Summer 2016

The influence of early life adversity and recent life stress on psychological trajectories in women with ovarian cancer

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THE INFLUENCE OF EARLY LIFE ADVERSITY AND RECENT LIFE STRESS ON PSYCHOLOGICAL TRAJECTORIES IN WOMEN WITH OVARIAN CANCER

by

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A thesis submitted in partial fulfillment
of the requirements for the Doctor of Philosophy
degree in Psychological and Quantitative Foundations in the
Graduate College of
The University of Iowa

August 2016

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CERTIFICATE OF APPROVAL

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PH.D. THESIS

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ACKNOWLEDGEMENTS

The author would like to extend gratitude and appreciation to those who were involved in supporting this work. For her primary mentorship on this project and throughout graduate school, I extend my sincerest and most gracious appreciation to Dr. Susan Lutgendorf. This work was supported by grants CA88293, CA104825, and CA 140933 to Dr. Susan Lutgendorf. Thank you to those involved in stress data collection, including George Slavich, Jen Bayer, Lauren Davis, Katie Collins, and Annie White, as well as the University of California – Los Angeles rating team, research coordinators, and undergraduate research assistants. Further, the support of Andrew Schrepf was essential to the development and execution of this project. Thank you importantly to the patients who contributed their time and life stories for this project.

ABSTRACT

Ovarian cancer is a malignancy characterized by poor prognosis, high levels of distress, and impaired quality of life (QOL). Investigation into the contributors to QOL is of psychological and prognostic significance in cancer. Contemporary stress theories and empirical accounts identify early life adversity and recent life stress as those sources which exert significant impact on physical and psychological health. To date, life stress research in cancer has yielded few designs which operationalize both indices of early life and recent life stress exposures. Moreover, despite the high-resolution stress data provided by the Life Events and Difficulties Schedule (LEDS) system, no studies to date comprehensively operationalize the early life adversity data obtained during each interview. Therefore, the proposed study is the first of its kind to comprehensively obtain ratings and examine effects of early life adversity data collected as part of the LEDS interview. It is also the first to examine independent influences of differentially timed life stress indices on psychological variables important to psychosocial functioning in ovarian cancer. Early life adversity was experienced by 43.1% of the sample. Adversity varied in content, number of occurrences, and severity. Ongoing difficulties, but not recent life events or early life adversity, were significantly associated with pre-surgical depression and QOL. Ongoing difficulties were also associated with lower depression, sleep, and QOL scores at all time-points. Early life adversity was associated with a poorer trajectory of sleep and QOL over the first year post-diagnosis. Findings are discussed with attention to behavioral and biological mechanisms. Applications to generative and cumulative theories of life stress are proposed. These findings lend support to the potential benefit of interventions aimed toward practical support and stress management in patients with

ovarian cancer, as well as provide guidelines for use of early life adversity data obtained through the LEDS interview.

PUBLIC ABSTRACT

Individuals with ovarian cancer often report changes in their sleep, symptoms of depression, and changes in quality of life (QOL) after they are diagnosed and begin treatment. Many factors may contribute to such changes. One such factor that is commonly considered as influential on these outcomes is life stress. Stress in life may occur at any time across the life span, and those stressors which have occurred recently as well as those early in life are often considered to have substantial impact on the individual. Using a gold-standard measure of life stress (the Life Events and Difficulties Schedule, or LEDS), this study examined how early life adversity and recent life stress impact sleep, depressive symptoms, and QOL during the first year after diagnosis with ovarian cancer. This study also was the first of its kind to develop methodology to characterize severity of early life adversity experiences on the life stress interview.

Early life adversity was experienced by 43.1% of the sample. Adversity varied in content, number of occurrences, and severity. Recent ongoing difficulties, but not recent life events or early life adversity, were significantly associated with pre-surgical depression and QOL. Ongoing difficulties were also associated with lower depression, sleep, and QOL scores at all time-points. These findings lend support to the potential benefit of interventions aimed toward practical support and stress management in patients with ovarian cancer. The methodology also provides guidelines for use of early life adversity data obtained through the LEDS interview.

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INTRODUCTION

Of the gynecological cancers, ovarian cancer is the second most common in incidence and is responsible for the most deaths per year (Siegel, Ma, Zou, & Jemal, 2014). Due to poor screening procedures for early detection of the disease and nonspecific physical symptoms (Hennessey, Coleman, & Markman, 2009), ovarian cancer is commonly diagnosed in an advanced stage and is often referred to as the "silent killer" (Goff, Mandel, Muntz, & Melancon, 2000; McCorkle, Pasacreta, & Tang, 2003). Seventy five percent of patients present with stages III or IV ovarian cancer, which are associated with a 10-30% likelihood of five year survival due to high rates of cancer recurrence after initial surgical and/or chemotherapy treatment (American Cancer Society, 2014; Hennessey, Coleman, & Markman, 2009).

After histological confirmation of ovarian cancer, two treatment modalities are typically utilized in two possible sequences. Surgical resection and staging is considered integral for disease management, even in early stage disease (Guppy, Nathan, & Rustin, 2005). Chemotherapy, which may be delivered systemically or directly into the abdomen ("intraperitoneal"), may be received by the patient either before (termed "neoadjuvant" therapy) or after ("adjuvant" therapy) surgical intervention (Hennessy, Coleman, & Markman, 2009; Guppy, Nathan, & Rustin, 2005). Following disease recurrence, chemotherapy is not considered curative (Hennessy, Coleman, & Markman, 2009), though it may prolong survival. This necessitates a focus on quality of life as patients face a particularly lethal cancer and the prospect of loss of life.

Factors such as extensive surgical interventions, rigorous treatment protocols, and poor prognosis contribute to distress, which is commonly observed in ovarian cancer

patients (Gryzankowski & Carney, 2011). Such distress has been noted throughout the treatment trajectory, and there are numerous psychological and behavioral correlates of quality of life (QOL), which may be defined as the relationship between an individual's observed perception of and satisfaction with their current functioning in multiple domains relative to their conceptualized ideal level of functioning (Anderson & Lutgendorf, 1997). For example, low levels of physical activity (Stevinson et al., 2007; Beesley et al., 2011; Kornblith et al., 1995), poor sleep (Clevenger et al., 2013; Sandadi et al., 2011), depressive symptomatology (Bodurka-Bevers et al., 2000; Arden-Close, Gidron, & Moss-Morris, 2008), anxiety (Bodurka-Bevers et al., 2000; Von Gruenigen et al., 2009; Roland, Rodriguez, Patterson, & Trivers, 2013), fatigue (Holzner et al., 2003), and demographic risk factors such as higher levels of education and younger age (Schulman-Green, Ercolano, Dowd, Schwartz, & McCorkle, 2008) have all been associated with poorer QOL in ovarian cancer patients.

A pattern has been described where patients experience the highest levels of distress and impaired QOL immediately pre- and post-initial surgery, after which QOL generally improves throughout the course of therapy and into maintenance and survivorship (Meraner et al., 2012; Clevenger et al., 2013; Norton et al., 2004). Patients may attribute improvements in QOL to factors such as spiritual growth (Roland, Rodriguez, Patterson, & Trivers, 2013) and improvement in personal relationships (Stewart, Wong, Duff, Melancon, & Cheung, 2001). However, specific concerns such as sexual difficulties, sleep difficulties, psychological distress, and fear of recurrence may be concurrently endorsed along with reports of improvements in global quality of life (Roland, Rodriguez, Patterson, & Trivers, 2013; Houck, Avis, Gallant, Fuller, &

Goodman, 1999; Stewart, Wong, Duff, Melancon, & Cheung, 2001; Ferrell, Smith, Cuillnane, & Melancon, 2003). This results in a mixed patient experience as time progresses, with some changes contributing to improved quality of life and others impairing QOL. In ovarian cancer, QOL has been significantly associated with shorter survival time (Kornblith et al., 1995; Lakusta, Atkinson, Robinson, Nation, Taenzer, & Campo, 2001). Given the prognostic significance of QOL, investigations into contributors to QOL may have relevance to clinical endpoints as well as to the patient's satisfaction with their life experience.

The following literature review will begin by providing a historical perspective on definitions of the term "stress" and discussing key pathways which constitute the biological stress response. Next, two sections will be devoted to discussing often investigated and specifically timed periods of life stress: recent life stress and early life adversity. Within these sections, definitions, potential pathways to adverse outcomes (on variables of interest in this study, such as sleep, depressive symptomatology, and QOL), and literature investigating outcomes (in healthy populations, cancer populations, and ovarian cancer) will be reviewed. A review of approaches to measurement of life stress which attends to methodological benefits and pitfalls will be conducted. Finally, an interim summary will be provided, followed by the proposed aims of the current study.

Defining Stress

Stress is a broad and multidimensional term which may be differentially defined, as it may relate to emotional, social, physical, or other domains (McEwen, 2008). Selye provided an early contribution in defining "stress" as the body's nonspecific response to any demand placed upon it (Selye, 1956). Selye's "General Adaptation Syndrome"

referred to the body's tendency to respond in a specific fashion to stimuli that disrupt homeostasis, which is the body's attempt to maintain physiological functions within a specific range (Selye, 1956). This "stress response" is composed of three chronological phases of biological activation and recovery: the alarm reaction, the stage of resistance, and the stage of exhaustion (Selye, 1975). Stress-producing activities or agents provoking the General Adaptation Syndrome were termed "stressors" (Seyle, 1973; Selye, 1975). Seyle (1956) also proposed a counterpart to stress called "eustress" which referred to the potential positive adaptations from encountering stressors (e.g., the assessment of external stimuli as challenges as opposed to threats). Eustress also encompassed activities which may produce a significant biological response (such as running a competitive race), yet may ultimately benefit the individual (Selye, 1973). Further refinement of the nature of stress resulted in classification of stressors as acute versus chronic in duration (Lazarus & Folkman, 1984). Lazarus and Folkman (1984) expanded stress conceptualization by proposing individual cognitive characteristics such as appraisal of the nature of the situation and its demands, perceptions of personal resources, and coping efforts as intervening, deterministic variables in the dynamic interplay between the environment and the individual. Life stress is also distinguished from emotional distress, or the negative psychological responses which may be related to or follow stressors (Ensel & Lin, 1991). An integrative definition describes stress as the longitudinal process of the interplay between the individual, their unique adaptive responses, and the environmental challenges they face (Monroe, 2008; Cohen, Kessler, & Gordon, 1995).

Physiology of Stress

In the face of a sufficiently threatening or arousing environmental challenge, the sympathetic nervous system (SNS) and the hypothalamic-pituitary adrenal (HPA) axis activate to translate external stimuli into biological signals (Weiner, 1992). The SNS engages to produce the "fight-or-flight" response, or the evolutionarily adaptive physiological changes that prepare individuals to fend off or escape threats such as increased heart rate and transfer of oxygenated blood to skeletal muscles (Selye, 1956). These SNS changes are primarily mediated by the rapid endocrine and neurotransmitter actions of epinephrine (E) and norepinephrine (NE; Weiner, 1992). The HPA response is initiated by the secretion of corticotropin-releasing hormone (CRH) from the hypothalamus (Chrousos & Gold, 1992), which stimulates the anterior pituitary to secrete adrenocorticotrophic hormone (ACTH). This results in the release of glucocorticoids, such as cortisol, from the adrenal cortex into the system (Chrousos & Gold, 1992). Glucocorticoids serve important regulatory functions in many physiological processes, including circadian rhythms, immune responses, and metabolic activities (Chrousos, 2009). In addition to E, NE, and glucocorticoids, the stress response influences other neuroendocrine factors, such as oxytocin and dopamine (Chrousos, 2009). As these allostatic systems are integrated, stimulation of one response is accompanied by responses in others, resulting in a cascade of multi-systemic actions (Danese & McEwen, 2012).

While the responses above primarily pertain to physiological actions related to acute stressors, activation related to chronic stressors results in different downstream effects. Appropriate adaptation to stress in day-to-day life has been termed as maintaining

a state of "allostasis," or the active process by which the body's physiological systems work to effectively accommodate challenges and maintain homeostasis (McEwen, 2008). If physiological stress processes are persistently or repeatedly challenged, however, one may enter a state of "allostatic load" or overload, where sustained activation of the body's homeostatic systems results in wear and tear on organs and alterations in systemic regulatory responses in the brain and body (McEwan, 2004). This can occur if the body fails to terminate physiological responses when a threat extinguishes, never initially produces an adequate response, or fails to habituate to a repeated threat (McEwen, 2008). Cumulative iterations of stress which produce alterations in homeostatic systems via allostatic load may culminate in mental and physical health disorders, or poorer health outcomes (McEwen, 2004; McEwan, 2008). In acute stress, the activation of the SNS supports a state of inflammation in the body and prepares to fend off potential infection by enhancing vasodilation and transmigration of leukocytes to areas of tissue damage (Bierhaus, Wolf, Andrassy, Rohleder, Humpert, & Petrov, 2003; McEwan, 2004). Chronic stress, conversely, can ultimately suppress cellular immune function via sustained signaling of the same neuroendocrine responses that enhance immunity in acute stress (Dhabar & McEwen, 1999; Kiecolt-Glaser, Marucha, Mercado, Malarkey, & Glaser, 1995). In the cardiovascular system, blood pressure may rise to keep the body upright and prepared for action during acute stress. Conversely, cumulative effects of stress have been implicated in cardiovascular pathology, as sustained elevated blood pressure and inflammation are associated with atherosclerotic processes (Robbie & Libby, 2001) and acute coronary syndrome (Ridker, Cushman, Stampfer, Tracy, & Hennekens, 1997). Stress responses are associated with metabolic changes, as well.

Excess glucocorticoids, helpful in the short term to signal the brain to increase appetite for food and replenish energy after fending off threats, may result in promotion of glucose uptake and poorer insulin action which may ultimately culminate in insulin resistance (McEwen, 2004).

