1-2018

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Bachelor of Science
Psychology
Loyola University New Orleans, 2014

Master of Science
Psychology
Florida Institute of Technology, 2016

A doctoral research project submitted to Florida Institute of Technology
in partial fulfillment of the requirements for the degree of

Doctor of Psychology
in
Clinical Psychology

Melbourne, Florida
January 2018

The undersigned committee hereby recommends that the attached document be accepted as fulfilling in part the requirements for the degree of Doctorate in Clinical Psychology.

# Posttraumatic Stress as a unique contributor to related health outcomes and healthcare utilization in adult survivors of childhood cancer

A Doctoral Research Project

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# Abstract

TITLE: Posttraumatic Stress as a unique contributor to related health outcomes and healthcare utilization in adult survivors of childhood cancer

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Despite its significance in medical populations, research on posttraumatic stress (PTSS) in this population is limited in existing studies by small sample sizes and lack of follow-up data. This manuscript provides review of literature on behavioral health outcomes, which include neurocognitive and psychosocial late effects of disease/treatment, engagement in health-promoting or risk behaviors, and healthcare utilization in the childhood cancer survivor population. The current study examined the impact of PTSS on these domains of functioning, using data from the Childhood Cancer Survivor Study (CCSS), a multi-institutional sample.

Results indicated 13.7% of survivors in our sample experienced PTSS. Survivors with PTSS were at significantly greater risk for emotional distress, poor health-related quality of life, and neurocognitive impairment than survivors without PTSS. PTSS also variably affected healthcare utilization, defined as frequency of contact with the healthcare system for medical services. These findings emphasize the role of PTSS in psychosocial and behavioral health outcomes in survivors already at increased risk for late effects and highlight the need to address PTSS in future preventative interventions.

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# Acknowledgements

I would like to start by thanking Dr. Kristi Van Sickle and Dr. Vida L. Tyc for their unwavering support, assurance and guidance throughout this project and my own professional development. I would also like to thank Dr. Nicholson and Dr. Follette for taking the time to serve on my committee, for their feedback, and perspective. Thank you to each of my close friends and family members who also supported me with endless encouragement and love. Lastly, I would also like to thank the CCSS team at St. Jude Children's Research Hospital, who made this research possible through grant funding and particularly through the guidance and input of Dr. Kevin Krull, Ph.D., Dr. Deo Kumar Srivastava, Ph.D. and Mingjuan Wang, M.S.

# Background

## Posttraumatic Stress Disorder (PTSD)

Posttraumatic Stress Symptoms (PTSS) include a unique manifestation of distress experienced by those who have been exposed to trauma as defined by a perceived threat to one's own life or that of a loved one. This is characterized by a) intrusive symptoms, such as recurrent, involuntary thoughts of a stressor; b) avoidance of external cues or reminders of the stressor, and c) hypervigilance, a heightened state of sensory arousal and behavioral reactivity following exposure to serious injury, interpersonal violence, death, or perceived threat of death (American Psychiatric Association, 2013). According to the National Comorbidity Survey (Yehuda, 2001), the prevalence of PTSD in the general population ranges from 5-6% of men and 10-14% in women. Subsequent review of special populations estimates the disorder to be most prevalent in those exposed to interpersonal violence, with 55% of sexual assault victims developing the disorder as compared to 7.5% of individuals involved in vehicular accidents (Yehuda, 2001).

Although less frequently discussed in the literature, a portion of medical patients also experience posttraumatic stress related to life-threatening illness, with pediatric cancer survivors yielding prevalence rates from 8-20% (Lee, 2006; Meeske, Ruccione, Globe & Stuber, 2005; Schwartz & Drotar, 2005; Schwartz, Kazak, Derosa, Hocking, Hobbie & Ginsberg, 2001; Stuber et al., 2010). Within the Childhood Cancer Survivor Study (CCSS) cohort, survivors were at four times greater risk of developing PTSD when compared to siblings, with symptoms often occurring in adulthood  (Stuber et al., 2010). It should be noted that most survivor studies report symptom levels of posttraumatic stress symptoms (PTSS), while few have used measures that allow for categorical diagnoses of PTSD (Meeske et al, 2005). In this study, PTSS was defined by an adapted form of the DSM-IV PTSD Checklist (PCL civilian).

While disease and treatment type have not been found to have a significant impact on the development of PTSS in survivors (Kazak et al., 2010; Stuber et al, 2010), the survivor's perception of their cancer experience and perceived intensity of treatment have been found to affect levels of distress (Lee, 2006). Age at cancer diagnosis has also been identified as a significant predictor of PTSS, with those diagnosed in adolescence experiencing poorer outcomes than those diagnosed at younger ages (Kazak et al., 2010; Stuber et al, 2010). This is seen across psychosocial outcomes, as the longer and more challenging treatment of adolescent cancers can delay or interrupt important developmental tasks (e,g, autonomy, peer pressure, interpersonal relationships with peers) and cause psychological distress that persists well into adulthood (Kazak et al., 2010). Adolescents also possess the awareness and cognitive maturity to remember and reflect on their cancer experience, and better understand the implications of their cancer treatment, which may further increase their distress (Kazak et al., 2010; Stuber et al, 2010). Socio-emotional factors, such as coping abilities and vulnerability to social exclusion, are also likely factors which contribute to negative views of self and perceptions of the event (Schwartz & Drotar, 2005) during this developmental stage.

In general, studies show that psychosocial difficulties and PTSS become more prevalent over time and often peak in young adulthood (Stuber et al., 2011), years after cancer treatment has ended. In addition to the tasks expected of any individual in this developmental phase of life, young adulthood is the time when late effects typically emerge and serve as a catalyst for recognition of the survivor's perceived limitations. As they approach adulthood, survivors are expected to incorporate formation of identity and self-concept, adaptation to personal autonomy, social functioning, and higher educational or vocational expectations (Meeske, Ruccione, Globe & Stuber, 2005; Stuber et al., 2010). Many survivors with PTSS struggle with these developmental tasks, secondary to the physical and cognitive impact of their cancer treatment. As a result, some young adult survivors report poor perceptions of health status, diminished Health Related Quality of Life, low satisfaction with healthcare, increased adjustment difficulties, psychosocial distress, and a higher perceived impact of prior illness on educational and vocational accomplishments (Meeske, Ruccione, Globe & Stuber, 2001; Schwartz & Drotar, 2005; Schwartz et al., 2011; Kazac et al., 2010).

## Late Effects

Medical advances in treatment of pediatric cancer have resulted in increasingly higher survivorship rates. Specifically, between the years of 2004-2010, it was found that more than 80% of patients diagnosed with cancer prior to age 20 achieved 5-year survival (Howlader, Noone, Krapacho et al [eds], 2011). With survivorship rates rising, a growing amount of attention has been given to the long- term impact of treatment, which often increases risk for chronic illness and second malignant neoplasms (Lee, 2006; Oeffinger, Nathan & Kremer, 2008; Stuber et al., 2010). This is an important area of research as survivors of pediatric cancer experience a variety of late-effects, or conditions and outcomes that arise 5 or more years after disease remission, with some emerging decades after treatment (Lee, 2006; Oeffinger, Nathan & Kremer, 2008; Stuber et al., 2010). Currently, it is estimated that nearly 50% of survivors experience moderate to severe late effects which include medical conditions, such as cardiovascular disease and fertility problems, as well as poor neurocognitive and psychosocial outcomes (Oeffinger, Nathan & Kremer, 2008). Survivors with PTSS are reported to be more likely among this group, reporting more moderate-severe late effects than those without PTSS (Meeske, Ruccione, Glove, & Stuber, 2001). Although some late effects can be effectively managed with pharmacological treatment, it is estimated that 35% of survivors develop disabilities that significantly impair their quality of life (Brinkman et al., 2013 [b]; Lee, 2006).

### Neurocognitive late effects.

Neurocognitive impairment is one of the most common late effects, with executive functioning deficits occurring in approximately 20-40% of survivors (Ford, Barnett & Werk, 2014; Krull et al., 2011). The Childhood Cancer Survivor Study Neurocognitive Questionnaire (CCSS-NCQ) was developed to assess neurocognitive impairment frequently seen in survivors. Abilities assessed include initiating and completing tasks, emotional reactivity, frustration tolerance, organization of materials or planning of events, attention, short-term memory, and long-term memory (Kenzik et al., 2015; Recklitis et al., 2006). Using the CCSS-NCQ, it has been estimated that survivors of non-central nervous system malignancies are at 50% higher risk of impairment than healthy siblings, particularly in domains related to task efficiency, memory, and emotional regulation (Kadan-Lottick et al., 2010; Krull et al., 2015). Survivors who were diagnosed before 6 years of age, were female, received cranial radiation, or had hearing problems demonstrated the greatest impairment (Kaden-Lottick et al., 2010). Survivors of central nervous system (CNS) malignancy, who received high-dose cranial radiation to frontal areas of the brain, were found to demonstrate significantly greater impairment in the areas of attention, processing speed, memory, task efficiency, and emotional regulation as compared to those with non-CNS malignancies, on the same measure (Ellenberg et al., 2009; Krull et al., 2015). Survivors presenting with symptoms of anxiety and depression were even more impaired in memory and task efficiency, as well as emotional regulation (Kaaden-Lottick et al.,2010).

Risk for neurocognitive impairment varies based on treatment type with higher rates of impairment reported in those who have been treated with cranial radiation, methotrexate, corticosteroids (dexamethasone), high-dose cytarabine, placement of a ventriculoperitoneal (VP) shunt, or had suffered a cerebrovascular incident (Ellenberg et al., 2009; Nathan & Kremer, 2008; Oeffinger). Additionally, patients treated with intrathecal methotrexate showed significantly greater impairment than those treated with systemic methotrexate only (Kaden-Lottick, 2010). Some of these effects may, in part, result from white matter changes in patients treated with these neurotoxic regimens (Kaden-Lottick, 2010).

