000 - $19,999 ☐ $40,000 - $59,999 ☐ Greater than $100,000

☐ Prefer not to answer

11. What is your height? _____

12. What is your weight (in pounds)? ☐☐☐

13. Please check the box next to the option that describes your current level of activity:

☐ Fully active, able to carry on all pre-disease performance without restriction.

☐ Restricted in physically strenuous activity but ambulatory and able to carry out work of a

light or sedentary nature, e.g. light housework, office work.

☐ Ambulatory and capable of self care, but unable to carry out any work activities. Up and

about more than 50% of waking hours.

☐ Capable of only limited self care, confined to bed or chair more than 50% of waking hours.

☐ Completely disabled. Cannot carry on any self care. Totally confined to bed or chair.

14. Have you used any prescription or non-prescription medications to help with sleep in the past

30 days? _____ Yes _____ No

If yes, what medication(s) have you taken? _____

_____

Activity Report

Instructions: Circle the *one* response that *best* matches your main daily activity on each day you wore the study watch.

Day 1

☐ Working outside the home   ☐ Working within the home (at home job)

☐ Leisure activities outside the home   ☐ Leisure activities within the home

☐ Other, please describe: _____

Day 2

☐ Working outside the home   ☐ Working within the home (at home job)

☐ Leisure activities outside the home   ☐ Leisure activities within the home

☐ Other, please describe: _____

Day 3

☐ Working outside the home   ☐ Working within the home (at home job)

☐ Leisure activities outside the home   ☐ Leisure activities within the home

☐ Other, please describe: _____

Day 4

☐ Working outside the home   ☐ Working within the home (at home job)

☐ Leisure activities outside the home   ☐ Leisure activities within the home

☐ Other, please describe: _____

Day 5

☐ Working outside the home   ☐ Working within the home (at home job)

☐ Leisure activities outside the home   ☐ Leisure activities within the home

☐ Other, please describe: _____

Day 6

☐ Working outside the home   ☐ Working within the home (at home job)

☐ Leisure activities outside the home   ☐ Leisure activities within the home

☐ Other, please describe: _____

Day 7

☐ Working outside the home   ☐ Working within the home (at home job)

☐ Leisure activities outside the home   ☐ Leisure activities within the home

☐ Other, please describe: _____

Appendix C

Daily Ratings

1. Rate your level of fatigue **right now**:

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Not at all   As fatigued
fatigued   as I could be

2. Rate how much fatigue interfered with your general level of activity **today**:

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

No   Extreme
interference   interference

3. Rate your level of fatigue at the time you felt **most** fatigued today:

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Not at all   As fatigued
fatigued   as I could be

4. Rate your **average** level of fatigue today:

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Not at all   As fatigued
fatigued   as I could be

5. What time did you go to bed last night with the intent to fall asleep? ☐☐ **:** ☐☐

6. What time did you wake up this morning? ☐☐ **:** ☐☐