Though outside the aims of the current investigation, it is important to note the role of stress in specific tumor processes. Several lines of research suggest that the stress response can support conditions that favor tumor growth both in the tumor microenvironment and in the organism as a whole (Lutgendorf, Sood, & Antoni, 2010; Armaiz-Pena, Lutgendorf, Cole, & Sood, 2009). Elevated levels of glucocorticoids and catecholamines associated with chronic stress may result in immune suppression enabling cancer cells to avoid surveillance by the immune system (Ben-Eliyahu, Page, Yimirya, & Shankher, 1999), and thus escape destruction (Khong & Restifo, 2002). *In vitro* and pre-clinical studies provide support for relationships between behavioral stress, neuroendocrine hormones and processes implicated in tumor growth including angiogenesis (Thaker et al., 2006), invasion and metastasis, (Sloan et al., 2010; Marchetti et al., 1991; Voss & Entschladen, 2010; Sood et al., 2006), and evasion of programmed cell death ("anoikis;" Sood et al., 2010). Thus, life stress has implications for important tumor-related activities as well as physical and psychological outcomes.

Recent Life Stress

Recent life stress: definition and relationships with depressive symptomatology. Recent life stress regards accounts of events, difficulties, and perceptions of stress occurring in a pre-defined, retrospectively recalled period of time relative to the assessment period. Well-established relationships between recent life stress

and depression are demonstrated in the literature in non-cancer populations. In qualitative reviews, there is a consistent association found between number and severity of recent life events and the onset of a major depressive episode (Kessler, 1997; Kendler et al., 1999). In community samples, a major life event occurred before the onset of the depressive episode in 80% of cases (Mazure, 1998). Though a full review of the pathways of recent life stress and depressive symptoms is outside of the scope and aims of this paper, one major pathway implicated involves immune dysregulation leading to alterations in proinflammatory cytokines (see reviews Miller, Maletic, & Raison. 2009; Slavich & Irwin, 2014). Further, epigenetic relationships of gene by life stress interactions appear to predict depressive symptoms following stressors (Kendler et al., 1995; Hammen, 2005; Heim & Binder, 2012). Psychological factors, such as a negative attribution style when interpreting events (Lewinsohn, Joiner, & Rohde, 2001) and personality characteristics such as high trait neuroticism (Kendler, Kuhn, & Prescott, 2004), are also commonly implicated as contributors to the influence of stress on depressive symptoms. Of note, relationships between recent life events and depressive symptomatology appear to strengthen depending on stress measurement strategy. For example, they become stronger when interview-based, contextual measures of stress such as the Life Events and Difficulties Schedule (LEDS, which will be discussed in detail in a later section) are employed as opposed to event checklists (Kessler, 1997). Further, the LEDS is highlighted as an advantageous assessment method when examining life stress and depressive symptoms as it may overcome personal biases and meaning factors, which may drive how individuals recall events (Hammen, 2005).

Recent life stress and sleep. Stressful events are also related to alterations in sleep in the general population. For example, events themselves and the appraisals of these events are related to insomnia (Healey et al., 1981; Morin, Rodrigue, & Ivers, 2002; Hall et al., 2000). Individuals who report that they experience stress-related sleep dysfunction (e.g., difficulty falling asleep and nighttime awakenings) demonstrate worse nighttime sleep in a laboratory, as measured by polysomnography, when compared to those who do not indicate high levels of stress-related sleep difficulties (Drake, Richardson, Roehrs, Scofield, & Roth, 2004). Sleep may be adversely affected by life stress due to psychological processes following the stressors (e.g., worry, rumination; Winbush, Gross, & Kreitzer, 2007). When one attempts to sleep and these processes arise, they further intensify the physiological arousal which makes sleep initiation increasingly difficult; eventually, this cycle may alter behavioral patterns which continue to exacerbate the cycle of poor sleep (Vgontzas & Kales, 1999). Further, proinflammatory cytokine influences on sleep are well documented. Primarily, interleukin-6, an important cytokine which mediates the interplay between the CNS and immune system, is considered a "sleepiness" cytokine: its secretion is directly influenced by sleep and it modulates the sleep drive, leading to regulation of the sleep cycle (Vgontzas et al., 1999, 2005; Rohleder, Aringer, & Boentart, 2012). In turn, as sleep loss influences the immune system via hypersecretion of IL-6, this may contribute to a cyclical relationship between life stress, IL-6, and maintenance and exacerbation of sleep disruption (Rohleder, Aringer, & Boentart, 2012; Opp, 2005; Vgontzas, 2004). Thus, psychological, behavioral, and physiological pathways may interact to predict poorer sleep following life stress.

Recent life stress and psychological outcomes in cancer populations. Recent life stress is related to psychological and QOL outcomes in cancer populations. In a sample of women with breast cancer, having a greater number of life events in the past year was significantly related to higher distress (Green et al., 2000). Among heterogeneous (i.e., multiple primary sites) cancer patients admitted to the hospital, recent life events were related to both clinical and subclinical depression symptoms (Bukberg, Penman, & Holland, 1984). Financial life events in the year prior to cancer diagnosis were associated with depressive symptoms in breast cancer patients (Golden-Kreutz & Andersen, 2004). Women reporting one or more stressful life events occurring between baseline and 6 months post-diagnosis experienced declines in their QOL through the 18 months after their diagnosis (DiSipio, Hayes, Battistutta, Newman, & Janda, 2011). Findings also link poorer quality of life and depressive symptoms to life events occurring in the year prior to a new diagnosis with melanoma, breast, and prostate cancers (Lehto, Ojanen, Vakeva, Aromaa, & Kellokumpu-Lehtinen, 2008). Unfortunately, no studies were identified which specifically examined the role of recent life stress and sleep disruption in cancer populations.

In ovarian cancer, no studies were identified which investigated recent life stress as related to depressive symptomatology and sleep, variables which are of clinical significance and contribute to QOL (Clevenger et al., 2013; Sandadi et al., 2011; Bodurka-Bevers et al., 2000; Arden-Close, Gidron, & Moss-Morris, 2008). However, two studies (both using checklist measures) explore the impact of recent life events on QOL. In the first, stressors occurring prior to surgery did not influence baseline psychosocial presentation; however, stressors and their subjective severity were prospectively

associated with QOL at one year post diagnosis (Lutgendorf et al., 2013). In early stage survivors of ovarian cancer, those reporting fewer recent life events reported better mental health compared to those reporting more stressful life events (Matulonis et al., 2008). In sum, these studies point to a role of life stress on psychosocial outcomes in cancer; however, the impact of recent life stress on depressive symptomatology and sleep in ovarian cancer is currently unknown. Given the well-supported evidence for the relationship between recent life stress and these outcomes in the general population, and the importance of these variables on the patient experience when they may face limited life, exploring life stress as it relates to depression, sleep, and QOL in ovarian cancer is of particular importance.

Early Life Adversity

Definition of early life adversity. Adverse experiences occurring in childhood and adolescence are viewed as particularly psychologically and physiologically impactful**.** Definitions of the types of relevant experiences vary in specificity. Childhood maltreatment, for example, occurs in the context of a relationship of trust, responsibility, or power, and encompasses all physical maltreatment, emotional maltreatment, sexual abuse, neglectful treatment, or exploitation of children which has the potential for or realization of harm to the individual's health, survival, development, or dignity (Krug, Dahlberg, Mercy, Zwi, & Lozano, 2002). However, some definitions of early life adversity consider other formative experiences and environmental conditions which may have long term deleterious effects. Adverse childhood experiences (ACE), for example, include sexual, physical, and emotional abuse and neglect experienced by the child; they also encompass other environmental factors such as domestic violence where the mother

(but not the child) was the victim, drug and alcohol abuse by a household member, marital discord, a household member going to prison, or a household member who experienced mental illness (Felitti et al., 1998). ACE, thus, encompass both direct experiences (i.e., those happening "to" the child) as well as contextual, environmental stressors (i.e., those happening "around" the child), which may exert toxic effects on the individual's health and well-being (Shonkoff et al., 2012). Adjustment and maladjustment to experiences in childhood is thought to result in a continuum of psychological and physiological consequences, whereby some individuals evidence good mental and physical health, whereas others may experience severe, persistent, and comorbid psychiatric and physical complaints (Ehlert, 2013). Effects of childhood adversity are considered to be additive, as experiences of multiple sources of stress that are interconnected are common and have the most powerful effects on adult outcomes (Kessler, Davis, & Kendler, 1997; Ehlert, 2013).

Impact of early adversity on the developing brain and inflammatory response. As the brain develops in childhood, adverse experiences may impact the architecture of the brain via hormonal modulation of brain structures. These effects, relating in part to the physiological stress response, have the capability to affect both physical and mental health. The size and architecture of the amygdala, hippocampus, and prefrontal cortex (PFC), all fundamental in the initiation and termination of the physiological stress response, may be influenced by chronic stress in childhood, as these structures contain glucocorticoid receptors (McEwan & Gianaros, 2011; Heim et al., 2000). The impact of childhood adversity on the amygdala may result in two types of outcomes. First, as the amygdala stimulates the hypothalamus to release CRH to initiate

the HPA response to stress, the amygdala's role in the feedback loop may be impaired, resulting in an over-responsive or persistently activated physiological stress state (Tottenham & Sheridan, 2010; Shonkoff et al., 2012). Second, emotional dysregulation becomes increasingly likely, manifested in experiences of fear and anxiety (Tottenham & Sheridan, 2010). Further, a state of persistent activation of the stress response reduces the ability of the hippocampus to terminate continued cortisol production. High levels of cortisol have been shown to inhibit neurogenesis in the hippocampus; thus, memory encoding and functional learning are impacted, leading to impaired development of cognitive, emotional, social, and behavioral skillsets (Pine et al., 2005; Dannlowski et al., 2012). The impact of chronic stress may influence connectivity in the PFC, which can yield consequences on executive functioning, impulse and behavioral control, and mood regulation; this has a significant impact for risky behavioral choices and poor health behaviors later in life (Boyce & Ellis, 2005; Shonkoff et al., 2012). Thus, alterations in these fundamental brain structures are linked to behaviors and emotional experience, lending support to the examination of the role of early childhood adversity on psychological and QOL outcomes in ovarian cancer.

In addition to the central nervous system, early life adversity also appears to modulate the inflammatory response. Individuals with a previous exposure to adversity show elevated inflammatory markers as compared with those without adverse experiences in childhood (Danese et al., 2010; Fagundes, Glaser, & Kiecolt-Glaser, 2013) as well as adulthood (Danese et al., 2007). Further, individuals with a history of early life adversity show more pronounced stress responses to acute, laboratory induced and daily occurring stressors than those without childhood stress (Pace et al., 2006; Carpenter et al.,

2010; Gouin, Glaser, Malarkey, Beversdorf, & Kiecolt-Glaser, 2012). Taken together, effects of childhood adversity are thought to occur via changes in brain architecture, functioning of the immune system, health behaviors, emotional reactivity, and social functioning. Necessarily, these domains tend to create numerous cascading pathways which may be consequential in adult ill-being. These interactive, bidirectional, and cumulative effects create a context for risk for multiple, comorbid psychological and physiological conditions.

The effect of childhood adversity on psychological health. There is clear support for a deleterious effect of childhood adversity on adult psychological functioning. The amygdala is critically involved in how the individual assigns emotional salience to environmental events (LeDoux, 2000). Alterations in the amygdala, as described above, precipitate emotional dysregulation as indicated by greater anxiety and fear (McEwan & Gianaros, 2011; Tottenham & Sheridan, 2010). Chronic stress may also enhance fear conditioning processes, which are mediated in part by the amygdala (Conrad, LeDoux, Magarinos, & McEwan, 1999) and impair new contextual learning (Shonkoff et al., 2012). Early adversity may sensitize individuals to experience stressors as more threatening than those without such childhood experiences (Miller, Chen, & Parker, 2011), leading to more pronounced emotional responses to stimuli. In total, immunological and anatomical brain changes related to early childhood adversity may impair resilience as the individual faces new challenges, appraises them, determines their significance, and develops an emotional response (McEwan & Gianaros, 2011). Further, the relationship between early life adversity and poorer psychological outcomes may be additive in nature, as studies in community samples report significantly poorer

psychological functioning in those endorsing more than one type of adversity as compared to those reporting a single source (Mullen, Martin, Anderson, Romans, & Herbison, 1996; Edwards, Holden, Felitti, & Anda, 2003).

Early life adversity and depressive symptomatology. An association between early life adversity and subsequent depressive symptomatology has been clearly described in non-cancer populations, as evidenced by greater occurrence of DSM-IV diagnoses of depression (Kessler et al., 2010), greater depressive symptomology, greater depressive affect, and increased suicide attempts in those with a history of childhood adversity (Norman, Byambaa, De, Butchart, Scott, & Vos, 2012; Felitti et al., 1998; Dube, Felitti, Dong, Giles, & Anda, 2003; Dube et al., 2001). Further, this effect may manifest as early as adolescence (Rao, Chen, Bidesi, Shad, Thomas, & Hammen, 2010) and pervade multiple types of adversity, including poor relationships with parents (Lizardi et al., 1995), parental loss (Agid et al., 1999), and more serious forms of maltreatment including abuse (Edwards et al., 2003). Importantly, a unique role for early life stress as predictive of subsequent depression independent of genetics has been identified using twin studies (Kendler, Thornton, & Gardner, 2001; Nelson et al., 2002). A key finding describes that changes in hippocampal volume observed in depressed adults appear to be driven by subgroups of patients who experienced early life adversity, and that these groups of individuals with both major depression and early adversity appear to benefit from different forms of treatment (Vythilingam et al., 2002; Nemeroff et al., 2003). This underscores the importance of investigations which carefully examine the differential effects of stressors timed in early life versus adulthood, as elucidation of the active ingredients contributing to depressive symptoms in a population such as

women with ovarian cancer could serve to guide selection of more effective clinical interventions.