Earlier studies reported significant cognitive deficits among children who received cranial radiation therapy at 18-24 Gy as prophylaxis against CNS leukemia, as well as those who received high dose systemic and intrathecal chemotherapies (Brown et al., 1992; Cousens, Waters & Stevens, 1988; Meadows et al., 1981; Mulhern, Wasserman, Fairclough & Ochs, 1988; Ochs et al.,1991). Likewise, survivors of CNS tumors requiring neurosurgery and high dose cranial radiation therapy have been found to experience global cognitive declines as severe as 20-40 IQ points (Mulhern, Wasserman, Farclough & Ochs, 1988). Although patients treated with contemporary approaches are expected to suffer less severe neurocognitive deficits, due to protective changes in treatment protocol, these individuals will likely experience mild declines that undermine daily functioning (Oeffinger, Nathan & Kremer, 2008). These underlying executive deficits, reported across studies, have been shown to adversely affect emotional, educational, and vocational functioning as well as achievement of adult life goals among survivors (Ellenberg et al., 2009; Kaden-Lottick et al., 2010).

Chronic stress in childhood and adolescence has been shown to correspond with both structural and chemical changes in the brain, most often manifested as emotional dysregulation and impairments in memory (Lupien, McEwen, Gunnary & Heim, 2009). High levels of PTSS in survivors have also been hypothesized to further exacerbate functional deficits associated with neurocognitive impairment (Meeske, Ruccione, Globe, & Stuber, 2001). Additionally, chronic PTSS is expected to have an indirect effect on cognition through higher levels of sleep disturbance and fatigue (Earle, Neville & Fletcher, 2007; Phillips-Salimi, Lommel & Andrykowski, 2011), each of which have been reported to lead to impaired task efficiency and memory among survivors (Clanton et al., 2011). In fact, the degree of neurocognitive dysfunction associated with PTSS-related health effects has been estimated to be comparable to the level of neurocognitive impairment resulting from high dose cranial radiation therapy (Clanton et al., 2011). These findings suggest the importance of targeting PTSS-related factors to improve functional outcomes among survivors.

### Psychosocial late effects.

Survivors often experience psychosocial late effects, which include mental health disorders as well as conditions such as chronic pain and fatigue (Oeffinger, Nathan & Kremer, 2008). Prevalence rates for psychosocial late effects differ across studies, due to variability in the outcome measures employed as well as the way in which distress or clinical impairment is defined (Brinkman et al.,2013 [b]; Meeske et al., 2001; Zeltzer, et al., 2009). Research from the CCSS cohort suggests 17% of cancer survivors experience symptoms of depression or anxiety, being twice as likely as siblings to report these outcomes (Oeffinger, Nathan & Kremer, 2008 & Zeltzer et al., 2009). However, this cross-sectional study was limited as it assessed symptoms experienced by survivors at a single point in time. Several long-term studies of psychological distress in survivors of childhood cancer have suggested that while most survivors of childhood cancer present with minimal distress (Michel et al., 2010; Zeltzer et al., 2008), some subsets report significant and variable levels of anxiety, depression, and somatization (Brinkman et al.,2013 [b]). For example, higher levels of depression are reported among survivors with CNS malignancies when compared to siblings and US norms, while greater somatic symptoms have been reported for survivors of Hodgkins and non-Hodgkins lymphoma (Zebrack et al., 2004; Zeltzer et al., 2008)). More recent longitudinal examination of distress among survivors at points in time was consistent with previous cross-sectional reports showing increased distress among subgroups of survivors (Brinkman et al., 2013 [b]). Specifically, survivors most at risk for chronic distress were those with worsening physical health and pain over time, suggesting that survivors with physical health morbidities should be regularly screened for mental health difficulties (Brinkman et al., 2013 [b]).

The reliance on survivors' self-report of psychosocial morbidity across most studies raises questions as to whether the reported rates accurately estimate their experienced symptoms. Brinkman and colleagues (2013 a) found that 19% of survivors in the CCSS cohort initiated antidepressant medication over a 10-year follow-up period; increased use of medication was associated with increased psychological distress over time. Additionally, survivors were significantly more likely to utilize antidepressants and other psychoactive medications when compared to sibling controls (Brinkman et al., 2013 [a]). Whether symptom rates reported across studies are a low estimate of actual distress secondary to effective pharmacological management of their symptoms or whether medication seeking behavior reflects elevated distress symptoms that may be underreported remains unclear. Longitudinal studies that monitor the course of symptoms concurrently with medication utilization are warranted to better understand the trajectory of psychological distress in survivors of childhood cancer.

Posttraumatic stress has been demonstrated to exacerbate psychosocial distress in survivors, with greater impairments seen in survivors with PTSS than those without. Schwartz & Drotar (2006) found that survivors with symptoms of PTSS reported significantly worse Health Related Quality of Life, more depressive symptoms and mood instability, and lower life satisfaction than a comparison group without PTSS. Similarly, a comparison of survivors of childhood cancer with and without a PTSD diagnosis, aged 18-37 years of age and off treatment for approximately 11 years, indicated that those with PTSD reported higher levels of anxiety, somatization, obsessive-compulsiveness, depression, paranoid ideation and interpersonal sensitivity than survivors without PTSD. Survivors in this study were dichotomized into a PTSD group and non-PTSD group based on formal DSM-IV diagnostic criteria for PTSD (Meeske, Ruccione, Globe & Stuber, 2001). These collective findings suggest that survivors with PTSS/PTSD have significant psychological comorbidity that warrants ongoing evaluation and intervention. Psychological late effects combined with neurocognitive deficits are often reflected in higher levels of occupational and employment difficulties as well as interpersonal problems (e.g. divorce) in survivors (Phillips, Salimi, Lommel, &

Andrykowski, 2011; Zeltzer et al., 2009). The impact of a diagnosis of cancer on interpersonal functioning has been well studied. Beginning at school-age and adolescence, young cancer patients are reported to experience a higher rate of familial conflict throughout the course of treatment, characterized by parental distress and emotional or behavioral disturbances in siblings (Forbasch & Thompson, 2003). Conflict continues throughout childhood, extending to multiple settings, as adolescent patients are likely to experience peer conflict and insecurity resulting from factors such as changes in body image and social isolation secondary to their disease (Forbach & Thompson, 2003). These difficulties carry through adulthood as survivors report fear that disease relapse or late effects, such as infertility problems, will impact their relationships. This often manifests in higher reports of isolation and hostility among adult survivors, despite an increased stated need for intimacy, when compared to the general population (Forbach & Thompson, 2003).

## Health Behaviors

It is important that cancer survivors practice a healthy lifestyle to reduce their risk for developing chronic cardiac, pulmonary, and other health conditions that may result from treatment of their disease. Because of their increased risk for late effects, even low to moderate levels of negative health behaviors in the survivor population are alarming and deserve clinical attention (Ford, Barnett, & Werk, 2014). Studies report variation in prevalence of health behaviors in adult survivors, with rates of tobacco use ranging from 8-29% and excessive alcohol use ranging from 8-84%

(Ford, Barnett & Werk, 2014). Twenty-eight percent of survivors in the CCSS cohort reported having smoked while 17% were identified as current smokers (Butterfield et al., 2003). Although prevalence rates for illicit drug use among survivors are relatively low and typically lower than the general population, recent studies suggest that a broader classification of drug use would yield higher rates. For example, adolescent and young adult survivors of childhood cancer demonstrate significantly less experimentation with cannabis when compared to their healthy peers, but show a significantly higher rate of abuse of pain medication for non-medical purposes (Bauld, Toumbourou, Anderson, Coffey & Olsson, 2005). Examination of a young adult cohort of 117 acute myeloid leukemia (AML) survivors found that 22% of survivors reported use of tobacco, approximately 25% reported binge drinking, and 10% reported current marijuana use in the last 30 days (Schultz et al., 2010); however, less than 10% of survivors reported engaging in cocaine, heroin, or methamphetamine use during that same period.

When examining nutritional status, studies report that less than 25% of survivors eat balanced meals and a significant number of survivors do not practice good dietary habits (Mulhern et al., 1995). Many adolescent and young adult survivors do not meet the guidelines for fruit and vegetable consumption, or caloric intake (Demark-Wahnerfried et al., 2005) and their dietary sodium and added sugar intake are often in excess of recommended levels (Robien, Ness, Kllesges, Baker & Gurney, 2008). Relatedly, less than half of the survivors in the CCSS cohort meet national guidelines for weekly exercise (Krull et al., 2011). Furthermore, although skin cancer is the one of the most common second neoplasms among childhood cancer survivors (Perkins et al., 2005), only 29% of young adult survivors report practicing sun protective behaviors to minimize these risks (Zwemer, Mahler, Werchiniak & Recklitis, 2012).

Numerous factors have been identified to influence the practice of health behaviors, including, but not limited to demographic factors, treatment variables, perceptions of risk, self-esteem, neurocognitive impairment, decision making skills, and emotional distress (Krull et al., 2011). For example, older age at diagnosis has been associated with more frequent engagement in health risk behaviors such as physical inactivity and unhealthy diet (Ford, Barnett & Werk, 2014). Similarly, risk factors for continued smoking among childhood cancer survivors include being older at diagnosis, being younger than age 14 at time of smoking initiation, not having graduated high school, and receiving cranial radiation treatment (De Moor et al., 2011, Miliam, Sussman, Ritt-Olson, 2000). In addition to tobacco use (Hollen & Hobbie, 1993; Miliam, Sussman, Ritt-Olson, 2000), CNS treatment has been positively associated with the practice of other risky behaviors such as poor diet (Landy et al., 2013) and inactive lifestyle (Ness et al., 2009) among young survivors. Low self-esteem, social withdrawal, and stress have also been associated with physical inactivity (Krull et al., 2010), while poor decision-making skills correspond with higher levels of substance use (Hollen, Hobbie, Donnangelo, Shannon, Erickson, 2007). Neurocognitive impairment has also been found to magnify the survivor's risk for not engaging in protective health behaviors (Krull et al., 2011)

In addition to the multitude of risk factors described above, PTSS has also been demonstrated to play a significant role in the health behavioral practices and associated health outcomes among childhood cancer survivors (Clarke & Eiser, 2007; Santacrose & Lee, 2006; Schwartz et al., 2012). Specifically, the increase in depression and anxiety related to PTSS, for example, can increase engagement in more harmful health behaviors and fewer health promoting behaviors among childhood cancer survivors, thereby exacerbating the survivor's late effects. For example, emotional distress has been found not only to predict smoking, but may also increase the intensity of tobacco use, and lead to heavier drinking among survivors (Hollen & Hobbie, 1993; Zeltzer et al., 2009). Additionally, PTSS has been related to the survivor's diminished self-efficacy, reduced self-awareness, and poor self-management skills, each of which has been found to interfere with the adoption of healthy lifestyle practices (Santacrose & Lee, 2006). Lastly, survivors with PTSS who avoid cancer- related information may not fully understand their health risks, ask the important questions, or acquire the information necessary to facilitate behavioral change to improve their health status (Lee, 2006; Tyc, Rai, Lensing & Klosky 2003).

Although considerable attention has been paid to tobacco use and smoking cessation interventions for survivors, fewer studies have focused on interventions that address alcohol and drug use, healthy nutrition, or physical activity in this high-risk group (Ford, Barnett & Werk, 2014). Much of the health behavior research conducted to date has been limited by small sample sizes, lack of standardized methodologies to assess health behaviors, failure to account for the influence of psychosocial risk factors such as PTSS, and failure to examine the full range of health behaviors relevant to the survivor's health status within a single cohort (Ford, Barnett, Werk, 2014). This is important as studies have demonstrated that survivors who engage in at least one health-risk behavior, such as smoking, typically engage in other health-risk behaviors and practice fewer positive health behaviors (Butterfield et al., 2003). For example, 82.8% of survivors who identified as smokers in one study engaged in at least one other risk behavior (characterized as lack of proper nutrition or physical activity, alcohol use, and lack of engagement with healthcare), with 38.5% engaging in two others, and 24.4% engaging in three unhealthy behaviors in addition to smoking (Butterfield et al., 2003). These collective findings suggest that targeting multiple health risk behaviors, while simultaneously reinforcing positive health behaviors and addressing the psychological morbidity of PTSS, may be necessary to promote maximal health-related behavioral change among survivors.

## Medical Screening and Healthcare Utilization

Appropriately addressing the long-term sequelae of their cancer diagnosis and treatment requires survivors engage proactively in sustained follow-up risk-based care and medical screening. The Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers were established by the Children's Oncology group, with the most recent (4th ed.) released in 2013, to promote risk-based care and provide information on suggested periodic evaluations as well as specific therapeutic modalities based on the survivor's prior treatment exposure and personal risk-factors (Oeffinger, Nathan, Kremer, 2008). A study by Krull et al. (2011) found, however, that survivors do not generally obtain the full recommended medical care per these guidelines, with only 17% of survivors receiving risk-based care, 58% receiving general healthcare and 12% receiving no medical treatment. Failure to receive recommended screenings and treatment may be due, in part, to lack of awareness regarding risks or understanding of the guidelines by both the survivor and primary care provider and lack of access to services (Oeffinger et al, 2004).

While socioeconomic factors such as lack of access to health insurance, male gender, and ethnic minority status influence low rates of healthcare utilization, cognitive and psychosocial and factors also play a substantial role (Krull et al., 2011; Oeffinger et al., 2004). Neurocognitive deficits, particularly impaired memory and executive functioning, have been found to be associated with a lack of adherence to guidelines for recommended screenings and medical care, while increased pain or somatic complaints typically predict more involvement in risk-based care (Krull et al., 2011; Nathan et al, 2008). In an earlier study of childhood cancer survivors, Oeffinger (2004) reported that survivors treated with high-risk therapies were more likely to report cancer-related medical visits. However, the likelihood of reporting a cancer-related medical visit or general physical exam decreased significantly with age and increasing time from diagnosis (Oeffinger, 2004). This trend is concerning as healthcare use declined among survivors at a time when the incidence of many late effects, (i.e. second cancers, cardiovascular disease, osteoporosis) emerged. For optimal risk-based care to occur, it is important survivors learn to effectively communicate with providers about health care needs, and that healthcare systems find ways to promote survivor engagement in their personal health care.

The relationship between emotional distress and healthcare utilization has been less well- established, given the variability in findings across studies. Specifically, some studies have shown that symptoms of anxiety and depression have no effect on healthcare use (Krull et al., 2011), while others suggest patients with greater psychological distress engage in more risk-based care (Nathan et al., 2008). Rates of health care use may also depend on the survivor's motivation for seeking out care. For example, studies have shown that although survivors with increased emotional distress are often more likely to seek out risk-based care than those who are psychologically healthy, they expect this care to be supportive (information about social or health issues) rather than clinically focused (identification and treatment of medical problems) (Krull et al., 2011; Michel, Greenfield, Absolom, Ross, Davise & Eiser, 2009; Nathan et al., 2008). Increased compliance with medical follow-up may, therefore, depends on a broad range of available services being offered within healthcare systems that match the types of information and/or level of support that survivors expect and prefer.

Health beliefs, perceptions of health status, and satisfaction with health care have similarly been shown to influence the survivor's adherence to recommended screening, monitoring, and treatment (Cox, Zhu, Hudson, Robison, Oeffinger, 2013; Ford, Barnett & Werk, 2014; Michael, Greenfield, Absolom, Ross, Davise & Eiser, 2009). These studies have demonstrated that survivors who report an increased sense of vulnerability to health risks and lower self-efficacy for health behavioral change may be more inclined to seek medical care. However, these studies did not account for PTSS distinctly, or degree of health problems among their samples of survivors. PTSS may, in fact, negatively impact engagement with healthcare secondary to the survivor's health beliefs and health-related competencies. Although the direct association between PTSS and healthcare utilization was not assessed in this study, Schwartz et al (2012) found that survivors with PTSS reported lower perceptions of health-related competence (i.e. less adaptive beliefs about their health status) as well as more dissatisfaction with their health care than survivors without PTSS. Increased PTSS was also reported among survivors with more health problems. It is likely, therefore, that survivors with PTSS who experience multiple health problems, feel dissatisfied with their care, and report less adaptive health beliefs, may choose to disengage from recommended follow-up medical care. The avoidance or arousal associated with PTSS may further interfere with the survivor's motivation to adhere to recommended health care visits (Schwartz et al., 2012). Therefore, interventions that attempt to modify survivor's beliefs about health competence and healthcare satisfaction may not only serve to reduce PTSS in this population, but also to facilitate better engagement in recommended follow-up medical care.

# Statement of Purpose

In general, research to date established that long-term adult survivors of childhood cancer report minimal psychological distress but practice unhealthy lifestyles and report low rates of healthcare utilization (Krull et al., 2011; Nathan et al., 2008). Moreover, some subgroups of survivors are more vulnerable to psychological and neurocognitive difficulties and overall poorer quality of life (Brinkman et al., 2013 [b]; Kazak et al., 2010; Stuber et al., 2010). Although neurocognitive, psychosocial, health behavior, and healthcare utilization outcomes are highly interrelated (Krull et al., 2011), few studies have examined multiple outcomes in a single cohort of survivors. PTSS is prevalent among childhood cancer survivors and has been found to exacerbate these reported outcomes and late effects (Meeske et al., 2011; Stuber et al., 2010; Schwartz et al., 2012). Additionally, because there is considerable overlap in the characteristics of PTSS and measures of psychosocial distress employed in other studies (Meeske et al., 2001; Santacrose & Lee, 2006), PTSS has rarely been included as an independent predictor in studies conducted with survivors. Methodologically, studies of PTSS in childhood cancer survivors have been plagued by small sample sizes, low response rates, and limited follow-up data (Lee, 2006; Meeske et al., 2001; Schwartz & Drotar, 2005).

This study built on existing literature by examining PTSS as a contributing factor in long-term cognitive, emotional, and behavioral health outcomes among survivors, utilizing a large and well-characterized sample with extensive follow-up data. This sample allowed for evaluation of demographic and treatment related variables, as well as outcomes that may arise years after cancer treatment. Unlike prior studies that typically follow survivors for a limited 5- or 10-year period, this study examined PTSS and related outcomes in survivors for an extended follow-up period. The use of long-term follow-up data is critical in this population, as many survivors begin to experience psychosocial, neurocognitive and other health-related effects later in life (Brinkman et al., 2013, [b]). The proposed study not only addressed the impact of PTSS in a large representative sample, but also sought to further add to the understanding and identification of at-risk survivors who may benefit from additional forms of long-term follow-up care.

## Aims and Hypotheses

Aim 1**:** To examine the association between posttraumatic stress and concurrent neurocognitive and emotional health conditions in adult survivors of childhood cancer

Hypothesis 1.1: PTSS will be associated with lower perceived neurocognitive functioning in all domains

Hypothesis 1.2: PTSS will be associated with higher emotional distress, perceived cognitive and physical limitations and diminished quality of life

Aim 2: To examine the association between posttraumatic stress and health behaviors (i.e. smoking, physical activity) in adult survivors of childhood cancer

Hypothesis 2.1: PTSS will be associated with more negative health behaviors

Hypothesis 2.2: PTSS will be associated with fewer positive health behaviors

Aim 3: To explore the association between posttraumatic stress and healthcare utilization (i.e. level of primary and risk-based care, presence of medical screening) in adult survivors of childhood cancer

Hypothesis 3.1: Participants who report clinically significant avoidance will demonstrate lower healthcare utilization compared to those who report posttraumatic stress without significant avoidance symptoms

Hypothesis 3.2: Participants who endorse clinically significant hyperarousal will demonstrate higher healthcare utilization, compared to those who report posttraumatic stress without this elevation

# Methods

## Sample

The Childhood Cancer Survivor Study utilizes a multi-institutional sample of individuals who have a history of diagnosis and treatment of leukemia, central nervous system malignancy (excluding meningioma and craniopharyngioma), Hodgkin Disease, non-Hodgkin lymphoma, neuroblastoma, soft tissue sarcoma, kidney cancer or bone cancer. These individuals were diagnosed prior to the age of 21, between the years of 1970 and 1986, who achieved 5-year survival. Baseline data collection took place between 1994-1998 among survivors from the United States and Canada (Robison et al., 2008) and follow-up data collection occurred between 2000-2005 (Robison et al., 2009). Additionally, siblings of these survivors were administered questionnaires and serve as a normative control group in multiple measures.