Early life adversity and sleep. Sleep, similarly, has been examined as it relates to early life stress, and a relationship is evident in childhood and adulthood. In childhood, numerous indices of sleep (including difficulties falling asleep or insomnia, frequent nighttime wakening, non-restorative sleep, and nightmares) are associated with childhood maltreatment (Glod, Teicher, Hartman, & Harakal, 1997), marital discord in the home environment (El-Sheikh, Buckhalt, Mize, & Acebo, 2006), poor relationships with parents (Liu et al., 2000), and familial conflict in the childhood home (Gregory, Caspi, Moffitt, & Poulton, 2006). Adults who experience adverse childhood events reported more difficulty falling and staying asleep compared to those without childhood adversity, an effect which appeared to demonstrate a dose-response relationship (Chapman et al., 2011; Chapman et al., 2013). In a large, population-based study of over 25,000 Finnish residents, poor relationships with parents, fear of family members, and serious environmental conflicts were associated with poor sleep quality in adulthood (Koskenvuo, Hublin, Partinen, Paunio, & Koskenvuo, 2010). While these studies describe self-reported sleep quality, designs using objective measures such as actigraphy and polysomnography support these findings (Bader, Schäfer, Schenkel, Nissen, & Schwander, 2007; Schäfer & Bader, 2012). Links between early adversity and sleep may be explained, in part, by immunological changes and proinflammatory cytokine influences (as described above), as well as longstanding conditioned fear responses which interfere with the ability for individuals to fall asleep and maintain restful sleep in a context associated with strife (Charuvastra & Cloitre, 2009). Lastly, poor sleep behaviors

related to the cycle of emotional distress contributing to increased arousal and exacerbation of difficulty sleeping (Vgontzas & Kales, 1999) may be long engrained and contribute to sleep disruption in adulthood.

Early life adversity and psychological outcomes in cancer populations. Regarding psychological outcomes of those experiencing early life adversity in cancer populations, in a prospective assessment of head, neck, and colorectal cancer patients, higher scores on a childhood trauma scale were related to high levels of depressive symptoms at baseline for all patients, and at one and two-year follow-ups for head and neck cancer patients (Archer, Hutchinson, Dorudi, Stansfeld, & Korzsun, 2012). Breast cancer patients endorsing greater childhood adversity reported worse depressive symptomatology and poorer sleep than those with comparatively fewer sources of childhood adversity (Fagundes, Glaser, Malarkey, & Kiecolt-Glaser, 2013). In a prospective study of early-stage breast cancer patients, emotional abuse and neglect were significantly associated with post-surgical depressive symptomatology, higher perceived stress, elevated levels of fatigue, and poorer QOL; further, childhood physical neglect was associated with a trend towards significantly less improvement in QOL over time (Janusek, Tell, Albuquerque, & Mathews, 2013). Despite evidence demonstrating relationships between early life adversity and psychological outcomes in cancer populations, at present, no studies exist which have examined the role of early life stress on psychosocial outcomes in ovarian cancer. Elucidating the role of early life adversity on psychological presentation and trajectory in women with ovarian cancer would extend existing literature and may provide insight into a possible contributor to psychological

functioning and outcomes in a malignancy characterized by high distress and impaired QOL.

Investigations Measuring Both Early Life Adversity and Recent Life Stress in Cancer Populations

In the context of cancer and psychological outcomes, few studies to date have operationalized early and recent life stress to examine their independent effects on psychological, or other, outcome measures. Fagundes and colleagues (2012) used the LEDS stress interview to assess current life stress and the Childhood Experience of Care and Abuse questionnaire to assess early life adversity in a population of patients with basal cell carcinoma. Patients who experienced maltreatment by their father in early life had higher subsequent depressive symptomatology, and recent life events were not associated with depression. Another study exploring stress exposure in women with breast cancer reported that those endorsing higher fatigue scores reported more early life and recent life stress exposures than were reported in non-fatigued breast cancer control patients (Bower, Crosswell, & Slavich, 2014). One study assessed both childhood trauma and recent life events (using questionnaire methods) in colorectal and head and neck cancer patients (Archer, Hutchinson, Dorudi, Stansfeld, & Korzsun, 2012). In colorectal cancer patients, childhood trauma scores were predictive of depression at baseline, 6 weeks, 12 weeks, and 24 weeks, whereas number of recent life events predicted depressive symptoms only at 24 week follow up. In head and neck cancer patients, number of life events emerged as a predictor of depression at baseline, 6 weeks and 24 weeks, whereas childhood trauma predicted higher depression at baseline, 12 weeks, and 24 weeks. This study highlights a differential pattern of prediction of specifically timed

life stressors in oncology populations. No studies were identified which examined both early life adversity and recent life stress in ovarian cancer populations.

Stress Measurement

Life stress has typically been measured according to three traditions. The first method utilizes checklists or life event lists where individuals endorse occurrence of specific events within important life domains cued to a specified time period (e.g., in the past year; Holmes & Rahe, 1967). A review of general stress methodology identified more than 10,000 publications relevant to stressful life events since 1967 (Dohrenwend, 2006), underscoring the ubiquitous conceptualization of stress as defined by life event experiences (or, external environmental "stressors"). Of note, assessment of early life adversity in research has often followed this tradition, with measures such as the Childhood Trauma Questionnaire (Bernstein et al., 1994) and the Adverse Childhood Experiences checklist (Felitti et al., 1998). This method has been advantageous as it is efficient, standardized in administration due to relative simplicity of the instructions, minimally labor intensive for researchers, and somewhat objective in its indication of life stress (Monroe, 2008; Dohrenwend, Link, Kern, Shrout, & Markowitz, 1990). However, event list measures have been extensively criticized. A primary criticism pertains to intra-category variability (Dohrenwend, 2006). When asked to endorse if a stressful event category occurred, the respondent may generate multiple salient variants within any given category which may differ in level of stress and influence the individual's rating (Dohrenwend, 2006; Dohrenwend, Link, Kern, Shrout, & Markowitz, 1990). For example, the category "job loss" may produce multiple exemplars one may use to guide their rating, such as the notification of the job loss or the end of working under stressful

conditions. These respondent-based endorsements of events and their impact have also been criticized as the presence of psychopathology and the rater's mood at the time of measurement may influence the individual's report (Monroe & Simons, 1991). Further, these measures typically do not distinguish acute from chronic stress (McQuaid et al., 1992) and may fail to provide information which accurately accounts for the implications of the event given the individual's broader personal biographical context, which likely impacts the experience of the stressor (Monroe & Roberts, 1990). Lastly, life event lists may suffer from a lack of reliability, as retested recall of events often produces different response sets (Raphael, Cloitre, & Dohrenwend, 1991; Steele, Henderson, & Duncan-Jones, 1990).

A second method of stress measurement focuses on the subjective experience of stress in one's general activities of day-to-day life. For example, the Perceived Stress Scale (PSS; Cohen, Kamarck, & Mermelstein, 1983) obtains ratings of the individual's perception of their daily life as "unpredictable, uncontrollable, and overloading" (Cohen, Kamarck, & Mermelstein, 1983, p.387). Perception ratings are different from event-based ratings in that specific events themselves are not considered sufficient indicators of stress (Cohen, Kamarck, & Mermelstein, 1983). Conversely, they may reflect the potential additive effects of multiple stressors (Dohrenwend & Dohrenwend, 1974) and they emphasize the theoretical role of the individual's cognitive appraisal process as important in the experience of life stress (Lazarus, 1977). This can be an advantageous method in that the individual may be better able to report on their personal, cumulative experience of life stress. Some have criticized perceived stress measures for reasons similar to those of event lists, as they may suffer from similar reporting biases such as the

influence of current mood on responses to items and lack of account for the individual's biographical circumstance (Monroe & Simons, 1991).

A third technique employs the use of semi-structured and structured interviews. These techniques are able to provide detailed accounts of the nature, impact, and overall meaning of events to the subject by obtaining contextual and biographical details of the individual's life in which to situate these events in the rating process. They also offer opportunity for the individual to report on more chronic, persistent forms of stress (Monroe, 2008). For example, Brown and Harris' Life Events and Difficulties Schedule (LEDS) obtains information regarding early life experiences and recent life stress, defines the severity of the threat for each event or chronic difficulty, obtains event timing, determines factors which may contribute to poorer outcomes after an event, and categorizes events and difficulties into groups and subgroups (Brown & Harris, 1978). Trained interviewers guide subjects to answer questions regarding their understanding of the event and its implications, as opposed to probing how the event made the individual feel; this may circumvent limitations of other measures where data from the individual may be influenced by their emotional response to the event or current mood. Raters utilize an extensive manual to provide event ratings of the information presented in summaries, which may overcome the limits of subjective stress impact ratings described previously (Brown & Harris, 1978; Monroe, 2008). Interview techniques typically differ from checklists in reports of stressful events, where checklists generally result in underreporting compared to interviews (Lewinsohn, Rohde, & Gau, 2003; Duggal et al., 2000). However, they are more time consuming and expensive to utilize in research due to the necessary training of interviewers, interview time, and rating procedures. Further,

they rely in part on the administrator's interpretation of the respondent's reports, as well as the individual's ability to accurately report their experiences in detail (McQuaid et al., 1992). Nevertheless, multiple reviews consistently advocate for interview-based life stress techniques as maximally preferable to their counterparts (Dohrenwend, 2006; Paykel, 2001), and the LEDS system is considered a gold standard of stress measurement.

Generally, measurement of stress has intrinsic drawbacks to consider. Stress assessment is inherently retrospective in the absence of objective data, obtained traditionally by record searches of sources such as national databases or census information. Further, in any stress assessment, the question of threshold is ubiquitous. For a given individual, there is a personal threshold utilized to determine if something is sufficient to be recalled as, and reported as, an event (Monroe & Roberts, 1990). While measures which utilize trained raters to determine event significance may serve to partially overcome this issue by probing for details, the respondent dictates what events are rated (as they may not consider it appropriate to mention some events when prompted). As with other retrospective techniques, general reliability of recall is questionable, particularly when the recall period is lengthy (i.e., multiple years; Monroe, 1982). For studies within the context of cancer, the response bias termed "effort after meaning" may be present when measurement takes place after diagnosis or recurrence. This refers to the individual's tendency to search their history for events and report events as stressful as a way to make sense of the diagnosis. This is thought to result in over-reporting of events one considers might have influenced their disease process (Brown & Harris, 1978; Paykel & Rao, 1984). Though often dependent upon longitudinal design,

prospective assessment of events prior to the outcomes of interest may circumvent this tendency and reduce bias in recall.

Despite collection of both recent stress and early adversity information, the LEDS system has generally been utilized in research mainly for the purposes of examining effects of recent life experiences, without exploration of the early life adversity data. One study to date has partially operationalized early childhood adversity from the LEDS interview, specifically focusing on early experiences of interpersonal loss (such as death or separation from a parent; Slavich, Monroe, & Gotlib, 2011). However, a system to extract and utilize information reflective of all early life experiences obtained in the LEDS has yet to be presented in the literature.

Brief Summary and Specific Aims of the Proposed Study

Ovarian cancer is a malignancy characterized by poor prognosis and high levels of distress. Impaired QOL is well documented in this patient population, and investigation into the contributors to QOL is of psychological and prognostic significance. Contemporary stress theories and empirical accounts identify early life experiences and recent life stressors as those which yield significant impact on psychological health. To date, life stress research in cancer has yielded few designs which operationalize both indices of early and recent life stress exposures. Moreover, despite the high-resolution stress data provided by the LEDS system, no studies were identified which comprehensively operationalized the early life adversity data obtained during each interview.

Therefore, the proposed study addressed three primary objectives. It is the first of its kind to comprehensively extract and examine effects of early life adversity data

collected as part of the LEDS interview in a cancer population. It also is the first to examine independent influences of specifically timed life stress indices on variables important to psychosocial functioning in ovarian cancer cross-sectionally as well as prospectively over one year of assessment. Exploration of dimensions of the patient's early life histories and recent life stress enabled unique examination of hypotheses anchored in stress theories delineating clear influences of early adversity on subsequent mental and physical health and the necessity of assessing and testing specifically timed life stress exposures.

Specific aim #1. To provide a detailed, descriptive account of the frequency and features of early life adversity in women with ovarian cancer and to examine the relationships between early life adversity and subsequent recent life stress (as obtained by standardized LEDS ratings).

Hypothesis 1: Women with ovarian cancer will report early life adversity experiences varying in number and severity, and consistent with previous research (Hammen, 2005), individuals experiencing early life adversity will report more instances of recent life stress.

Specific aim #2. To examine the influences of early life adversity and recently experienced life stress on the psychological presentation of patients prior to diagnostic surgery for ovarian cancer.

Hypothesis 2a: Women who report a higher number and greater severity of early life adversity experiences will endorse worse depressive symptoms, sleep, and QOL prior to surgery.

Hypothesis 2b: Recent life stress alone, measured as 1) number of life events, 2) combined threat of life events, 3) number of ongoing difficulties, and 4) combined threat of ongoing difficulties (referred to as "recent life stress" herein), will not be associated with depression, sleep, and quality of life at pre-surgery, replicating findings previously documented by our laboratory (Lutgendorf et al., 2013).

Specific aim #3. To examine effects of early life adversity and recent life stress on the trajectory of psychosocial functioning over time using longitudinal data collected from pre-surgery, six months after diagnosis, and one year after diagnosis.

Hypothesis 3a: Those experiencing a higher number and greater severity of early life adversity will evidence poorer recovery in depressive symptomatology, sleep, and QOL over time.

Hypothesis 3b: Recent life stress will be associated with impaired recovery in depressive symptomatology, sleep, and QOL over time.

RESEARCH DESIGN AND METHOD

Participants

Women were recruited as part of a larger study examining biobehavioral influences on tumor progression in epithelial ovarian cancer. Potential participants presented at gynecology oncology clinics at the University of Iowa Hospitals and Clinics and Washington University in St. Louis for assessment of a pelvic mass suspicious for ovarian, fallopian tube, or primary peritoneal cancers, as these cancers are similar in morphology, clinical management, and trajectory (Hennessy, Coleman, & Markman, 2009); these cancers will be referred to as "ovarian cancer" herein. Patients were deemed eligible for inclusion in the present study if they were between 18 and 100 years of age, without severe cognitive impairment (e.g., dementia), not using systemic corticosteroid medications within the last month, not currently pregnant, not diagnosed with medical conditions with known effects on the immune system (i.e., hepatitis, human immunodeficiency virus) or cirrhosis of the liver, not diagnosed with cancer of another primary site within the last five years (including recurrences), and proficient in English or Spanish languages. Patients receiving surgical intervention followed by adjuvant treatment as well as those who received neoadjuvant chemotherapy were eligible for inclusion.