This analysis examined the reports of survivors from the original cohort who completed the 2003 follow-up survey, completed between the years of 2000-2005. As the aim of this study was to examine posttraumatic stress as a unique predictor of outcomes, the portion of survivors who did not show signs of posttraumatic stress were used as a reference group in the analysis. Siblings were excluded from the analyses as only 2% of siblings, as compared to 9% of survivors, in this cohort have demonstrated signs of Posttraumatic Stress Disorder (Stuber et al., 2010).

## Measures

### The Childhood Cancer Survivor Study Neurocognitive Questionnaire (CCSS-NCQ).

Comprised of selected items on the 2003 follow-up survivor and sibling questionnaires, this is the primary outcome measure of neurocognitive health. This measure, created by researchers within the CCSS, assesses for executive functioning deficits commonly seen in those who have undergone radiation and antimetabolic chemotherapy (Krull et al., 2008). The recent revision was conducted according to the Behavioral Rating Inventory of executive Functioning, and validated on the survivor population to accurately identify a variety of mild- moderate impairments. It has been found to adequately correlate with direct assessments of cognitive functioning and to adequately capture daily functioning as compared to other parent-report measures (Krull et al., 2008). This self-report questionnaire contains 25 items on a Likert scale based on frequency of occurrence over the last 6 months. Responses are scored onto scales representing four areas of functioning: task efficiency, emotional regulation, organization, and memory (Krull et al., 2008; Kenzik et al., 2015; Zeltzer et al., 2009). Totals are then converted to t- scores and interpreted based on normative sibling data, with impairment defined as falling into the bottom 10th percentile of siblings (Krull et al., 2008; Kenzik et al., 2015). For this analysis, Neurocognitive outcomes were coded according to distribution as impaired or not impaired. Analyses examined perceived functioning in each domain individually.

### The Brief Symptom Inventory- 18 (BSI-18).

The BSI-18 is used as presented on the 2003 follow-up survivor and sibling questionnaires, this served as a measure of emotional distress. This self-report inventory contains 18 items on a Likert scale based on severity over the past 7 days. Scores are placed onto three dimensions: somatization, depression, and anxiety. A cumulative global distress scale is also calculated (Recklitis et al., 2006). Endorsed items are totaled, converted to t-scores based on community norms and interpreted against a clinical cutoff at the top 10th percentile (Recklitis et al., 2006). In addition to its adequate validity and reliability in the general population, the validity of this measure has been studied in pediatric cancer survivors. Findings of these studies indicate the measure has adequate validity, though interpretation should consider effects of response shift and bias (Recklitis et al, 2006). For this analysis, emotional distress was coded as a high (above clinical cutoff of 65) and moderate-low (below clinical cutoff) experience of overall distress as well as on specific scales of somatization, depression and anxiety.

### The Short-Form Survey-36 (SF-36).

The SF-36 is used as presented in the 2003 follow-up survivor/sibling questionnaires, this self-report questionnaire measures patient-reported physical and mental health outcomes. It contains 36 items on a Likert scale regarding the presence of various conditions, as well as their frequency and severity, over the last 4 weeks. Items endorsed are scored to the following scales: vitality, physical function, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and general mental health (Brandeis University, n.d.). Weighted scores are calculated for each section and transformed into standard T-scores, though z-scores are also available (Brandeis University, n.d.). Perceived health-related quality of life will be coded as high- moderate ($\geq$60) and low ($\leq$40) on each of these scales. As in the BSI-18, studies showed survivors demonstrate a high presence of response shift and bias when compared to informant-reports; however, subsequent analyses indicate this had a non-significant impact on the validity of the measure.

### Health behaviors.

Positive and negative health behaviors are present on questionnaires as they pertain to smoking status and physical activity. Specific outcomes related to smoking status included presence and frequency of tobacco use, with frequency measured as fewer than 10 or at least 10 cigarettes a day and the presence of smoking cessation attempts. With regards to physical activity, analyses examined the frequency of moderate/vigorous exercise as compared to national recommendations of at least 3 times per week

### Healthcare/medical screening.

Adherence to guidelines with regards to routine medical care and screening were examined. Primary care visits were examined with regards to low (0 visits), average (1-6 visits), or frequent (7+ visits) utilization. Frequencies considered average or frequent were determined by annual reports from the Center for Disease Control (Center for Disease Control, National Center for Health Statistics, 2009). Participation in risk-based care and medical screening were examined similarly with regards to whether an individual has received this care at least once in the previous year. Questionnaire information regarding the frequency, type and content of healthcare visits were used to determine factors associated with use of general and risk-based healthcare and medical screening.

#### The Posttraumatic Stress Symptom Scale – Self Report.

The posttraumatic stress measure presented in the 2003 follow-up survivor and sibling questionnaires served as the predictor variable. This measure was adapted from the DSM-IV PTSD checklist – civilian edition. This self-report questionnaire contains 17 items that represent the symptom criteria of PTSD assessed on a Likert scale of 0-3 based on severity (Foa, Riggs, Dancu & Rothbaum, 1993). A total raw score is determined by number of items endorsed and compared against a clinical cutoff score of 13, which suggests high likelihood of PTSD (Foa, Riggs, Dancu & Rothbaum, 1993). The presence of a likely diagnosis (yes, no) was coded as the predictor variable. Although it had a greater presence of false-negatives, when compared to the Posttraumatic Stress-Interview, this measure was found to be valid when compared to similar inventories (Foa, Riggs, Dancu & Rothnbaum, 1993).

### Procedure

Descriptive statistics (including mean, standard deviation and frequencies) were calculated for survivor demographics, each of the primary outcomes (NCQ, BSI-18, SF-36, Tobacco Consumption, Physical Activity, Medical Screening and

Healthcare Use), the primary predictor (Posttraumatic stress) and all covariates (Table 1). Logistic regression models were constructed between posttraumatic stress and each of the outcome variables, including adjustment factors as described below (Tables 2-6). For each model described below, confounding factors were included if their inclusion modified the association between posttraumatic stress and each outcome of interest by more than 10%. To account for the high number of covariates and collinearity between them, analyses were run separately using two models. Model 1 included demographic and treatment characteristics while model 2 included demographic and disease variables. Model 1 was selected for use in the primary results, as treatment related variables had a higher predictive power with both PTSS and related outcomes as compared to disease variables. Odds ratios and relative risk were calculated.

### Aim 1

Multivariable log-binomial regression models were used to examine the association between posttraumatic stress (yes, no) and emotional health conditions (BSI-18) and overall health-related quality of life (SF-36). The primary analysis was based on the BSI Global Distress Score as well as the SF-36 physical and mental composites, for which relative risk of impairment was calculated (Table 2). Univariate analyses of variance were also conducted to examine the association between PTSS and each composite score of these measures (Table 1b) and frequencies were calculated.

Multivariable log binomial models were also used to examine the association between posttraumatic stress (yes, no) and neurocognitive functioning (NCQ-2). Univariate analyses and frequencies (table 1b) as well as relative risk for impairment (table 3) were calculated. For each of these, covariates included: treatment type, years since diagnosis, age at evaluation, second malignant neoplasm, sex, race/ethnicity, employment status, household income and marital status.

### Aim 2

Multinomial logistic regression models examined the impact of posttraumatic stress (yes, no) on smoking status (never, current, or former). Odds ratios were calculated and presented in Table 4a. Multivariable log-binomial models were then used to examine the impact of PTSS on frequency of use (greater or less than 10 cigarettes per day) and cessation attempts. Relative risk of high frequency use were calculated and presented in Table 4b. Table 4b also displays the relative risk of failure to meet CDC guidelines for exercise, as calculated in log-binomial regression models. Univariate analyses and frequencies for each outcome were also calculated (Table 1b). Covariates included: body mass index, treatment type, years since diagnosis, age at evaluation, second malignant neoplasm, disease recurrence, sex, race/ethnicity, employment status, household income, marital status.

### Aim 3

Multinomial logistic regression models were used to examine the impact of posttraumatic stress on primary healthcare use. Consideration was given to the overall presence of PTSS (yes, no) (Table 5) and the degree of symptoms in the intrusive, avoidance, or hyperarousal subscales (per unit increase) (Table 5). Odds ratios were calculated and presented in Table 5. Univariate analyses and frequency calculations are also presented in Table 1b. Multivariable log binomial regression models were then used to examine the impact of posttraumatic stress (yes, no) (Table 6) and symptom manifestations (per unit increase) (Table 6) on cancer-specific/risk-based care. Relative risk was calculated and presented in Table 6 while univariate analyses and frequency calculations are presented in Table 1b. For each of these, covariates included: body mass index, health insurance, treatment type, years since diagnosis, age at evaluation, second malignant neoplasm, disease recurrence, sex, race/ethnicity, employment status, household income, marital status.

# Results

## Characteristics of Sample

Table 1a displays the demographic characteristics, as well as diagnosis and treatment protocols, for study participants with PTSS (n=832) and those without PTSS (n=5227). Of the total sample of survivors, 13.7% (n=832) met the clinical cutoff criteria for posttraumatic stress (see Table 1b). There was no significant difference in mean age at diagnosis or at follow-up between groups with and without PTSS (p>.05). The proportion of survivors with and without PTSS significantly differed, however. On the basis of gender (p=.0003) and race (p<.0001) (see Table 1a). An examination of frequencies showed that among survivors with PTSS, 57.9% identified as being female and 42.1% identified as male. Additionally, 13.6% of survivors with PTSS identified as being a member of a racial minority, compared to 8.1% of those without PTSS (see Table 1a).

Significant group differences (PTSS vs. no PTSS) were also found with regard to educational and occupational achievement as well as household income (p<.0001). Significantly more survivors with PTSS identified as unemployed (27.7%), compared to those without PTSS (8.5%) (p<.0001) (see Table 1a). Similarly, survivors with PTSS reported a lower household income on average than those with no PTSS. Upon inspection, 20.5% of survivors with PTSS reported an income below $20,000 per year, compared to 8.6% of those without PTSS (see Table 1a).

With regard to cancer diagnosis, Leukemia was the most prevalent diagnostic group (33.4%) followed by Lymphomas [Hodgkin + non-Hodgkin; (21.7%)], Sarcomas [bone cancer + soft tissue; (18.5%)], solid tumors [Wilms + neuroblastoma; (15.8%)] and Central Nervous System tumors (10.6%). There was no significant difference in diagnosis between survivors with and without PTSS (p>.05, See Table 1b). Disease recurrence, which occurred in 11.2% of the sample, was significantly more prevalent in those with PTSS (p=0.0005); occurrence of second malignant neoplasms occurred in 6.5% of the sample and did not significantly differ between PTSS and non-PTSS groups (p>.05) (see Table 1b). With regards to treatment type, 60.2% of the sample had received cranial radiation, 49.7% had been treated with Alkylating agents, 38.8% with Anthracyclines, 33.5% with Intrathecal Methotrexate, and 19.0% with Intravenous Methotrexate. Although there was no significant difference in chemotherapy type between groups, a history of having received cranial radiation was more prevalent among those with PTSS than those without (p=0.0047) (see Table 1b).

## Outcomes

### Psychosocial outcomes.

Table 2 displays the relative risk, predicted by multivariable log binomial models, for survivors with PTSS to report clinical distress and impairments in health-related quality of life (HRQOL) as compared to those without PTSS, when controlling for demographic variables and those related to disease or treatment-type.[1] Results indicated survivors with PTSS were at 8.58 times greater risk to report clinical distress than those without PTSS (RR=8.58, 95% CI= 7.13-10.32, p<.0001) (see Table 2). Examination of frequencies showed that 44.4% of survivors with PTSS reported a clinical degree of overall emotional distress, as compared to 4.4% of those without PTSS (see Table 1b). There were also a significant association between presence or absence of PTSS and reported clinical distress across individual domains which included depression, somatization, and anxiety (p<.0001). Relative to those without PTSS, a greater proportion of survivors with PTSS reported clinical distress across these domains (see Table 1b).

With regard to HRQOL, survivors with PTSS were at significantly greater risk to report impairment in both physical (RR=2.26, 95% CI: 1.96-2.61, p<.0001) and mental (RR=3.42, 95% CI: 3.05-3.85, p<.0001) domains of functioning (see Table 2). An examination of frequencies showed that 33.1% of survivors with PTSS, compared to 10.9% of those without, reported physical impairments in HRQOL while 51.0% of those with PTSS, and 12.9% of those without, reported mental impairments (see Table 1b). In the domains of physical functioning, significantly more survivors with PTSS reported low general health perception (p<.0001), impairment resulting from bodily pain (p<.0001), and low vitality (p<.0001) (see Table 1b). In the domain of mental

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[1] Across this analysis, separate models were used to account for disease and treatment-related covariates. Results did not differ significantly across models. Results in the text are presented using treatment-related covariates, as they were found to have a greater statistical significance to PTSS and related outcomes.

functioning, significantly more survivors with PTSS reported impairment in emotional (p<.0001) and social (p<.0001) role functioning (see Table 1b)

### Neurocognitive outcomes.

Table 3 displays the relative risk, as predicted by multivariable log binomial models, for survivors with PTSS to report impairment in the various cognitive domains when controlling for demographic variables, disease, and treatment type. When compared to survivors without PTSS, survivors with PTSS were at more than 3 times greater risk for perceived impairments in task efficiency (RR= 3.09, 95% CI= 2.72- 3.51, p<.0001) and emotional regulation (RR=3.67, 95% CI= 3.30-4.09, p<.0001). They were also at more than twice the risk for perceived impairment in working memory (RR=2.55, CI=2.30-2.83, p<.0001) and organization (RR=2.11, CI=1.78-2.50, p<.0001) (see Table 3). Examination of frequencies showed that close to half of survivors with PTSS reported impairments in task efficiency, while more than half identified impairments in emotional regulation and working memory (see Table 1b).

### Health behaviors.

Frequencies presented in table 1b show that 25.3% of survivors with PTSS (13.0% of those without PTSS) reported being a current smoker and 17.4% (15.8% of those without) identified as former smoker. Of those who identified as current smokers, 71.0% of survivors with PTSS (65.7% of those without) acknowledged smoking 10 or more cigarettes a day and 63.9% (59.6% of those without) reported having attempted to quit smoking at least once. Table 4a displays the likelihood of survivors with PTSS as compared to those without PTSS to be a current or former smoker, based on multinomial logistic regressions. As expected, survivors with PTSS were significantly more likely to be a former (OR=1.44, 95%CI= 1.13-1.83, p=.0027) or current (OR=2.34, 95%CI=1.88-2.91, p<.0001) smoker, as opposed to having never smoked, when compared to survivors without PTSS (see Table 4a). The presence or absence of PTSS was not significantly related to the number of cigarettes smoked or cessation attempts (p>.05, see Table 4b).

Univariate analyses revealed a significant association between the presence or absence of PTSS among survivors and body mass index (p=.0009) (see Table 1a). Approximately 24% of survivors with PTSS were obese in contrast to almost 19% of those without PTSS. There was also a significant difference in the proportion of survivors with and without PTSS who met the CDC guidelines for intensity of exercise (p=.0298). Almost 34% of survivors without PTSS engaged in vigorous exercise per CDC guidelines compared to 29.4% of those with PTSS (see Table 1b). Based on multivariable log binomial regression models displayed in tables 4b1 and 4b2, however, PTSS was not significantly related to either meeting or failure to meet CDC guidelines for exercise overall (p>.05).

**Healthcare utilization.**

Table 5 displays the likelihood, as measured by multinomial logistic regressions, that survivors with PTSS, as compared to those without, engaged in high or low frequency healthcare utilization relative to average use. As expected, survivors with PTSS were significantly more likely than those without PTSS to not engage in general healthcare use, as defined as having had no primary care visits in the past 2-years (OR=1.63, 95% CI= 1.32-2.01, p<.0001) (see Table 5) relative to average use, defined as 1-6 visits. Compared to survivors without PTSS, those with PTSS were also significantly more likely to have reported a high frequency of medical visits, as defined as more than seven visits in the past 2-years (OR= 1.89, 95% CI= 1.50-2.39, p<.0001) (see Table 5) relative to average use. Frequency of primary care visits for the PTSS and no PTSS groups are presented in Table 1b.

Table 5 also displays the results of multinomial logistic regressions which examined the relationship between specific symptom manifestations of PTSS on engagement with primary care. Results indicated that as symptoms of hyperarousal increased, survivors were significantly more likely to engage in too few (OR=1.04 per unit increase, 95% CI= 1.01-1.08, p=.0117) or a high frequency of primary care medical visits (OR= 1.04 per unit increase, 95% CI= 1.00-1.08, p=0.0349) (see Table 5) rather than average use. Increases in intrusive symptoms also corresponded with a high frequency of primary care medical visits relative to average use (OR=1.08 per unit increase, 95% CI= 1.02-1.14, p=.0052) (see Table 5).

Multivariate log binomial regressions, presented in Table 6, predicted the likelihood of survivors with PTSS to participate in recommended cancer-specific, risk-based care as compared to those without PTSS. Survivors with PTSS were significantly more likely to have participated in a cancer-specific healthcare visit in the previous 2-year period (RR=1.31, 95% CI= 1.18-1.46, p<.0001) and complied with survivorship guidelines to obtain bone density tests (RR=1.41, 95% CI= 1.15-1.74, p=.0011) (see Table 6). PTSS did not significantly impact engagement in other recommended screenings, however, which included echocardiograms, colonoscopies, mammograms (for female survivors) or pap smears (for female survivors) (p>.05; See Table 6). Frequency of risk-based visits for the PTSS and no PTSS groups are represented in Table 1b.

Table 6 also displays results of multivariable log binomials which examined the significance of specific symptom manifestations of PTSS on risk-based care. Results indicated that as reported symptoms of hyperarousal increased, survivors were more likely to engage in cancer-specific healthcare visits (RR=1.04 per unit increase, 95% CI= 1.02-1.06, p<.0001) and recommended colonoscopies (RR=1.10 per unit increase, 95% CI= 1.02-1.19, p=0.0118) (see Table 6). Avoidance was found to have no significant impact on primary or risk-based care (p>.05, see Table 6).