Procedures

Patient Screening and Recruitment. Research coordinators at both sites screened new gynecologic oncology referrals for potential ovarian patients and discussed the patient's likelihood of diagnosis with ovarian cancer in person with the attending physician. Eligible women were informed that participation in the current study included

completion of three assessments involving questionnaires and biological specimens, as well as completion of an interview following their surgery or initiation of neoadjuvant chemotherapy. The unifying criteria for eligibility for the study was a suspicious pelvic mass, and eligibility was confirmed following histological diagnosis of epithelial ovarian cancer. Participants who were diagnosed with benign, low-malignant potential tumors, and cancers of other primary sites were not included in the present study. Study participants were offered the option of a free local hotel stay the night prior to their surgery and $25 for completion of each follow-up assessment. This study was approved by Institutional Review Boards at the University of Iowa and Washington University in St. Louis.

Assessments. Following consent, participants were provided materials to complete for the pre-surgical or pre-neoadjuvant chemotherapy time point. The initial assessment involved completion of questionnaires. After definitive diagnosis of epithelial ovarian cancer, women were contacted either in person (as inpatients in the post-operative recovery period or at scheduled post-surgical clinic follow-up appointments) or by phone to schedule a time to complete the life stress interview. Approximately six months and one year after initially consenting to participate, women completed two additional assessments. At each time, participants received surveys in the mail to be completed and returned to the research staff at a scheduled visit to the clinic, or by mail if the participant did not have a planned upcoming visit.

Measures

Depression. Depressive symptomatology was assessed using the Center for Epidemiological Studies-Depression Scale (CES-D; Radloff, 1977). This 20-item self-

report measure assesses for mood ratings cued to the previous seven days, where a higher score on the CES-D indicates greater depressive symptomology. Items are rated from 0 ("rarely") to 3 ("most of the time"). A cut off score of 16 and above has been established as indicative of clinical depression (Radloff, 1977). The CES-D is considered both valid and reliable for assessment of depressive symptoms in cancer patients. It demonstrates construct validity, strong correlation with other measures of psychological distress, discrimination of patients with depressive symptoms from a reference group, adequate test-retest reliability, and internal consistency ($\alpha = .85$) in both healthy and oncology populations (Hann, Winter, & Jacobsen, 1999; Schroevers, Sanderman, van Sonderen, & Ranchor, 2000). The total depression score was used in the current study.

Sleep. The Pittsburgh Sleep Quality Index (PSQI) includes 19 self-reported items assessing type and frequency of sleep disturbances cued to the previous month. A global sleep score is obtained by summing seven component scores which assess for subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction (Buysse, Reynolds III, Monk, Berman, & Kupfer, 1989). A cutoff score of greater than five discriminates those who experience poor sleep and has a diagnostic sensitivity of 89.6% and specificity of 86.5% (kappa=.75; Buysse, Reynolds III, Monk, Berman, & Kupfer, 1989). The PSQI has a high degree of internal consistency ($\alpha = .83$) and correlates well with objective sleep measures such as polysomnography (Buysse, Reynolds III, Monk, Berman, & Kupfer, 1989). The PSQI has demonstrated reliability and validity in cancer patients as well, with good internal consistency (α's range from .77-.81) and construct validity (Beck, Schwartz, Towsley,

Dudley, & Barsevick, 2004) documented. Sleep data was collected for participants at the University of Iowa, but not those at Washington University – St. Louis.

Early adversity and recent life stress. The Life Events and Difficulties Schedule (LEDS) interview was completed once following confirmed diagnosis of ovarian cancer as the primary measure of early life adversity and recent life stress. The LEDS assesses life stress as contextually driven: a life experience is situated within the individual's broader life context, which shapes their meaning and understanding of an event (Brown & Harris, 1989). Therefore, the interview begins with collection of biographical circumstances, including current family, family of origin and location of upbringing, history of romantic relationships, employment, and the individual's current social network and primary confidants. The interviewer then probes 10 domains of life (health, role changes, leisure/interaction, housing, employment/school, financial, marital/other relationships, interactions with parents/other relatives, children, and crises, as well as general section regarding life regrets and satisfaction) for stressors experienced in the defined time frame. For the present study, information on potential stressful experiences was probed for a one-year period prior to diagnosis. While the participant may provide emotional responses and reactions to events, the interviewer obtains contextual details of events (such as specific impact on day-to-day life, functioning in typical activities, and financial impact). The interviewer then creates a summary providing the biographical context, current support network, and other notable experiences of the individual, followed by a summary of the events and difficulties, including date, nature of the event, and impact on life. Summaries are presented to the rating team, who initially review each summary and ask clarifying questions of the interviewer. Afterward, the rating team

utilizes a standard procedure described below to operationalize summaries into numeric data.

Training of interviewers. Interviewers received approximately 16 hours of primary training, followed by close supervision throughout the study's duration. Sessions began with review of the didactic materials, clarification of the goals and intention of the interview, and answering of initial questions (approximately 2-3 hours in total). Next, trainees conducted live practice interviews with volunteer participants who had been provided a standardized interview role detailing demographic circumstances and all recent life events with the trainer observing. Interviewers conducted approximately 3-5 practice interviews over the two-day training, and the trainer provided feedback regarding successful aspects as well as areas for improvement regarding comprehensive stressor assessment and rapport. Interviewers were then trained on composition of summaries. New interviewers were closely supervised through their first interviews by the author using electronic review of summaries and in-person supervision. Afterward, interviewers received ongoing supervision and frequently asked questions regarding rapport, interviewing technique, and clarification of key information to obtain.

Interview ratings. Becoming a reliable LEDS rater is a process which involves an intensive and lengthy training experience. Therefore, an expert team of 2-4 trained LEDS system raters at the University of California – Los Angeles (UCLA) conducted the ratings of life events and difficulties data. Each individual reviewed summaries and provided ratings of stressors using a 520-page manual. The coding manual provides two sources of information used in conjunction to rate stressors: rules and criteria for rating life stress and case vignettes, which are used as standardized anchors on which personnel

base their ratings (Brown & Harris, 1989). Next, all members of the team met to discuss their independent ratings to arrive at consensus values. For the purposes of this study, raters were aware that all participants had ovarian cancer but were kept blind to other clinical characteristics such as the stage and grade of cancer (unless those arose by participant report in the LEDS).

Two major categories of stress are obtained from the LEDS: acute life events and ongoing difficulties. Acute life events are experiences that are generally considered unpleasant and have some degree of threat for the individual (Brown & Harris, 1989). Life events typically happen to the subject (for example, the subject loses their job); however, events occurring to other individuals who are in the close social network of the subject (spouses, household members, close relatives, and confidants) are also included (for example, the subject's partner loses their job). Each event receives a threat rating, which is an assessment of the degree to which a given event has significant implications for the subject's goals, future plans, and aspirations given their unique contextual background (Brown & Harris, 1978). Threat ratings range from "1", or a stressor with very little negative impact, to "4", or stressors with marked threat (Brown & Harris, 1978). For the purposes of the current study, two indices of recent life stress were utilized: number of life events and cumulative threat experienced by these life events. Further, for the purposes of this study, the term "severity" will be used as a proxy for "contextual threat."

Ongoing difficulties, conversely, are problematic circumstances which last, at minimum, four weeks in duration (Brown & Harris, 1989). Ongoing difficulties generally arise from an initial acute event; however, not all of the onset events are captured by the

LEDS interview due to the longstanding nature of many life difficulties. Examples of ongoing difficulties may be providing long-term financial support to a relative or prolonged marital discord. Ongoing difficulties also receive a contextual threat rating on the one to four scale described above. Two indices of ongoing difficulties were utilized for analyses: number of ongoing difficulties and severity (contextual threat) of difficulties.

Early life adversity coding. While the LEDS interview obtains information regarding early life adversity, coding or rating of this data was not completed by the rating team at UCLA. The interview probes numerous sources of potential childhood adversity by asking standardized questions regarding the individual's biographical history. For example, questions regarding the area of upbringing, siblings, birth order, death of siblings, death of parents, separation or divorce of parents, who primarily raised the participant, and any instances of memorable separation (and their causes) of the individual from their parents prior to the age of 17 are asked. Throughout the course of the interview, a question regarding history of experiences of being sexually approached against one's will was also asked. The responses to these questions served as the basis for the LEDS early life adversity data coded by the author, operationalized as indications of these experiences prior to the age of 18. Following completion of interview, the author reviewed each of the 137 interview summaries and extracted any information relevant to the interview questions described above. This information was transferred onto an Excel spreadsheet where each statement constituted an individual event. In order to create the most sensitive measure of early life adversity based upon the interview questions, statements were treated as independent so that potential linkages between experiences

would not obscure assessment of an additional source of stress. For example, should a respondent's summary read "Parental divorce at age 13. Subject then did not see her father again until adulthood," two events would be listed ("parental divorce at age 13" and "subject separated from her father from age 13 to adulthood") separately and assigned individual severity ratings.

In conjunction with another of the research study's master's-level trained LEDS interviewers, a system for coding severity of early life adversity was developed. Utilizing the original LEDS system threat rating values as an exact template, the author and second coder independently rated each event using the following system: 4 indicating "marked threat/unpleasantness," or threat to the subject expected to be considerable in commonsense terms (such as a death of a close relative); 3 indicating "moderate threat/unpleasantness," or threat to the subject rated as decidedly unpleasant or threatening where a situation did not considerably improve in terms of impact felt after 10-14 days; 2 indicating "some threat/unpleasantness," or sources where the implications of the situation carry little threat after 10-14 days; and 1 indicating "little or no threat/unpleasantness," or situations where the negative implications of events have completely cleared by the end of 10-14 days or the event was positive in nature.

Each rater was provided an Excel sheet for independent coding, and raters attempted a first coding and met to discuss themes of coding difficulty. Examples include situations which would likely have a level 3 rating (e.g., parental divorce) that were indicated by the subject to have solved a difficult home situation. The author compiled ratings using SPSS v. 21.0 and calculated an interrater reliability coefficient (Kappa), which was rated at .55. Raters then had a joint meeting to discuss and provide guidelines

for commonly occurring events. For example, any stressor where the respondent indicated a situational improvement afterward received a rating of "1," any death of an immediate family member received a rating of "4," and divorce related stressors received ratings of "3." Following establishment of new guidelines, raters again independently coded each stressor and had a second meeting to calculate Kappa, which reached a level of .82, indicating very good agreement (Fleiss, 1981). Lastly, raters met for a third session and discussed any remaining discrepant severity ratings and reached a consensus agreement for a final rating value.

Numerous variables were created based upon the early life adversity data, including a dichotomous variable indicating any experience of early child adversity and a summed variable reflecting the number of sources of childhood adversity (as multiple sources of adversity tend to be associated with outcomes and reflect the true picture of early life stress experiences; e.g. Shonkoff et al., 2012). For example, an individual with a biographical history of a medical hospitalization in youth and the death of a sibling would receive a "1" on the dichotomous adversity variable, and a "2" on the number of sources of adversity variable. Next, a summary of total severity ratings for all adversity experiences was created. Finally, a dichotomous variable describing whether or not a participant experienced any level 4 (marked threat) experience was coded for use, as well. For the present analyses proposed in the specific aims, number of early adversity stressors and total severity of early adversity were utilized.

Quality of life. The Functional Assessment of Cancer Therapies – Ovarian Form (FACT-O) provides a global assessment of QOL derived from component scores reflecting physical, emotional, functional, spiritual and social domains of life (Cella et al.,

1993). Additionally, there are ovarian-specific questions (e.g., "I have swelling in my stomach area"). Higher scores indicate better QOL; patients rate items according to their experiences in the past seven days from 0 ("not at all") to 4 ("very much"). The FACT-O demonstrates good reliability as measured by Cronbach's alpha (α's between .74-.88 for individual subscales, .92 for the overall score), as well as adequate convergent, criterion, and divergent validity (Basen-Engquist et al., 2001).

Demographic and clinical variables. Sociodemographic information including age, race, ethnicity, level of education, employment, living situation, and yearly income were completed via a self-report measure. Clinical information describing the patient's ovarian cancer, such as stage (I-IV) and grade (low versus high) of disease, tumor histology, and receipt of chemotherapy were obtained from the medical record, as was information regarding medication use.

Data Analysis Strategy

Preliminary steps. Data analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 23.0. First, distributions of data were examined for outliers and violations of assumptions of normality prior to analysis. Analyses were conducted with and without outliers; non-normal distributions received appropriate transformations. Second, differences in the LEDS variables (e.g., number of stressful events and difficulties, severity of events and difficulties) which may have occurred based upon site-specific differences were examined using one-way analysis of variance. Third, for cross-sectional analyses, individuals with missing data were excluded on a case wise basis; however, participants who completed only one (or two) of the three psychosocial outcome variables of interest were included for the analyses on their

completed measure(s). The statistical description of specific aim 3 describes missing data procedures in longitudinal analyses.

Analysis of specific aim 1. Descriptive statistics including mean, minimum, and maximum were conducted to describe early life adversity experiences in the sample. Further, frequencies of particular types of experiences are reported. Relationships between early life adversity (number and severity) and recent life stress indices were analyzed using Pearson correlations and multivariate linear regressions. The following demographic and medical variables were tested for exertion of significant effects on the independent and dependent variables: stage, age, disease grade (high versus low), histopathological tumor type (serous versus non-serous), use of antidepressant/anxiety/pain/sleep medications, BMI, marital status, race, ethnicity, income, and education. In all cross-sectional regression analyses, the following variables were including as covariates: stage, age, site of recruitment, and antidepressant medication use.

Analysis of specific aim 2. Multivariate linear regression models were used to test hypotheses from aim 2. Early life adversity (number and severity) and recent life stress were entered as independent variables, and depressive mood, sleep score, and QOL were entered as dependent variables. Again, stage, age, site, and antidepressant use were included as covariates. Secondary analyses to test mediation effects of early life adversity on psychological symptomatology via ongoing difficulties were conducted using the PROCESS procedure for SPSS. Inferences about indirect effects were determined by examining bootstrap 95% bias-corrected confidence intervals (samples = 1,000) (Preacher & Hayes, 2004; Hayes, 2012).

Analysis of specific aim 3. All longitudinal analyses used the SPSS MIXED procedure for mixed effect models. Individuals missing demographic or covariate information were excluded on a case wise basis. When participants provided psychosocial data, however, on two out of three assessment points, their information was included for analyses. The SPSS MIXED procedure allows for estimation of parameters when data is missing using maximum likelihood methods, which produces more reliable estimates than listwise deletion (Newman, 2003). Thus, individuals completing at least two of the assessments were included in longitudinal analyses. All longitudinal models included stage of disease, age, site of recruitment, antidepressant medication use, and chemotherapy status (on versus off) at one year as covariates.

Mixed effects model structure was evaluated for the inclusion of random intercept and slope terms by likelihood ratio testing, as their inclusion when appropriate can improve estimates of fixed effects (Laird & Ware, 1982). For each model, fit of covariance structure was examined using Wald-z tests of rho covariance parameters and comparison of Schwarz's Bayesian criterion (BIC) between models with the candidate covariance structures (Chou & Bentler, 1990; Littell, Pendergast, & Natarajan, 2000). An auto-regressive covariance structure was examined first. This is believed to be appropriate for the data because it implies that the residual errors of observed scores for a given individual are correlated, a strong possibility in longitudinal data. A diagonal covariance structure was also examined; diagonal covariance structures suggest that error terms for a given individual are independent from one another (Littell, Pendergast, & Natarajan, 2000).

Predictor variables were those representing early life adversity, recent life stress, main effect of time, and life stress*time terms. The outcome variables were changes from baseline to one year in depressive mood, sleep score, and QOL. The interaction of measures of stress with the effect of time tested whether trajectories in psychosocial outcomes differed by history of adversity and stress (i.e. if patients with early life adversity experience less change in symptoms over the first year post-diagnosis). Parameter estimates were utilized to examine effects at each level of life stress*time (and main effect) terms to interpret directionality. Main effect terms tested whether or not life stress indices exerted effects on outcome variables when longitudinal assessment time points are examined independently. Estimated marginal means provided descriptive statistics for scores from baseline to 6 months, and 6 months to one year. Pairwise comparisons examined statistically significant differences in changes between these periods of time using a Sidak adjustment.

RESULTS

Participant Characteristics

137 women enrolled in the study completed LEDS interviews following surgery. 76 women were interviewed at the University of Iowa while 61 were recruited from Washington University – St. Louis. Participants had a mean age of 59.11 years (SD =.93) at recruitment and were primarily Caucasian and non-Hispanic. Women were primarily diagnosed with stage III ovarian cancer, with 73.8% of the sample diagnosed with stage III or IV disease. Further, 89.1% of the sample evidenced high-grade disease and the majority had tumor histopathology classified as serous. Women were most commonly married and had a wide distribution of household annual income, from <$5,000 to >$80,000. There was a similar breadth of response in regards to education completed, though the majority of the sample reported a maximum education of a high school degree (31.9%) or a college degree (25.2%) completed. See Table 1 for complete participant information.

Table 1. Patient Characteristics.

Characteristic	Ovarian Cancer Patients
Age, years	
Mean (S.D)	59.12 (10.86)
Ethnicity	
Non-Hispanic	99.2%
Hispanic	0.80%
Race	
Asian	0.70%
Black/African American	3.00%
White	96.3%
Education	
Less than high school graduate	2.90%
High school graduate	31.9%
Trade school/some college	28.2%
College graduate	25.2%
Postgraduate	11.9%
Income	
<5,000	2.60%
5,001-10,000	3.50%
10,001-20,000	17.5%
20,001-30,000	11.4%
30,001-40,000	11.4%
40,001-50,000	9.60%
50,001-60,000	11.4%
60,001-80,000	11.4%
>80,000	21.1%
Marital status	
Single	13.1%
Divorced/Separated	13.1%
Widowed	5.80%
Married/Living with Partner	67.9%
Stage	
I	18.4%
II	7.40%
III	65.4%
IV	8.80%
Grade	
Low grade	10.9%
High grade	89.1%
Tumor histology	
Serous	69.1%
Endometrioid	3.70%
Mucinous	2.90%
Clearcell	9.60%
Other/Unknown	14.7%
Surgical Debulking	
Optimal	74.2%
Suboptimal	25.8%
Site	
University of Iowa	55.5%
Wash. U – St. Louis	44.5%
Chemotherapy Status – One Year	
On Chemotherapy	16.7%
Off Chemotherapy	83.3%

Analyses were conducted to identify potential differences in characteristics by site. Women from the St. Louis site reported more recent life events ($F_{1,135}$=6.51, p=.01), more recent ongoing difficulties ($F_{1,135}$=27.75, p<.001), and greater total severity of ongoing difficulties ($F_{1,135}$=20.82, p<.001). Further, women at St. Louis reported a slightly lower household annual income ($F_{1,112}$=3.91, p=.05). Income was marginally related to severity of recent ongoing difficulties (r=-0.18, p=.06), but not to other measures of recent life stress (all p>.16) or early life adversity (all p>.42). There were no significant differences between sites with regards to early life adversity variables (all p>.20), nor were there statistically significant differences observed between sites with regards to reports of depressive symptoms (all p>.14) or QOL (all p>.07) at baseline, 6 months, or one year.

Recent life stress was experienced in varying degrees by women in this sample. Women reported an average of 5.10 (SD = 2.18) recent life events with a range of 2-13. An average of 3.00 (SD = 1.80) ongoing difficulties were experienced, with a range of 0-7. Total severity of events was 26.51 (SD = 9.67; range: 12-69) and 8.28 for difficulties (SD = 5.79; range 0-27). At baseline, 39.8% of women reported levels of depressive symptomology which were at or above the cutoff for symptoms consistent with clinical depression (CESD = 16). These rates of depressive symptomatology decreased to 21.1% and 21.0% at 6 months and one year, respectively. Further, 56.9% of women reported disturbed sleep (PSQI > 5) at baseline, which remained relatively consistent at 6 months (57.4%) and improved slightly at one year (48.1%). Nevertheless, approximately half of the sample consistently reported disturbed sleep over the course of the first year post-diagnosis. Information regarding means and standard deviations of recent life stress,

depressive symptomatology, global sleep, and QOL at baseline, 6 months, and 1 year is provided in Table 2.

Table 2. Means and Standard Deviations of Psychosocial Measures.

	Baseline			Six Months			One Year		
Measure	*N*	*M*	*SD*	*N*	*M*	*SD*	*N*	*M*	*SD*
Number of Life Events	137	5.10	2.18	-	-	-	-	-	-
Severity of Life Events	137	26.51	9.67	-	-	-	-	-	-
Number of Difficulties	137	3.01	1.80	-	-	-	-	-	-
Severity of Difficulties	137	8.28	5.79	-	-	-	-	-	-
CES-D[a] Total Score	133	16.11	10.47	114	11.01	9.03	100	9.49	9.06
Global Sleep	72	7.36	3.98	61	6.40	3.50	52	6.79	4.63
Quality of Life	131	74.43	16.68	109	80.11	12.47	92	83.95	14.53

[a]: CES-D = Center for Epidemiological Studies Depression Scale

Experiences of Early Life Adversity

Frequency and types of stressors. Of the 137 women included in this study, 43.1% reported any experience of early life adversity (N=59). Of those women, 21 (15.3%) experienced an early life adversity situation which was rated as markedly threatening (a rating of 4), and the average number of early life adversity experiences was 2.13 (SD = .18, range 1-7) with an average summed severity score for early life adversity of 5.52 (SD = 5.40, range 1-20).

Women described many types of early life adversity. Events rated as less severe included the following: separation from one's father which was planned with a known resolution date; divorces which resolved a troublesome home environment; planned, extended absences away from the home to attend camp; and illnesses (such as nephritis) or surgeries (appendectomy) which reportedly resolved in a short period of time. More

impactful stressors included chronic disagreements with parents which did not constitute abuse; parental divorces; persistent separations from parents following divorces; parental mental health conditions (such as bipolar disorder or alcoholism) occurring when the participant was in their childhood home; and inconsistent parental relationships (for example, describing one's parents as in an "on and off relationship" throughout upbringing). The most severely rated stressors constituted experiences of verbal, physical, and sexual abuse; death of siblings, death of grandparents, death of parents, and suicides. Further, many women reported stressors which stemmed from a primary cause but had a variety of potential additive effects due to separable elements of the experience. For example, one woman reported that her father was an alcoholic, was physically abusive toward her mother in the home, was unfaithful, and her mother subsequently sought treatment in a mental health facility due to these difficulties. Each of these events was given a separate rating using procedures described in the methods.

Ten subjects (7.3%) described instances of prolonged sexual abuse, and three (2.2%) described physical abuse. Eight additional women (5.8%) reported instances of attempted sexual approaches which did not culminate in reported (or perceived) sexual assault but still warranted disclosure by the subject. For example, instances of "flashing," older men attempting to "kiss and grab at" them, older men "making advances toward [them] while babysitting," and "physically sexually aggressive" boyfriends in teen years were reported.

Deaths in early life were experienced by many participants (n=23; 16.8%). These included deaths of parents, step-parents, grandparents, and siblings. For example, subjects reported deaths of parents due to illnesses such as lung cancer, angina, cirrhosis,

ruptured spleen, heart attack, and appendicitis, as well as unexpected accidents. One subject (1%) also reported a chronic illness experienced by her mother (breast cancer) which led to ongoing hospital visits. Further, two subjects (1.4%) reported parental deaths by suicides that the subject either witnessed or found the parent deceased. One (1%) participant reported a parental death by heart attack that the subject witnessed and one (1%) reported that a parent was murdered. Siblings were reported to die due to unexpected causes, stillbirth, diarrhea, heart defect, viral pneumonia, and meningitis.

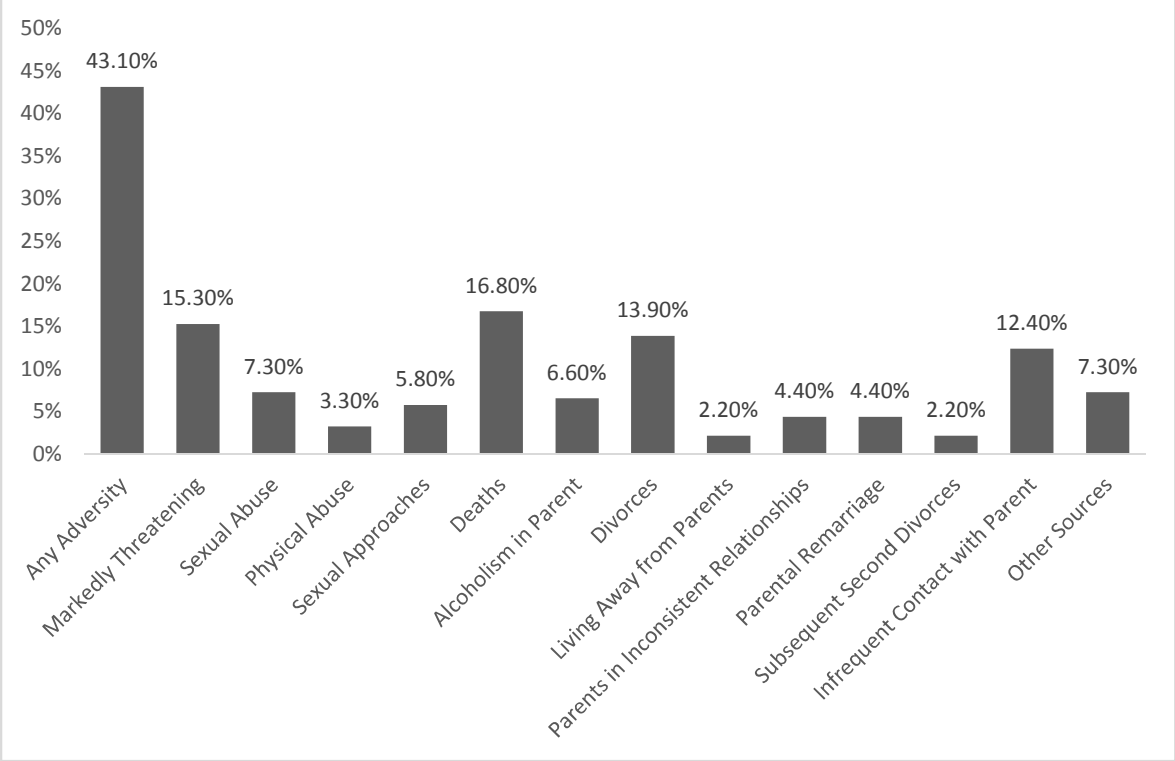
Numerous subjects reported mental health or substance-related difficulties experienced in the home. These include parents who were described as alcoholics (n=9; 6.6%), a sibling described to have Asperger's disorder, a parent with bipolar disorder, and a parent with numerous suicide attempts. Further, one subject (1%) reported her own diagnosis with depression in her teenage years.

Parental divorces (n=19; 13.9%) and other household disruptions were reported which led to numerous subsequent events. For example, some women (n=3; 2.2%) noted living with siblings and grandparents following divorce or relationship disruption. Further, participants described parents with "off and on relationships" (n=6; 4.4%), some of whom who separated and reunited. Reports of one or both parents remarrying following divorce were given (n=6, 4.4%) as well as subsequent second divorces (n=3, 2.2%). Moreover, women (n=17; 12.4%) reported seeing parents infrequently due to custodial arrangements following divorce.

Less frequently reported sources of stress arose from some subjects. For example, two subjects (1.4%) reported marriages at age 16 solely due to pregnancies which led to leaving their home of origin. Another subject (1%) described experience of neglect which

almost resulted in death, as well as attendance of military camp due to parents "not want[ing] to care for" the participant. One subject (1%) reported a move out of the country at age 9. See Figure 1 for a summary of early life adversity experiences.

Figure 1. Early Life Adversity Experiences



Relationships between early life adversity, recent life events, and ongoing difficulties. Linear regression models examined relationships between early and recent life stress and controlled for covariates. Contrary to expectations, there were no relationships found between recent life events and number (all $p>.39$) or severity (all $p>.20$) of early life adversity experiences (Table 3).