# Discussion

## Impact of Study

Long-term survivors of childhood cancer have been found to experience a number of late effects which include psychological distress, neurocognitive impairment, and physical health conditions. Due to these increased risks, promotion of psychosocial adjustment and healthy lifestyles is particularly important for this population. A body of research on late effects in childhood cancer survivorship has sought to both characterize outcomes and identify those who may be at greater risk; however, relatively few studies have examined multiple outcomes together. Additionally, few have examined posttraumatic stress as a unique variable, and those who have are limited by small sample size and lack of extended follow-up data (Lee, 2006; Meeske et al., 2001; Schwartz & Drotar, 2005). Our study examined posttraumatic stress as a unique predictor of emotional, cognitive, and behavioral health outcomes among survivors. Of the long-term survivors, 13.7% reported PTSS at an extended time-period following completion of their cancer treatment. When compared to survivors without PTSS, those who experienced PTSS were at increased risk for experiencing emotional distress, poor health-related quality of life, and neurocognitive impairment. They were also more likely to have smoked, and variably utilized healthcare.

The finding that survivors with PTSS in our sample were significantly more likely to report poor psychosocial outcomes, characterized by higher levels of distress and lower health-related quality of life than survivors without PTSS, is consistent with previous research on adult cancer survivors (Meeske, Ruccione, Globe, Stuber, 2001; Oeffinger, Nathan & Kremer, 2008; Zeltzer et al., 2009). Specifically, survivors were at significantly greater risk of experiencing clinical distress characterized by depression, anxiety, and somatization. They were also more likely to report diminished quality of life resulting from lower perceived mental and physical functioning that appeared related to bodily pain, vitality, social and emotional role functioning. These outcomes likely impact the survivors' interpersonal relationships as well as affect their sleep, activity level, and overall functioning (Phillips Salimi, Lommel & Andrykowski, 2011; Zeltzer et al., 2009). Given the relationship between PTSS and overall distress, ongoing mental health screening and monitoring of psychological symptoms is critical to minimize the degree of psychosocial late effects and functional impairment experienced by survivors. Assisting survivors in coping with the physical sequelae of their disease, including pain, will also be important in affecting their quality of life.

As predicted, results from this study also found that survivors with PTSS were significantly more likely than their peers without PTSS to experience perceived impairments across domains of neurocognitive functioning, which was evident in emotional regulation, task efficiency, working memory, and organization. While we controlled for demographic, disease, and treatment-related variables when evaluating neurocognitive impairment in our study, it remains difficult to determine if the emotional distress associated with PTSS contributes to the cognitive impairment reported or if the cognitive deficits lead to increased clinical distress. Early identification and remediation of these functional deficits is important, however, given the association between neurocognitive impairment and poorer adult adaptation, including occupational and educational functioning (Ellenberg et al., 2009; Krull et al., 2011). Disruptions in neurocognitive functioning may also affect the survivors' decision making related to the practice of unhealthy behaviors and compliance with recommendations for follow-up medical care (Krull et al, 2011). For survivors whose cognitive skills cannot be significantly improved with traditional cognitive rehabilitation efforts, vocational rehabilitation, job training, placement services, and access to programs that promote independent living may also be critically important in facilitating more positive functional outcomes (Ellenberg et al., 2009).

As it has been well demonstrated that survivors, in general, tend to engage in fewer positive health behaviors (Krull et al., 2011), and emotional distress is often associated with their practice of harmful health behaviors (Clarke & Eiser, 2007; Santacrose & Lee, 2006; Schwartz et al., 2012), the current findings related to tobacco use and exercise in our sample were not surprising. Consistent with results reported in other studies, close to 31% of survivors in the study sample were current or former smokers and survivors with PTSS were more likely to smoke now or in the past when compared to survivors without PTSS. Similarly, fewer than half of survivors in the sample reported engaging in regular exercise. Although PTSS did not affect survivors' overall adherence to CDC guidelines for exercise, many survivors with PTSS identified as obese. While exercise is an important factor in maintaining a healthy weight, it is likely that other factors not assessed in this study (i.e. endocrine dysfunction, nutritional status) may interact with PTSS to affect weight outcomes. Nonetheless, providers should monitor and counsel the subgroup of survivors who have PTSS, are obese, engage in limited physical activity, and use tobacco, which can increase their risk for chronic health conditions.

While it is important that all survivors sustain long-term follow-up medical care, our findings showed that survivors with PTSS were significantly more likely to engage in adequate risk-based care, including cancer-specific health visits and selected medical screenings, than those without PTSS. However, with respect to primary care, survivors with PTSS were either significantly more likely to disengage from medical care (defined as no visits in the prior two years) or to engage in frequent health care visits (defined as more than 7 visits) as compared to survivors without PTSS. Examination of unique symptom manifestations of PTSS showed that with increases in hyperarousal and intrusive symptoms, survivors reported significantly higher rates of risk-based and primary care utilization. On the basis of our data, it may be that a certain degree of hyperarousal or intrusive thoughts are protective in that they facilitate survivor engagement in medical care. For some survivors, however, PTSS-hyperarousal may interfere with adherence to medical care in the primary care setting. The relationship between PTSS and health care utilization is obviously complex and may be attributed to a number of factors, including but not limited to levels of pain and number of somatic complaints, health beliefs and perceptions of health status or competence, expectations and satisfaction with care, knowledge of health risks, barriers in accessing care, and/or the desire for supportive care (Cox et al., 2013; Ford, et al., 2014; Michel et al., 2009; Nathan et al., 2008). Understanding what motivates survivors to engage in medical care and adhere to recommended clinical guidelines is a promising area of further study.

Based on the findings of our study, posttraumatic stress has been found to influence psychosocial late effects, neurocognitive functioning, healthcare utilization, and health behaviors among long-term cancer survivors. Childhood cancer survivors who present with PTSS and who are clinically distressed, cognitively impaired, and do not seek follow-up medical care to promote a healthy lifestyle are ideal candidates for prophylactic intervention. Although we did not directly examine the relationship between each of the outcomes assessed in this study, it is likely that multiple negative outcomes are likely to co-occur in some survivors. Therefore, promoting change in one area of functioning may positively impact other areas of functioning, suggesting multiple targets for intervention. Targeting posttraumatic stress, a potentially modifiable factor, is likely to be a central component of the survivor’s long-term preventative follow-up care, given its association across various domains of functioning. Identifying multi-component supportive care interventions that prevent PTSS and help survivors cope with the multiple late effects of treatment is certainly warranted. Additionally, survivors with PTSS are likely to benefit from psychoeducation regarding health promotion, particularly as it relates to an increased sense of health-related competence. This may be expected to increase survivors' ability to maintain a healthy lifestyle while seeking needed health care as recommended by survivorship guidelines.

### Limitations of Study & Future Directions

Although this study was able to meet its aims to better characterize late effects and the impact of posttraumatic stress in the survivor population, consideration should be given to some methodological limitations. One limitation of this study is that, while the sample is large, it is described as predominantly Caucasian, such that we may not be able to adequately examine the long-term health outcomes among minority survivors. While this is consistent with the general childhood cancer survivor population (Kazak et al., 2010), the limited number of minority participants restricts the generalizability of our findings to potential high risk groups (Oeffinger, Nathan & Kremer, 2008; Robison et al., 2008). Research on the long-term morbidity among minority survivor populations is certainly warranted to offer race/ethnicity-targeted recommendations and interventions as well as optimize their follow-up care. In addition, our study did not account for the potential influence of multiple traumas experienced by survivors, including childhood experiences and family stressors that may have been present at the time of illness. Future studies should aim to examine such factors in order to differentiate the contribution of cancer-specific versus other trauma on the degree and types of symptoms manifested among survivors.

Concerns have also been raised about reliance on self-report data in the CCSS cohort as survivors may under- or over-report their symptoms, in comparing themselves to other survivors or in an effort to more closely resemble their healthy peers (Brandeis University, n.d.; Recklitis et al, 2006). It has also been suggested that survivors who experience traumatic stress may be more avoidant, less willing to revisit their cancer experience, and therefore less likely to participate in the CSSS study, resulting in a biased sample of survivors. (Stuber et al., 2010). Consequently, the observed prevalence of PTSS in survivors may be underestimated in this study. The use of self-report data to assess perceived neurocognitive functioning may also represent an additional limitation of the study. Although the CCSS neurocognitive questionnaire (NCQ) has been validated against self-report and performance based measures (Krull et al., 2008), future studies may benefit from inclusion of objective, performance-based data to better understand the nature and degree of survivors' neurocognitive impairment.. Additionally, although our study made progress in examining utilization of healthcare among survivors, future studies should better address reasons for medical visits and account for covariates such as chronic or acute health conditions, pain severity, and satisfaction with care received. This information would be most helpful in promoting better engagement of survivors in general and risk-based follow-up care. Likewise, the scope of this study was limited in the inclusion of only a few health behaviors. Future research should give more consideration to healthy lifestyles across a broader behavioral health domain.

Lastly, this study was limited in its use of cross-sectional data. Because of the nature of the questionnaire data, directionality and causality cannot be established, leaving a degree of uncertainty regarding the relationship between predictors and outcomes. The cross-sectional design of this study also limits our evaluation of the longitudinal patterns of PTSS and related outcomes following cancer treatment. Future research should include a longitudinal approach and seek to utilize increased intervals to better understand directionality of outcomes over time. This will also enable more precise timing for delivery of targeted interventions for vulnerable cancer survivors at varying levels of risk.