Table 3. Early Life Adversity and Recent Life Stress Correlations.

		Total Number of Recent Life Events	Total Severity of Recent Life Events	Total Number of Difficulties	Total Severity of Difficulties
Early Life Adversity - Number	r	-0.01	0.04	.20*	.22*
	p	0.91	0.69	0.02	0.01
	N	137	137	137	137
Early Life Adversity - Severity	r	-0.05	0.005	.21*	.23**
	p	0.60	0.96	0.02	0.01
	N	137	137	137	137

*$p<.05$; **$p<.01$

However, consistent with Hypothesis 1, a greater number and severity of early life adversity experiences were related to greater severity of ongoing difficulties (number of early life experiences: β= .17, p=.04; severity of early life experiences: β=.19, p=.02). In addition, there was a possible trend indicating that those with a greater number or greater severity of early life adversity experiences reported a greater number of ongoing difficulties (number of early life experiences: β=.14, p=.09; severity of early life experiences: β= .15, p=.07). See Table 4 for complete models.

Table 4. Regression Models of Ongoing Difficulties and Early Adversity – Presurgery.

Outcome Variable	R of final model	Δ R^2	Beta	t	F
Model I	**.466**	**.018**			**7.150*** **
Difficulties (Number)	*Covariates*				
	Stage		0.109	1.390	
	Site		0.388	4.901***	
	Age		-0.041	-0.516	
	Antidepressants		0.114	1.428	
	ELA Number		**0.137**	**1.723 *p*=.087**	
Model II	**.452**	**.027**			**6.606*** **
Difficulties (Severity)	*Covariates*				
	Stage		0.172	2.173*	
	Site		0.339	4.244***	
	Age		0.002	0.019	
	Antidepressants		0.104	1.294	
	ELA Number		**0.168**	**2.096***p*=.038**	
Model III	**.469**	**.021**			**7.264*** **
Difficulties (Number)	*Covariates*				
	Stage		0.111	1.415	
	Site		0.386	4.890***	
	Age		-0.038	-0.483	
	Antidepressants		0.115	1.455	
	ELA Severity		**0.147**	**1.851 *p*=.067**	
Model II	**.458**	**.033**			**6.843*** **
Difficulties (Severity)	*Covariates*				
	Stage		0.174	2.208*	
	Site		0.336	4.231***	
	Age		0.005	0.066	
	Antidepressants		0.105	1.319	
	ELA Severity		**0.185**	**2.316* *p*=.022**	

*p<.05, **p<.01, ***p<.001

Life Stress and Psychological Symptomatology Prior to Surgery

Linear regression models were used to explore relationships between early and recent life stress and psychological symptomatology prior to surgery. All models controlled for covariates.

Early life adversity and psychological outcomes. Contrary to predictions from Hypothesis 2a, no significant associations were observed with regard to number of early life adversity experiences or severity of early life adversity with depression (number: β=-0.02, p=.83; severity: β=-0.01, p=.94), sleep (number: β=.004, p=.97; severity: β=.02, p=.87), or QOL (number: β =-0.06, p=.48; severity: β =-0.08, p=.37) prior to surgery.

Recent life events and psychological outcomes prior to surgery. Consistent with predictions from Hypothesis 2b, no statistically significant relationships were observed with regard to number or severity of recent life events and depressive symptomatology (number of events: β= -0.003, *p*=.98; severity of events: β= -0.01, *p*=.92), sleep (number of events: β=.17, *p*=.15; severity of events: β=.12, *p*=.31), or QOL (number of events: β=.05, *p*=.62; severity of events: β=.02, *p*=.80) prior to surgery.

Recent ongoing difficulties and psychological outcomes prior to surgery. In contrast to predictions from Hypothesis 2b, total number of ongoing difficulties (β=.22, *p*=.02) and severity of these difficulties (β=.21, *p*=.03) in the year before surgery were associated with significantly worse depressive symptomatology prior to surgery. Further, number of ongoing difficulties (β=-.21, *p*=.03) and severity of ongoing difficulties (β=-.23, *p*=.02) were associated with significantly lower total QOL prior to surgery, as well. Lastly, there were no statistically significant relationships observed between global sleep and number of difficulties (β =.18, *p*=.13) or severity of ongoing difficulties (β =.20, *p*=.10). (Table 5).

Table 5. Regression Models of Outcomes and Ongoing Difficulties – Presurgery.

Outcome Variable	R of final model	ΔR^2	Beta	t F
Model I	**.271**	**.040**		**1.974**
Depression	*Covariates*			
	Stage		0.124	1.419
	Site		-0.049	-0.512
	Age		-0.078	-0.891
	Antidepressants		0.046	0.520
	Difficulties (Number)		**0.223**	**2.324* *p*=.022**
Model II	**.261**	**.035**		**1.835**
Depression	*Covariates*			
	Stage		0.111	1.256
	Site		-0.032	-0.337
	Age		-0.087	-0.994
	Antidepressants		0.047	0.530
	Difficulties (Severity)		**0.207**	**2.175* *p*=.032**
Model III	**.352**	**.031**		**2.304**
Sleep	*Covariates*			
	Stage		0.194	1.659
	Age		-0.208	-1.783
	Antidepressants		0.065	0.560
	Difficulties (Number)		**0.179**	**1.526 (ns)**
Model IV	**.361**	**.038**		**2.440**
Sleep	*Covariates*			
	Stage		0.182	1.546
	Age		-0.215	-1.852
	Antidepressants		0.073	0.631
	Difficulties (Severity)		**0.197**	**1.680 (ns)**
Model V	**.290**	**.036**		**2.260**
Quality of Life	*Covariates*			
	Stage		-0.126	-1.441
	Site		-0.027	-0.284
	Age		0.117	1.340
	Antidepressants		-0.013	-0.144
	Difficulties (Number)		**-0.211**	**-2.196* *p*=.030**
Model VI	**.305**	**.045**		**2.518***
Quality of Life	*Covariates*			
	Stage		-0.109	-1.236
	Site		-0.031	-0.333
	Age		0.126	1.452
	Antidepressants		-0.009	-0.104
	Difficulties (Severity)		**-0.232**	**-2.460* *p*=.015**

**p*<.05, ***p*<.01, ****p*<.001, ns = not statistically significant

Follow up analyses: examining links between early life adversity, ongoing difficulties, and psychological outcomes. Secondary analyses to test indirect mediation of the effects of early life adversity on psychological symptomatology via ongoing difficulties were conducted using bootstrap models with bias corrected estimates (to produce conservative estimates). There were statistically significant indirect effects of early life adversity (severity and number) on depressive symptoms due, in part, to recent ongoing difficulties (both number and severity). Specifically, greater early life adversity

was related to higher levels of depressive symptoms, mediated by ongoing difficulties. A similar pattern was observed when QOL was examined as an outcome, where greater number of early life adversity experiences was associated with lower QOL due, in part, to greater number of ongoing difficulties. Also, greater severity of early life adversity was associated with lower QOL due, in part, to higher severity of ongoing difficulties. (Table 6).

Table 6. Confidence Intervals for Indirect Mediation Effects.

Independent Variable	Dependent Variable	Mediator Variable	Confidence Interval: Lower Limit+	Confidence Interval: Upper Limit+
Early Adversity - Number	Depression	Difficulties (Number)	0.02	0.88*
Early Adversity - Number	Depression	Difficulties (Severity)	0.01	1.04*
Early Adversity - Severity	Depression	Difficulties (Number)	0.01	.31*
Early Adversity - Severity	Depression	Difficulties (Severity)	0.003	.35*
Early Adversity - Number	Quality of Life	Difficulties (Number)	-1.23	-0.01*
Early Adversity - Number	Quality of Life	Difficulties (Severity)	-1.48	0.01
Early Adversity - Severity	Quality of Life	Difficulties (Number)	-0.46	0.0003
Early Adversity - Severity	Quality of Life	Difficulties (Severity)	-0.57	-0.02*

+: Bias-corrected estimates based on bootstrap indirect mediation models (samples = 1,000). Models adjusted for stage of disease, age, and antidepressant medication use.
*p<.05.

Life Stress and Psychological Symptomatology over the First Year Post Diagnosis

Analyses examining psychological symptomatology over the first year post diagnosis were conducted utilizing mixed effects models. Estimated marginal means of

psychological measures at each time point are shown in Table 7. All mixed effects models below control for covariates.

Table 7. Estimated Marginal Means of Psychosocial Measures.

Measure	Pre-surgery - M(SE)+	6 Month – M(SE)+	One Year – M(SE)
Global Sleep (PSQI)[a]	7.16 (0.68)	6.20 (0.68)	6.29 (0.78)
Depression (CES-D)[b]	16.23 (1.21)***	11.30 (1.12)***	9.85 (1.14)
Quality of Life (FACT-O)[c]	74.14 (1.76)***	79.40 (1.56)***	83.35 (1.71)

*p<.05, **p<.01, ***p<.001; +: reference group: one year.

[a]: PSQI= Pittsburgh Sleep Quality Index
[b]: CES-D = Center for Epidemiological Studies Depression Scale
[c]: FACT-O= Functional Assessment of Cancer Therapies-Ovarian.

Early life adversity and psychological symptoms over time. The change in depression over the three visits was not significantly associated with either the number or severity of early adversity experiences (interaction effect for number of early adversity experiences by time: $F_{2,124}$=.84, p=.44; severity of early adversity by time: $F_{2,124}$=0.51, p=.60), nor was there a significant main effect for early adversity observed (number of early adversity experiences: $F_{1,102}$=.56, p=.46; severity of early adversity: $F_{1,101}$=.59, p=.60), indicating that early life adversity was not associated with the level or trajectory of depressive symptomatology over the first year post diagnosis.

Further, there were no significant main effects observed of early adversity on sleep (number of early adversity experiences: $F_{1,51}$=1.59, p=.21; severity of early adversity: $F_{1,51}$=1.90, p=.17) or QOL (number of early adversity experiences: $F_{1,109}$=2.33, p=.13; severity of early adversity: $F_{1,109}$=2.47, p=.12). However, early life adversity impacted the change in sleep over the three visits as indicated by the significant interaction terms (interaction effect for number of early adversity experiences by time:

$F_{2,57}$=3.56, p=.04; severity of early adversity by time: $F_{2,57}$=3.24, p=.05). Similarly, an interaction term indicated that the number of early life adversity experiences was significantly associated with the change in QOL over time (number of early adversity experiences by time: $F_{2,118}$=3.38, p=.04). There was also a possible trend indicating that the severity of early adversity experiences was associated with change in QOL over time (severity of early adversity experiences by time: $F_{2,117}$=2.63, p=.08). Specifically, decomposing these interactions indicated that those who experienced a higher number of early life adversity experiences report less improvement of sleep (β=-1.23, t=-2.54, p=.01) and QOL (β=1.78, t=1.62, p=.11) between their pre-surgical and one year post diagnosis visits. In addition, those who experience greater severity of early life adversity report less improvement of sleep (β=-.44, t=-2.31, p=.02) and a trend to poorer improvement in QOL (β=.49, t=1.21, p=.23) between pre-surgery and one year follow up. These effects were in the expected directions.

Recent life events and psychological symptoms over time. The change in depressive symptoms (interaction effect for number of recent events by time: $F_{2,124}$=.22, p=.81; severity of recent events by time: $F_{2,124}$=.15, p=.87), sleep scores (number of recent events by time: $F_{2,57}$=1.31, p=.28; severity of recent events by time: $F_{2,57}$=.52, p=.60), or QOL (number of recent events by time: $F_{2,118}$=.53, p=.59; severity of recent events by time: $F_{2,118}$=.10, p=.90) over the three visits was not significantly associated with either the number or severity of recent life events. Additionally, there were no main effects of number or severity of recent life events on depression (number of recent events: $F_{1,100}$=.001, p=.97; severity of recent events: $F_{1,101}$=.38, p=.54), sleep (number of recent events: $F_{1,51}$=1.40, p=.24; severity of recent events: $F_{1,51}$=1.74, p=.19),

or QOL (number of recent events: $F_{1,105}$=.17, p=.68; severity of recent events: $F_{1,106}$=.19, p=.66). Overall, this indicates that number and severity of recent life events were not associated with levels or trajectory of depression, sleep, or QOL during the first year post diagnosis.

Recent ongoing difficulties and psychological symptoms over time. The change in depressive symptoms (interaction effect for number of ongoing difficulties by time: $F_{2,125}$=.83, p=.44; severity of ongoing difficulties by time: $F_{2,124}$=1.53, p=.22), sleep scores (number of ongoing difficulties by time: $F_{2,57}$=.855, p=.43; severity of ongoing difficulties by time: $F_{2,57}$=.77, p=.47), and QOL (number of ongoing difficulties by time: $F_{2,122}$=.48, p=.62; severity of ongoing difficulties by time: $F_{2,122}$=.66, p=.52) over the three visits were not significantly associated with either the number or severity of ongoing difficulties. However, there were main effects for each model indicating that ongoing difficulties experienced in the year prior to surgery were significantly associated with higher depressive symptomatology (number of difficulties: β=1.65, $F_{1,102}$=9.18, p=.003; severity of difficulties: β=.57, $F_{1,104}$=11.12, p=.001), poorer sleep scores (number of difficulties: β=.87, $F_{1,50}$=4.56, p=.04; severity of difficulties: β=.29, $F_{1,49}$=4.35, p=.04), and poorer QOL (number of difficulties: β=-2.74, $F_{1,107}$=14.85, p<.001; severity of difficulties: β=-.92, $F_{1,108}$=17.43, p<.001) across all time-points. Thus, number and severity of ongoing difficulties appear to be associated with worse depression, sleep, and QOL at each time-point but not with trajectories of these outcomes.

DISCUSSION

This study sought to elucidate the role of early and recent stressful life experiences on psychological functioning in women with ovarian cancer during the first year post-diagnosis. To the author's knowledge, this project is the first of its kind to 1) operationalize and utilize early life data from the LEDS, including assigning severity ratings to such data; 2) describe the early life experiences of women with ovarian cancer; and 3) examine the role of specifically timed stress experiences as they relate to psychological indices in women with ovarian cancer.