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# Tables

## Table 1a

*Demographic Frequencies and Univariate Analyses*

| Variable | Category | w/o PTSS (n=5227) | with PTSS (n=832) | |
|---|---|---|---|---|
| | | **M (SD)** | **M (SD)** | |
| **Age at diagnosis** | | 8.7 (5.9) | 8.5 (5.7) | 0.1990$^{t}$ |
| **Age at baseline** | | 24.2(7.8) | 23.9 (7.7) | 0.2784$^{t}$ |
| **Age at follow-up 2** | | 31.9 (7.6) | 31.5 (7.5) | 0.1470$^{t}$ |
| | | **N (%)** | **N (%)** | |
| **Diagnosis** | | | | 0.0959 |
| | CNS tumor | 610 (10.4) | 117 11.8) | |
| | Sarcoma (bone cancer + soft tissue | 1072 (18.3) | 191 (19.2) | |
| | Lymphoma (Hodgkin +NHL) | 1285 (22.0) | 204 (20.5) | |
| | Solid tumor (Wilms+ neuroblastoma) | 945 (16.2) | 133 (13.4) | |
| | Leukemia | 1937 (33.1) | 350 (35.2) | |
| **Recurrence** | | | | 0.0005** |
| | Yes | 625 (10.7) | 144 (14.5) | |
| | No | 5224 (89.3) | 851 (85.5) | |
| **Second Malignant Neoplasm** | | | | 0.4321 |
| | Yes | 372 (6.4) | 70 (7.0) | |
| | No | 5477 (93.6) | 025 (93.0) | |
| **Sex** | | | | 0.0003** |
| | Female | 3022 (51.7) | 576 (57.9) | |
| | Male | 2827 (48.3) | 419 (42.1) | |

| | | | | |
|---|---|---|---|---|
| **Race/Ethnicity** | | | | <.0001** |
| | White/non-Hispanic | 5353 (91.5) | 857 (86.1) | |
| | Other | 473 (8.1) | 135 (13.6) | |
| | Missing / no response | 23 (0.4) | 3 (0.3) | |
| **Education** | | | | <.0001** |
| | High school or less | 1211 (20.7) | 281 (28.2) | |
| | Some college | 1731 (29.6) | 318 (32.0) | |
| | College graduate or higher | 2868 (49.0) | 390 (39.2) | |
| | Missing / no response | 39 (0.7) | 6 (0.6) | |
| **Employment Status** | | | | <.0001** |
| | Employed or student | 5242 (89.6) | 750 (75.4) | |
| | Unemployed | 496 (8.5) | 226 (22.7) | |
| | Missing/no response | 111 (1.9) | 19 (1.9) | |
| **Household Income** | | | | <.0001** |
| | <20,000 | 501 (8.6) | 204 (20.5) | |
| | 20,000 – 39,000 | 1156 (19.8) | 239 (24.0) | |
| | 40,000 – 59,000 | 1080 (18.5) | 153 (15.4) | |
| | 60,000+ | 2418 (41.3) | 271 (27.2) | |
| | Missing / no response | 694 (11.9) | 128 (12.9) | |
| **Marital Status** | | | | <.0001** |
| | Single | 2747 (47.0) | 596 (59.9) | |
| | Married or living as married | 3046 (52.1) | 391 (39.3) | |
| | Missing / no response | 56 (1.0) | 8 (0.8) | |
| **Health Insurance** | | | | >.0001** |
| | No | 590 (10.1) | 155 (15.6) | |
| | Yes | 5227 (89.4) | 832 (83.6) | |
| | Missing / no response | 32 (0.5) | 8 (0.8) | |
| **Body Mass Index** | . | | | 0.0009** |
| | Normal / underweight | 2865 (49.0) | 445 (44.7) | |

|  |  |  |  |  |
|---|---|---|---|---|
| **Anthracyclines in 1st 5 years** |  |  |  | 0.4486 |
|  | Yes | 2113 (36.1) | 369 (37.1) |  |
|  | No | 3364 (57.5) | 556 (55.9) |  |
|  | Missing | 372 (6.4) | 70 (7.0) |  |
| **Alkylating agents 1st 5-yr** | Missing | 378 (6.5) | 75 (7.5) |  |
|  | No | 2763 (47.2) | 450 (45.2) | 0.3723 |
|  | Yes | 2708 (46.3) | 470 (47.2) |  |
| **Methotrexate IV 1st 5-yr** | Missing | 432 (7.4) | 91 (9.1) |  |
|  | 0: No | 4393 (75.1) | 724 (72.8) | 0.4749 |
|  | 1: Yes | 1024 (17.5) | 180 (18.1) |  |
| **Methotrexate IT 1st 5-yr** | Missing | 523 (8.9) | 117 (11.8) | 0.2588 |
|  | 0: No | 3555 (60.8) | 569 (57.2) |  |
|  | 1: Yes | 1771 (30.3) | 309 (31.1) |  |
|  |  | **M (SD)** | **M (SD)** |  |
| **Anthracycline dose >0** |  | 289.4(150.2) | 296.6(148.4) | 0.4220$^{t}$ |
| **Alkylating agents dose >0** |  | 9024.8(9109.2) | 9096.8(8389.6) | 0.8761$^{t}$ |
| **Methotrexate IV dose >0** |  | 3529.1(81670.8) | 35969.1(73401.1) | 0.9169$^{t}$ |
| **Methotrexate IT Dose >0** |  | 159.7 (168.5) | 157.5 (104.3) | 0.7635$^{t}$ |
| **Cranial Radiation (dose >0) (4119)** |  | 1407.5 (1716.5) | 1628.0 (1826.1) | 0.0047$^{t}$ |
|  | Overweight | 1689 (28.9) | 273 (27.4) |  |
|  | Obese | 1103 (18.9) | 236 (23.7) |  |
|  | Missing / no response | 192 (3.3) | 41 (4.1) |  |

## Table 1b

*Frequencies and Univariate Analyses for Predictor and Outcome Variables*

| Variable | Category | **w/o PTSS** (n=5227) | **w/PTSS** **(**n=832**)** | |
|---|---|---|---|---|
| | | **N (%)** | **N (%)** | **p-value** |
| **Posttraumatic Stress** | | 5227(86.3) | 832 (13.7) | |
| **Brief Symptom Inventory (BSI)** | | | | |
| **Global Distress** | | | | <.0001** |
| | Not elevated (<65) | 5569(95.2) | 549 (55.2) | |
| | Elevated at 65+ | 258 (4.4) | 442 (44.4) | |
| | Insufficient Responses | 22 (0.4) | 4 (0.4) | |
| **Somatization** | | | | <.0001** |
| | Not elevated (<65) | 5298(90.6) | 560 (56.3) | |
| | Elevated at 65+ | 529 (9.0) | 431 (43.3) | |
| | Insufficient Responses | 22 (0.4) | 4 (0.4) | |
| **Depression** | | | | <.0001** |
| | Not elevated (<65) | 5466(93.5) | 545 (54.8) | |
| | Elevated at 65+ | 363 (6.2) | 447 (44.9) | |
| | Insufficient Responses | 20 (0.3) | 3 (0.3) | |
| **Anxiety** | | | | <.0001** |
| | Not elevated (<65) | 5621(96.1) | 671 (67.4) | |
| | Elevated at 65+ | 207 (3.5) | 321 (32.3) | |
| | Insufficient Responses | 20 (0.3) | 3 ().3) | |
| **HRQOL -Short-Form 36** | | | | |
| **Physical Composite** | | | | <.0001** |
| | Not elevated (<60) | 5148(88.0) | 649 (65.2) | |
| | Elevated at 60+ | 638 (10.9) | 329 (33.1) | |
| **Mental Composite** | | | | <.0001** |

| | | | | |
|---|---|---|---|---|
| | Not Elevated (<60) | 5030 (86.0) | 471 (47.3) | |
| | Elevated at 60+ | 756 (12.9) | 507 (51.0) | |
| | Insufficient Responses | 63 (1.1) | 17 (1.7) | |
| **Vitality** | | | | <.0001** |
| | Not elevated (<60) | 4683 (80.1) | 436 (43.8) | |
| | Elevated at 60+ | 1152 (19.7) | 554 (55.7) | |
| | Insufficient Responses | 14 (0.2) | 5 (0.5) | |
| **Bodily pain** | | | | <.0001** |
| | Not elevated (<60) | 4956 (84.7) | 551 (55.4) | |
| | Elevated at 60+ | 873 (14.9) | 439 (44.1) | |
| | Insufficient Responses | 20 (0.3) | 5 (0.5) | |
| **General Health Perception** | | | | <.0001** |
| | Not elevated (<60) | 4745 (81.1) | 466 (46.8) | |
| | Elevated at 60+ | 1084 (18.5) | 523 (52.6) | |
| | Insufficient Responses | 20 (0.3) | 6 (0.6) | |
| **Emotional Role Function** | | | | <.0001** |
| | Not elevated (<60) | 5033 (86.0) | 498 (50.1) | |
| | Elevated at 60+ | 781 (13.4) | 489 (49.1) | |
| | Insufficient Responses | 35 (0.6) | 8 (0.8) | |
| **Social Role Function** | | | | <.0001** |
| | Not elevated (<60) | 5323(91.0) | 548 (55.1) | |
| | Elevated at 60+ | 517 (8.8) | 445 (44.7) | |
| | Insufficient Responses | 9 (0.2) | 2 (0.2) | |
| **Smoking Status** | | | | <.0001** |
| | Never smoker | 4156(71.1) | 568 (57.1) | |
| | Former smoker | 927 (15.8) | 173 (17.4) | |
| | Current smoker | 758 (13.0) | 252 (25.3) | |
| | Missing / no response | 8 (0.1) | 2 (0.2) | |