Women reported on varied experiences of early life adversity. Both number and severity of early life adversity stressors were related to subsequent reports of ongoing difficulties, but not to recent life events, which occurred in the year prior to diagnostic surgery. Interestingly, number and severity of early life adversity experiences emerged as predictors of less improvement in sleep and QOL over the first year post diagnosis. Ongoing difficulties, but not recent life events, were related to depression and QOL prior to surgery. Further, ongoing difficulties were related to greater depression, worse sleep, and poorer QOL at each assessment. Overall, this reveals a pattern whereby ongoing difficulties as an index of recent life stress appeared to be a more relevant predictor of psychological symptomatology than acute life events in women with ovarian cancer. Specific considerations with regard to each point will be discussed below, including a review of the major findings.

Early Life Adversity: Comparisons to Reported Rates of Adversity

Nearly half the sample (43.1%) of women with ovarian cancer reported events or circumstances occurring early in life which would constitute adversity. Further, reports of

interactive, unfolding early life adversity experiences were provided by participants allowing for qualitative description and operationalization of number and severity. These findings are consistent with those in other populations, such as the Adverse Childhood Experiences study cohort of over 9,000 American adult men and women, where rates are reported that between 34.6% and 64% of participants are exposed to early life adversity (e.g., Felitti, et al., 1998; Dube, Anda, Felitti, Chapman, Williamson, & Giles, 2001; Edwards, Holden, Felitti, & Anda, 2003). Similarly, in an epidemiological study of Australian citizens, 59.5% experienced some form of early adversity and 37% experienced more than one adversity (Rosenman & Rodgers, 2004). A large British cohort study found that 30% of the sample reported one or more adversity in early life (Clark, Caldwell, Power, & Stansfeld, 2010). Rosenman and Rodgers (2004) also reported a high co-occurrence of unfolding adversity experiences, such as divorce and subsequent parental absence, lending support for the methodology employed in the current study which separates aspects of early life adversity that appear to stem from a primary event.

Recent Life Stress: Comparing Events and Ongoing Difficulties

A primary finding of the study documented the differential influence of life events versus ongoing difficulties. Consistent with hypothesis 2b, number or severity of recent life events were not related to psychological functioning prior to surgery or to the trajectory of recovery of sleep, depression, and QOL over the first year post diagnosis. In contrast, ongoing difficulties demonstrated significant associations with depression and QOL prior to surgery. Also, there was a consistent effect where number and severity of ongoing difficulties were associated with worse depression, poorer sleep, and poorer

QOL at each time point. This highlights the importance of separating acute events and chronic difficulties to examine their potential influences, and an advantage of utilizing the LEDS system to assess life stress.

Current findings are consistent with a wider body of literature that finds that chronic stressors may have a greater impact on depression than acute events (McGonagle & Kessler, 1990). Traditionally, acute events have often been implicated as influential in the "impending onset" (Slavich & Irwin, 2014) of depression, where numerous studies document that major stressful life events are those which predict depressive episodes (Kendler, Karkowski, & Prescott, 1999; Kendler, Hettema, Butera, Gardner, & Prescott, 2003). Chronic or ongoing stressors have been noted to be equally predictive of onset of depressive episode as acute events (Rojo-Moreno et al., 2002), related to general depressive symptomatology (McGonagle & Kessler, 1990), and related to persistently depressed mood (Mirowsky & Ross, 1989). In fact, the influence of acute life events on depressive symptoms may be mediated by the chronic nature of how acute events tend to unfold over time (Kessler, 1997; Tennant, 2002). Chronic stressors, thus, may affect symptomatology years following their assessment (Swindle, Cronkite, & Moos, 1989; Tennant, 2002). Others have noted a relationship whereby acute events are more predictive of depression in those who do not experience high levels of ongoing, chronic stress (Cairney, Boyle, Offord, & Racine, 2003). A consideration drawn from these findings concerns the possibility for a "saturation effect," where high levels of chronic stress may be associated with minimal effects of acute stressors on psychological symptomatology as those individuals are less reactive (or desensitized) to the effects of acute events. This is in contrast to those who do not manage day-to-day, ongoing stress,

who may be more vulnerable to the impact of an acute event (Cairney, Boyle, Offord, & Racine, 2003). In a previous study within a subset of the same sample of women with ovarian cancer, greater number of life events was a better predictor of QOL than higher severity, which led the authors to suggest that the cumulative nature of stress may most affect QOL (Lutgendorf et al., 2013). This suggestion is consistent with the observed effect in the current study regarding ongoing difficulties. Taken together, the above literature supports the findings in the present study and suggests that the effects of ongoing difficulties may eclipse those of acute life events. Underlying this finding are the possibilities that ongoing difficulties may reflect unfolding sequelae of acute stressors or that high levels of underlying stress render the effects of more acute life events to be relatively benign.

Relationships Between Early Life Adversity and Ongoing Difficulties: "Life Course" Stress

The present study found that higher levels of early life adversity were associated with significantly greater severity (and, to some degree, number) of subsequent ongoing difficulties. There was not a direct relationship between early life adversity and depression, sleep, and QOL prior to primary surgery for ovarian cancer. However, ongoing difficulties were related to these symptoms prior to surgery, as well as at each of the follow-up assessments. Indirect mediation models supported relationships where early life adversity impacted depression and QOL in part via recent ongoing difficulties. Theoretical models that consider stress in a "life course" conceptualization and discuss associations between stress timed at different points during an individual's life are discussed below.

Life course stress perspectives: Cumulative stress burden. Links between differentially timed stressors over the life course have led some to propose that stress may be operationalized best by examining lifetime stress burden, or sum of lifetime stress experiences (e.g., Turner & Lloyd, 1995, 2004). This represents a perspective whereby pathways to adult psychological symptomatology are considered to be reflective of the additive nature of stress over the individual's lifetime. Designs employing this framework yield results that note significant effects of cumulative stress on psychiatric disorders and cancer-related fatigue (Turner & Lloyd, 1995; Bower, Crosswell, & Slavich, 2014). Given the relationships between early life adversity and ongoing difficulties and the observed impact on psychological outcomes in the present study, this stress framework would suggest that the impact of ongoing difficulties in the context of associations with early adversity may represent an effect of cumulative stress exposure.

Life course stress perspectives: Early adversity as a marker of intermediate stress experiences. Early life adversity was predictive of trajectories of sleep and QOL during the first year post diagnosis. One framework in line with these findings posits that early life adversity serves as a "marker" of ongoing exposure to stressful life situations, including those in adolescence (Pearlin, 1989), particularly as early life adversity experiences are frequently related to higher numbers of life stressors in adolescence and adulthood (e.g., Turner & Butler, 2003; Turner & Turner, 2005). While this perspective also underscores the importance of conceptualizing stress over the life course, it is distinct in that it emphasizes early life adversities as a benchmark for future exposures (in contrast to operationalizing early stressors as instances to be added to the cumulative burden). Therefore, early life experiences themselves do not hold a particular "special

status," but represent a continuity with later life stress (Hazel, Hammen, Brennan, & Najman, 2008). This perspective may underlie associations where trajectories of sleep and QOL are impacted by level of early life adversity, where early life adversity may serve as a proxy for stress experiences that occurred across the life span.

Further, the present study examined potential pathways of stress influence. Post-hoc analyses supported indirect effects of early life adversity on psychological symptomatology due, in part, to ongoing difficulties. Similar analyses have demonstrated that early life adversity may affect adult symptomatology via recently experienced life stress, where effects of early adversity on inflammatory markers in adulthood are mediated by chronic stress in young adults (Raposa, Bower, Hammen, Najman, & Brennan, 2014) and associations between early adversity and depression were mediated by the effect of recent stressors in adolescents (Hazel, Hammen, Brennan, & Najman, 2008). Considered within the theoretical perspective described above, it may be that early life adversity itself may not emerge as a predictor of psychological outcomes without also measuring recently experienced stress and testing for indirect effects. Pathways to stress-related outcomes, where recent stress may mediate the effects of early adversity, may be appropriate to measure the potential cascade of stress occurrences throughout the life course.

Life course stress perspectives: The stress generation hypothesis. Hammen's (1991) theory termed stress generation provides an additional potential framework which may underlie the associations between early life adversity and recent ongoing difficulties observed in the present study. This model suggests that while many stress theories position the individual as a recipient who interprets and is impacted by stressors,

experiencing greater levels of stress may be in part attributed to the person's behavior. Hammen (1991) noted that among women with depression, greater numbers of stressful life events were experiences that were caused, in part, by actions attributable to the participants. Further work notes that this effect is observed even in times when women are not actively experiencing depressive episodes (Daley et al., 1997; Hammen & Brennan, 2002). This suggests that it is not exclusively depressive symptomatology, or reactions to a depressive episode, that may lead to generating more stressful events.

Numerous mechanisms may underlie stress generation. As reviewed in the introduction, early life experiences may shape the individual biologically, cognitively, and emotionally so that many pathways to subsequent stress may be elucidated (including impacts on perceptions of stress and engaging in risky behaviors, among others). Additional mechanisms consider the roles of interpersonal factors such as attachment style (Bowlby, 1969) and dependency on others (Shahar, Henrich, Blatt, Ryan, & Little, 2003). Lastly, individuals may be "locked in" to highly stressful family environments characterized by discord (Hammen, 1992, 2003), as well as socioeconomically disadvantaged environments, which confer elevated risk for life stress (Hammen, 2005). This framework provides another theoretical perspective that may explain how early stressors can impact individual factors and lead to generation of subsequent chronic life stressors, which may underlie the relationships between early adversity and ongoing difficulties observed in the present study.

Effects of Early Life Events on Sleep Over Time

Early life adversity appeared to have the most influence on the trajectory of sleep symptoms over the first year post diagnosis. This suggests a difference in trajectories of

symptoms, as well as the potential for a specific role of early life stress as a predictor of sleep over time. The findings in the current study regarding symptom trajectories are consistent with those which we and others have reported in women with ovarian cancer (Schrepf et al., 2012; Hipkins, Whitworth, Tarrier, & Jayson, 2004; Wenzel et al., 2002; Meraner et al., 2012; Norton et al., 2004). These note a common pattern of improvement of depression and QOL as time progresses after diagnosis, treatment, and into survivorship. In contrast, sleep in ovarian cancer has emerged as a factor which may not follow this trajectory, as it remains poor over time and is associated with impaired QOL (Clevenger et al., 2012, 2013; Sandadi et al., 2011).

While numerous pathways to poor sleep that may underlie relationships with early adversity are outlined in the introduction (e.g., negative cognitive and affective associations with the home or bedroom, poor health behaviors), one potential mechanism of note concerns the influence of proinflammatory cytokines on sleep. Proinflamatory cytokines are implicated in sleep regulation (Opp & Toth, 2003), sleep architecture modulation (Kapas et al., 1992; Opp, Obal, & Krueger, 1991), and circadian sleep (Vgontzas et al., 2005). Further, the relationship between circulating IL-6 and sleep disturbance may reflect a bi-directional feedback loop where sleep becomes disrupted and in turn affects cytokine production (Irwin, 2002). In ovarian cancer, persistent difficulties with sleep disturbance over the first year post diagnosis have been linked to elevations in peripheral IL-6 (Clevenger et al., 2013) which may be tumor derived (Tempfer, Zeisler, Sliutz, Haeusler, Hanzal, & Kainz, 1997).

The potential independent influence of inflammatory cytokines on sleep disturbance is well supported by the early life adversity literature, as is discussed in the

introduction. Although mechanisms underlying these alterations are complex, it has been proposed that the immunologic alterations seen in individuals with early life adversity may result from more pronounced stress-induced HPA activation (Heim et al., 2000) and impaired glucocorticoid sensitivity secondary to persistently high levels of cortisol, which may contribute to poorly controlled inflammation (Miller, Chen, & Parker, 2011). Miller, Chen, and Parker (2011) proposed a framework for this inflammatory modulation as the "biological embedding" hypothesis, which posits that early life difficulties adjust the functioning of bodily systems after the occurrence of significant stress. These adjustments might be transcriptional or epigenetic, and likely interact with behavioral patterns in adulthood (Miller, Chen, & Parker, 2011). It has been proposed that early life exposure to chronic stress reprograms monocytes and macrophages, which are essential in initiating and maintaining inflammation in the body (Miller, Chen, & Parker, 2011). These alterations in physiological functioning following early adversity, in the context of known relationships between sleep and inflammatory markers, may serve as a mechanism which underlies the associations between early adversity and trajectory of sleep over time.

Findings Related to Main Effects of Early Life Adversity: Potential Factors of Influence

While early adversity had an influence on trajectory of improvement of sleep and QOL, pre-surgical measures of depression, sleep, and QOL were not significantly associated with early life adversity. As these findings were inconsistent with those which were hypothesized, it is possible that factors not assessed in the current study may have moderated effects of early adversity on psychological symptomatology. Resilience is one

such construct which may influence how early life stressors may subsequently impact individuals. Resilience "refers to a dynamic process encompassing positive adaptation within the context of significant adversity" (Luthar, Ciccheti, & Becker, 2000). While definitions of the construct of resilience vary in their conceptualizations of time course and primary features (Garmezy & Masten, 1990; Luthar & Zigler, 1991), three components may contribute to developing resilience in childhood: personal attributes of the child, aspects of the child's family, and broader characteristics of the social context and environment (Masten & Garmezy, 1985; Werner & Smith, 1982). Resilience factors, whether dispositional or environmental in nature, may have had effects on the sequelae of early adversity experiences.

Impact of Recent Life Events: Potential Influences

The present study did not find significant associations between recent life events and psychological symptomatology. Other factors which were not tested in the current study but may have moderated the influence of recent life events are discussed below.

Domain of life stress. While it may be the case that the effects of life events in the current sample are better captured through the influence of ongoing difficulties, it is also possible that effects of acute events were not observed because cancer-related events were included among the acute event variables. This would potentially have influenced acute event variables such that women with more lengthy and complicated diagnostic processes may have had higher acute event counts that would have been primarily reflective of medical (or cancer-related) stress. Non-cancer life events have been significantly related to QOL in ovarian (at one year post-diagnosis; Lutgendorf et al., 2013), breast (Golden-Kreutz et al., 2005), and melanoma (Lehto, Ojanen, Väkevä,

Aromaa, & Kellokumpu-Lehtinen, 2008) patients. Further, in Hispanic women with breast or gynecological cancers, economic stress was significantly and prospectively related to depression, anxiety, and QOL over a period of 12 months (Ell, Xie, Wells, Nejat-Haiem, Lee, & Vourlekis, 2008). The operationalization of acute events used in the present study considered all stressors within one index regardless of type (category, feature) thereby including cancer-related stressors with all others, and such broad conceptualization may have obscured potential effects of acute events.

Psychological features of stress. Additionally, the lumping of all stressor categories together may have concealed effects of specific types of experiences. The broader stress literature points to refinement of stressors into specific categories based on sociopsychological features which may have particularly negative sequelae. Specific features of stressors have been found to be related differentially to emotional experiences, and events characterized by interpersonal loss have emerged as related to both depression and anxiety experiences (Kendler, Hettema, Butera, Gardner, & Prescott, 2003; Farmer & McGuffin, 2003). Social bonds are essential to processes including nurturance, social status, and reproductive potential, and disruption or loss of these bonds may naturally provoke distress in the individual (Paykel, 2003). Further, different features of events may predict sleep, and one study reports that changes in sleep were more commonly reported by individuals following chronic stress and failure events (Keller, Neale, & Kendler, 2007). Therefore, it is possible that examination of specific features of life stress, which were outside of the scope of the current investigation, may have supported findings consistent with those which were hypothesized but not observed.

Protective factors: Effects of moderating variables on the impact of recent life stress. Adult resilience concerns the capacity for adults to maintain stability and healthy functioning, as well as the possibility for positive emotions and generative experiences, following exposure to stressful circumstances (Bonanno, 2004). With regard to adult resilience, numerous individual factors (such as age, gender, and minority status; Brewin, Andrews, & Valentine, 2000) and protective mechanisms (Rutter, 1990) have been identified that may confer increased likelihood for positive adaptation following life stress. Two protective mechanisms, social support and coping, are considered to be both potentially moderating on effects from life stress as well as relevant to ovarian cancer. Access to social and material resources confers protection in the context of life stress (Bonanno, Galea, Bucciarelli, & Vlahov, 2007), and social support may benefit an individual by "buffering" or protecting one from the potentially harmful sequelae of stressors (Cohen & Wills, 1985). Additionally, coping styles are relevant to how a stressor is perceived and managed (Lazarus and Folkman, 1984), and numerous coping styles are employed in individuals with cancer (Carver et al., 1993). In women with ovarian cancer, social support (Hill, 2015; Roland, Rodriguez, Patterson, & Trivers, 2013) and coping styles (Ferrell, Smith, Cullinane, & Melancon, 2003; Canada, Parker, de Moor, Basen-Engquist, Ramondetta, & Cohen, 2005; Lutgendorf et al., 2002) appear to be important variables in regards to psychological symptomatology and QOL. Further, in oncology patients, coping style may interact with level of life stress in predicting psychological outcomes (Low, Stanton, Thompson, Kwan, & Ganz, 2006). Therefore, the impact of acute events may be moderated by both the availability of social support as well as individual coping styles, mechanisms which may also have independent

influences on the outcome measures of interest. The moderating influence of support and coping may have led to a lack of observations between recent acute events and psychological symptomatology in the current study.

Future Directions: Methodological Considerations for Early Life Adversity Data

As the methodology employed in the present study constituted a first attempt at a comprehensive operationalization of early life adversity data from the LEDS, a discussion regarding assessment of early adversity, benefits of utilizing the LEDS for such data, and future directions to refine procedures is provided.

Considerations in assessing early life adversity. Selecting an assessment strategy for early life adversity may be subject to the same weighing of costs and benefits as measurement of recent life stress as described above with regard to interview versus questionnaire measures (e.g., Monroe, 2008). For example, questionnaire measures may allow an ease of time and administration across large patient cohorts, but may also introduce compromising elements such as misunderstanding of the nature of written questions (Monroe, 2008). Face-to-face strategies for obtaining early life data have been questioned due to the potential influence of unease of disclosure by participants. Truthful reporting may be compromised when individuals must describe painful or personal details of early life experiences, and interview measures may then be prone to obtaining conservative rates (e.g., Sanders & Becker-Lausen, 1995). However, others posit that interview methods for early adversity are preferable to questionnaires, as contextual information which may be better predictive of later life outcomes (Bernstein et al., 1994) may be more easily elicited.

Few reports have undertaken the challenge of comparing formats when obtaining early life experiences data. One was identified (Dill, Chu, Grob, & Eisen, 1991) which compared reports of childhood abuse histories from two formats: one standard psychiatric intake interview and a self-report questionnaire measure. Findings showed that while 92% of reports were consistent between modalities when patients endorsed no abuse histories, over one third of patients reporting abuse in questionnaire format endorsed no abuse history in intake interview. Conversely, in a review of the literature, Brewin, Andrews, and Gotlib (1993) advocate for the benefits of semi-structured interviews, which allow participants to communicate personal and meaningful stories of their memories; they also cite interviews as particular useful for obtaining data regarding fine-grained adverse childhood experiences such as parental indifference or lack of parental control (e.g., Harris, Brown, & Bifulco, 1986).

Lastly, the difficulty of establishing validity and reliability when measuring early life experiences has often led authors to suggest comparing rates obtained in research settings to objective data (such as data from police reports) as a gold standard of establishing validity. This poses a particular difficulty in regards to early life adversity in that many of the categories of adversities would not necessarily lead to formalized reports. In sum, the above considerations regarding assessment of early life adversity describe mixed perspectives regarding the best methodology, but support notable benefits of an interview format. It is important to note that the present methodology is limited as it did not establish convergent validity, and this represents a future area of exploration should early adversity data be routinely extracted from LEDS interviews. Establishing convergent validity by comparing rates of early adversity obtained from the LEDS to

those obtained with others measures of early life adversity with established reliability and validity would lend further support to the methodology utilized in the present study.

Benefits of utilizing the LEDS for early adversity data. Numerous benefits arise from utilizing LEDS interview data in analyses of early life adversity. First, this represents a measurement strategy that provides a parallel to early life adversity literature which describes impactful experiences as those occurring both "to" the child/adolescent as well as those "around" (or in the environment of) the individual (Shonkoff et al., 2012). The LEDS system was originally developed to assess numerous circumstances in early life so that life stressors may be rated contextually (Brown & Harris, 1978). Utilizing data which provides information to describe the individual's early life context may serve as an excellent method to parallel the notion of capturing events happening to and around the child. Further, the LEDS four point rating system provides set guidelines for which one may assign severity ratings, which lends toward a parallel early adversity severity (or, contextual threat) rating system. For purposes of time burden on subjects, utilizing data situated within a measure already to be employed is beneficial as compared to employing a separate interview or questionnaire method. Lastly, the lengthy training of LEDS interviewers to establish both reliability as well as skills to create an atmosphere where participants feel comfortable to disclose experiences may be of particular benefit when eliciting such sensitive information.

Interviewer training. One area for continued exploration should future studies choose to utilize early life adversity data from the LEDS concerns training of interviewers. Traditional training of LEDS interviewers involves imparting specific sets of intentions for defining events, difficulties, threat, and impact on the subject for recent

life experiences. Such specifics are not employed regarding attempts to obtain early life data, as this information was not traditionally intended to define acute versus chronic stress and the nature of the impact on the individual. Standardization of assessment measures to produce a reliable assessment of early life experiences is essential, and has emerged as a criticism of early life and trauma interviews (Briere, 1992). This is a critical point in examining a potential limitation to the current design, where early life adversity experiences may have been underestimated due to lack of comprehensive early life probes. Therefore, specific training of interviewers to follow probes may be utilized in order to facilitate reliability and future refinement of the early life data into event and difficulty categories with severity ratings.

Rating early life adversity data. A further consideration concerns the nature of providing ratings. Should LEDS data routinely aim to define early life adversity, training of LEDS raters would include establishing set rating procedures. For example, the current rating manual includes several exemplars which assist raters in deciding how a given individual with specific life circumstances would be impacted by a particular life stressor (Brown & Harris, 1978). Comprehensively expanding the rating procedures to include early life adversity would, ideally, involve expanding the existing manual to include similar exemplars from early life to provide guidance in rating. Further, as this project was conducted by analyzing summaries retrospectively, opportunities for raters to ask clarifying questions of the interviewer had passed (due to time elapsed since interviewing). Future studies may incorporate earlier review of early life data so that raters may ask questions in close proximity to the interview. Lastly, reliability of severity ratings may be improved by employing a third trained rater with regard to early life

adversity data, similar to the process utilized for rating recent life stress in the current study.

Limitations

The current study has limitations which must be considered when interpreting findings. First, findings with regard to early adversity must be examined with caution as further work is necessary to establish clear validity and reliability of the methodology to collect, extract, and rate early life stressors. Second, a larger sample size would have allowed for investigations of sub-categories of types of stressors (by domain or sociopsychological feature). Third, the sample was primarily diagnosed with late-stage disease, and women were predominantly Caucasian, non-Hispanic, and well-educated. Future investigations incorporating greater diversity with respect to demographic and disease variables may be of benefit in maximizing generalizability. Further, mechanisms which underlie observed outcomes were not tested, including biological, cognitive, affective, and social dimensions which may serve to explain findings. Future studies may incorporate an approach which examines multifactorial influences which parallel stress theories (such as those which test the influence of biological markers, as well as resilience and buffering factors). Despite these limitations, there are many strengths to the current design. The present study benefitted from methodology utilizing a gold standard stress interview. Further, the prospective, longitudinal nature allowed for examination of temporal associations which may not be examined in cross-sectional designs. Moreover, patient procurement from multiple sites allowed for a sample with increased diversity and improved generalizability.

Clinical Implications

The present findings point to specific assessment and intervention strategies which may be of benefit in ovarian cancer patients. In particular, addressing underlying stress may be of value to patients as they approach diagnostic surgery or treatment. Mindfulness-based stress reduction (MBSR) interventions, which emphasize skills for self-regulation of stress and emotional management (Bishop, 2002), have been commonly utilized in cancer patients (Smith, Richardson, Hoffman, & Pilkinton, 2005). MBSR has been found to be an effective intervention in cancer populations; one meta-analysis produced small to medium effect sizes (d=.48) for the benefit of MBSR on mental health variables, which included improvements in sleep, depression, QOL, and stress relief (Ledesma & Kumano, 2009). In oncology populations, MBSR may benefit mood and reduce stress (Carlson, Ursuliak, Goodey, Angen, & Speca, 2001) as well as impact sleep when sleep disturbance is associated with life stress (Carlson & Garland, 2005; Shapiro, Bootzin, Figueredo, Lopez, & Schwartz, 2003; Smith, Richardson, Hoffman, & Pilkington, 2005). Yoga interventions may also target underlying stress (as well as psychological and physical symptomatology) and have shown benefits with regard to reductions in perceived stress in individuals with cancer (Vadiraja et al., 2009; Banerjee et al., 2007; Bower et al., 2012).

Further, cognitive behavioral stress management shows benefit in improving mood and QOL up to 15 years after initial training (Stagl et al., 2015; Antoni et al., 2006). It also shows specific benefit in reducing stress in women with breast cancer, though in one study, stress reduction was not maintained at 12 month follow-up (Groarke, Curtis, & Kerin, 2013). Applied progressive deep muscle relaxation training is

associated with reduced stress levels in men with prostate cancer (Isa, Moy, Razak, Zainudin, & Zainal, 2013). Stress inoculation training, or SIT (Meichenbaum, 1977), is a short-term intervention which was designed to provide individuals with skills to assist in adjustment to stressors. This intervention has been adapted for internet delivery and promising findings regarding stress reduction have been found across numerous populations when this modality is delivered electronically (for review, see Serino, Triberti, Villani, Cipresso, Gaggioli, & Riva, 2014). This may serve to be a future area for exploration in oncology populations, particularly given the benefits of utilizing an online approach to increase access.

Assessment of ongoing difficulties may allow for meaningful intervention by provision of instrumental support. Should patients experience ongoing difficulties related to factors such as home environment or financial burden, screening and coordination of resources may have a profound benefit to ease impact of these circumstances on psychological functioning. In cancer centers, due to high incidence of distress and potentially unmet needs, conducting needs assessment via screening tools is considered to be an appropriate step to facilitate referrals regarding resource counseling (Carlson, Waller, & Mitchell, 2012). One review noted that over 25 potential needs assessment measures are utilized within cancer populations, and guidelines regarding successful implementation of these programs are provided in the literature (Carlson, Waller, & Mitchell, 2012). Such coordination of services may target underlying stress due to difficulties and have benefits on psychological functioning.

Further, early life adversity appears to predict the trajectory of sleep symptomatology, which remains impaired in the majority of patients throughout the first

year post diagnosis. Therefore, screening for early life adversity may serve as a measure to identify those as risk for poorer sleep over time. This may lend itself toward identifying patients who may receive greater benefit from specific sleep interventions, such as MBSR (as noted above) and CBT for insomnia (Garland et al., 2014; Savard, Simard, Ivers, & Morin, 2005).

CONCLUSION

Early life adversity experiences were reported by nearly half of the women in the current sample. These experiences were varied in content, number, and severity, and were linked to subsequent reports of ongoing difficulties in adulthood. Greater number and severity of ongoing difficulties emerged as a specific correlate of worse depression, poorer sleep, and impaired QOL. Early life adversity predicted less recovery in sleep and QOL over the first year post diagnosis. Given the links between early adversity and ongoing difficulties, pathways to outcomes whereby early adversity may indirectly affect psychological functioning were suggested as well. These findings lend support to methodology which examines stress utilizing a life course framework when attempting to explore potential effects on women with ovarian cancer. Further, findings identify factors that underlie problematic and impactful psychological indices, which assists in establishing clear targets for interventions in this population. Interventions may include early screening, provision of practical support, and psychological interventions to ultimately benefit sleep, mood, and stress management in women as they adjust to ovarian cancer over the first year post-diagnosis.

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