| | | | | |
|---|---|---|---|---|
| **Frequency of use** | | | | 0.1216 |
| | <9 cigarettes per day | 253 (33.4) | 71 (28.2) | |
| | 10+ cigarettes per day | 498 (65.7) | 179 (71.0) | |
| | Missing / no response | 8 (0.1) | 2 (0.2) | |
| **Cessation attempts** | | | | 0.2737 |
| | 0 attempt | 273 (36.0) | 82 (32.5) | |
| | 1+ attempt | 452 (59.6) | 161 (63.9) | |
| | Missing / no response | 33 (4.4) | 9 (3.6) | |
| **Exercise (overall)** | | | | 0.0975 |
| | Not meeting criteria | 3245 (55.5) | 578 (58.1) | |
| | CDC by moderate | 566 (9.7) | 109 (11.0) | |
| | CDC by vigorous | 1969(33.7) | 293 (29.4) | |
| | Meeting overall criteria | 2535(43.3) | 402 (40.4) | |
| | Missing/no response | 69 (1.2) | 15 (1.5) | |
| **Primary care/2yr** | | | | <.0001** |
| | 0 visits | 1974(33.7) | 397 (39.9) | |
| | 1-6 visits | 2667(45.6) | 311 (31.3) | |
| | 7+ visits | 1178(20.1) | 281 (28.2) | |
| | Missing / no response | 30 (0.5) | 6 (0.6) | |
| **Cancer-specific visit** | | | | <.0001** |
| | Not in past 2 yr | 4097(70.0) | 561 (56.4) | |
| | Yes in past 2 yr | 1702(29.1) | 420 (42.2) | |
| | Missing / no response | 50 (0.9) | 14 (1.4) | |
| **Echocardiogram** | | | | 0.0360* |
| | Not following guidelines | 916 (15.7) | 127 (12.8) | |
| | Following guidelines | 412 (7.0) | 79 (7.9) | |
| | Missing / no response | 148 (2.5) | 36 (3.6) | |
| **Colonoscopy** | | | | 0.2317 |
| | Not following | 636 (10.9) | 106 (10.7) | |
| | Following guidelines | 107 (1.8) | 24 (2.40 | |

| | | | | |
|---|---|---|---|---|
| **Bone Density test** | | | | <.0001** |
| | Not following | 1864(31.9) | 291 (29.2) | |
| | Following guidelines | 507 (8.7) | 135 (13.6) | |
| | Missing / no response | 283 (4.8) | 62 (6.2) | |
| **Mammogram (for women)** | | | | 0.5196 |
| | Not following | 524 (17.3) | 99 (17.2) | |
| | Following guidelines | 356 (11.8) | 60 (10.4) | |
| | Missing / no response | 11 (0.4) | 5 (0.9) | |
| **Pap smear (women)** | | | | 0.0047** |
| | Not following | 633 (20.9) | 151 (26.2) | |
| | Following guidelines | 2172 (71.9) | 384 (66.7) | |
| | Missing / no response | 32 (1.1) | 9 (1.6) | |
| **Neurocognitive Questionnaire** | | | | |
| **Task efficiency** | | | | <.0001** |
| | Not impaired | 5058(86.5) | 513 (51.6) | |
| | Impaired | 753 (12.9) | 471 (47.3) | |
| | Insufficient Responses | 38 (0.6) | 11 (1.1) | |
| **Emotional regulation** | | | | <.0001** |
| | Not impaired | 4946 (84.6) | 411 (41.3) | |
| | Impaired | 867 (14.8) | 570 (57.3) | |
| | Insufficient Responses | 36 (0.6) | 14 (1.4) | |
| **Organization** | | | | <.0001** |
| | Not impaired | 5219 (89.2) | 732 (73.6) | |
| | Impaired | 595 (10.2) | 252 (25.3) | |
| | Insufficient Responses | 35 (0.6) | 11 (1.1) | |
| **Working memory** | | | | <.0001** |
| | Not impaired | 4689(80.2) | 449 (45.1) | |
| | Impaired | 1123(19.2) | 535 (53.8) | |
| | Insufficient Responses | 37 (0.6) | 11 (1.1) | |

## Table 2

*Relative Risk for High Emotional Distress and Impairments in Health-Related Quality of Life Based on Presence of PTSS*[1]

| Variable | Category | BSI[2] Global Distress Index n=4798)[3] | | | SF-36 [4] Physical Composite (n=4757)[3] | | | SF-36 Mental Composite (n=4757)[3] | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | RR | 95% CI | p- | RR | 95% CI | p- | RR | 95% CI | p-value |
| PTSS | No | 1.00 | . | . | 1.00 | . | . | 1.00 | | |
| | Yes | 8.58 | 7.13-10.32 | <.0001* | 2.26 | 1.96-2.61 | <.0001* | 3.42 | 3.05-3.85 | <.0001* |
| | . | . | | | | | | | | |

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*p<.01

[2] Brief Symptom Inventory

[3] number of participants who completed corresponding measure on questionnaire

[4] Short-Form 36

## Table 3

*Relative Risk for Neurocognitive Impairment Based on Presence of PTSS*[1]

| Variable | Category | **Task Efficiency (n=4779)**[4] | | | **Emotional Regulation (n=4781)**[5] | | | **Working Memory (n=4781)**[5] | | | **Organization (n=4781)**[5] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **RR** | **95% CI** | **p-** | **RR** | **95% CI** | **p-** | **RR** | **95% CI** | **p-** | **RR** | **95% CI** | **p-** |
| PTSS | No | 1.00 | . | . | 1.00 | . | . | 1.00 | . | . | 1.00 | . | . |
| | Yes | 3.09 | 2.72- 3.51 | <.0001* | 3.67 | 3.30- 4.09 | <.0001* | 2.55 | 2.30- 2.8 | <.0001* | 2.11 | 1.78- 2.50 | <.0001* |

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*p<.01

[4] number of participants who completed corresponding portion of neurocognitive questionnaire

Table 4a

*Odds Ratio for Effect of PTSS on Smoking Status*[1]

| Variable | Category | Category | **Smoking status (n=4690)**[5] | | |
|---|---|---|---|---|---|
| | | | **OR** | **95% CI** | **p-** |
| PTSS | No | Never Smoker | 1.00 | . | . |
| | Yes | Former smoker | 1.44 | 1.13- 1.83 | 0.0027* |
| | Yes | Current smoker | 2.34 | 1.88- 2.91 | <.0001* |

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*p<.01

[5] Number provided an answer regarding smoking status on the questionnaire

<u>Table 4b</u>

*Relative Risk of Not Meeting CDC Guidelines for Exercise and of High Frequency Tobacco Use, Based on Presence of PTSS*

| Variable | Category | **Exercise (CDC criteria) (n=4656)[6]** | | | **Frequency of use for current smokers (n=667)[7]** | | | **Previous cessation for current smokers (n=646)[7]** | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | **RR** | **95% CI** | **p-** | **RR** | **95% CI** | **p-** | **RR** | **95% CI** | **p-** |
| PTSS | No | 1.00 | . | . | 1.00 | . | . | 1.00 | . | . |
| | Yes | 0.99 | 0.90-1.08 | 0.7520 | 1.06 | 0.95-1.18 | 0.2836 | 1.04 | 0.92-1.17 | 0.5618 |

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*p<.05

[6] answered corresponding question(s) on questionnaire

Table 5

*Effect of PTSS and its Individual Symptom Manifestations on Frequency of Primary Care Engagement*

| Variable | Category | **primary care physician visits (n=4659)[7]** | | | |
|---|---|---|---|---|---|
| | | **Category** | **OR** | **95% CI** | **p-** |
| PTSS | No | 1-6 visit | 1.00 | . | . |
| | Yes | 0 visits | 1.63 | 1.32- 2.01 | <.0001* |
| | Yes | 7+ visits | 1.89 | 1.50- 2.39 | <.0001* |
| Hyperarousal | Per unit | 0 visits | 1.04 | 1.01-1.08 | 0.0117* |
| Hyperarousal | Per unit | 7+ visits | 1.04 | 1.00-1.08 | 0.0349 |
| Avoidant | Per unit | 0 visits | 1.01 | 0.98-1.04 | 0.4735 |
| Avoidant | Per unit | 7+visits | 1.01 | 0.98-1.05 | 0.4965 |
| Intrusive | Per unit | 0 visits | 1.04 | 0.99-1.09 | 0.1702 |
| Intrusive | Per unit | 7+ visits | 1.08 | 1.02-1.14 | 0.0052 |

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*p<.01

[7] completed corresponding portion of questionnaire

## Table 6

*Effect of PTSS and its Individual Symptom Manifestations on Frequency of Primary Care Engagement*

| | | **Cancer-specific health (n=4646[8])** | | | **Echocardiogram (n=1164[9])** | | | **Colonoscopy (n=683[10])** | | | **Bone Density (n=1950[11])** | | | **Mammogram (n=748[12])** | | | **Pap smear visit (n=2318[13])** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **RR** | **95% CI** | **p-value** | **RR** | **95% CI** | **p-value** | **RR** | **95% CI** | **p-value** | **RR** | **95% CI** | **p-value** | **RR** | **95% CI** | **p-value** | **RR** | **95% CI** | **p-value** |
| PTSS | No | 1.00 | . | . | 1.00 | . | . | 1.00 | . | . | 1.00 | . | . | 1.00 | . | . | 1.00 | . | . |
| | Yes | 1.31 | 1.18-1.46 | <.0001* | 1.19 | 0.94-1.50 | .1442 | 1.24 | 0.76-2.03 | .3869 | 1.41 | 1.15-1.74 | .0011* | 0.94 | 0.72-1.22 | .6193 | 0.98 | 0.91-1.04 | .4613 |
| Hyper. / unit | | 1.04 | 1.02-1.06 | <.0001* | 1.01 | 0.97-1.05 | 0.6403 | 1.10 | 1.02-1.19 | .0118* | 1.03 | 1.00-1.07 | .0846 | 1.10 | 0.96-1.04 | .8187 | 1.0 | 0.99-1.01 | .4476 |
| Avoidance / unit | | 1.00 | 0.98-1.01 | .5978 | 0.99 | 0.95-1.03 | .5667 | 0.95 | 0.88-1.03 | .2021 | 1.10 | 0.96-1.03 | .8140 | 1.10 | 0.97-1.05 | .7132 | 1.01 | 0.99-1.01 | .9409 |
| Intrusive / unit | | 1.04 | 1.02-1.07 | .0014* | 1.07 | 1.02-1.12 | .0048* | 1.01 | 0.89-1.14 | .9227 | 1.03 | 0.98-1.08 | .2947 | 1.10 | 0.94-1.06 | .9986 | 1.00 | 0.98-1.02 | .9979 |

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p<.01

[8] number of participants who completed portion of questionnaire

[9-13] number of participants who were eligible for screening and completed related portion of questionnaire